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Dynamics of a Fractional Order Htlv-1 Model with Both Cell-To-Cell Transmissions and Mitosis

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Abstract

A fractional-order HTLV type -1 model with transmission from an infected cell to uninfected cell and also through mitosis is constructed and investigated. The requirements for the existence of equilibrium points are established. We have generalized the integer theorem introduced by LaSalle into the fractional system and given some adequate requirements for the infection-free equilibrium plus chronic equilibrium being globally asymptotically stable. We employed a numerical technique established for changing the fractional-order derivative to the integer-order derivative to work out the HTLV type- 1 model. Numerical simulations are given to illustrate our results. The fractional-order derivatives are defined using the Caputo definition.
Key words: *Fractional order, HTLV-1 dynamics, Global stability, Lyapunov functional.*

1.0 INTRODUCTION

Human T-cell lymph tropic virus type 1 which attacks the $CD4^+$T-cells is more prevalent in Central and South America, the Caribbean islands, Africa and in Japan [1, 2]. Today it is estimated to infect up to 20 million people around the world [3, 4]**.** Currently, no proven direct treatment or cure for Human T cell lymph tropic virus type 1 has been found nor a vaccine to prevent it and there is neither an adequate treatment for Human T cell lymphotropic virus type 1 associated pathologies [4] . During the lifetime of people who carry HTLV type 1 will develop the following diseases; Tropical spastic paraparesis/HTLV associated myelopathy (TSP/ HAM) and Adult T-cell leukemia/lymphoma (ATL) [5].

A high percentage of the estimated 20 million carriers of the HTLV-1 virus will not become symptomatic during their lives. The small percentage remaining which is less than 3% of people with HTLV type 1 develops Tropical spastic paraparesis/HTLV associated myelopathy (TSP/ HAM) [5]. The most efficient manner in which the virus is transmitted is through blood or blood products. Since the cell free virions are almost undetectable in vivo in the peripheral blood, the percentage of peripheral blood mononuclear cells that carry an integrated copy of the viral genome in an individual infected with HTLV-1, called the proviral load, is a measure of the viral burden. A proviral cell is an infected cell containing viral DNA while the provirus is an integrated viral DNA within an infected cell. About 90–95% of the proviral load in chronic HTLV-1 infection is carried by $CD4^+$T-cells and about 5–10% is carried by $CD8^+$ T-cells, [6, 7, 8].

HTLV-1 transmission primarily happens through two routes:

- Horizontal transmission – which is the spread of the provirus through cell-to–cell contact [9].
- Clonal expansion, which would actively advance cell division of infected cells. This route is known as vertical or mitotic transmission.

HTLV type 1 infection in an individual is assumed to occur in two stages; first the HTLV type 1 is believed to first spread via infected lymphocytes, mainly $CD4^+$ helper T-cells, and thereafter by clonal expansion of cells which are infected [8].

Mathematical approaches and experimental approaches have been combined to propose a model of HTLV-1 persistence in order to identify the fundamental mechanism of HTLV-1 persistence in vivo and the key factors defining the HTLV type 1 provirus load and the disease danger [2].

It has been noticed that replication of the virus mainly occurs through mitosis and HTLV type 1 protein, especially Tax, needs to be expressed so that expansion of cells that shelter a provirus are selectively promoted**,** though expression of viral protein Tax occur in minority of cells which are infected [10, 11].

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It was also noticed that the level of expression of tax mRNA by cells of $CD4^+T$ is greater in TSP/ HAM patients than in those who carry the virus asymptotically**;** therefore there is an association between rate of high expression of viral protein and a high probability of developing HAM/TSP disease, and Tax expression is a significant predictor of the disease [12].

Most of the models that have been formulated have investigated the persistence and pathogenesis of HTLV-1 infection on cells of $CD4^+T$. Mathematical models that take into consideration the two major routes of transmissions have also been established to give the description of the interaction in vivo among HTLV-1 [9, 13, 12, 14].

An integer order model with three sections; healthy $CD4^+$Tcells, latently or inactively infected $CD4^+$T-cells, and of Tax-expressing infected $CD4^+$T-cells has been formulated to examine the dynamics of the HTLV-1 infection.[15] .

From the above research done, it is evident that a lot of research needs to be done to understand the dynamics of HTLV-1. In this research, we carried out a study on dynamics of a fractional order HTLV-1 infection model consisting of cell – to- cell contact and mitotic infectious routes. We modified work done in [15] mainly because fractional order models possess memory while integer order models do not.

2.0 FORMULATION OF HTLV-1 FRACTIONAL MODEL

In this category, we take into consideration HAM/TSP alone among nonmalignant HTLV type 1 infection diseases; the dynamics of ATL and other aggressive malignancies may be rather dissimilar. Even though mitotic division takes place naturally in all $CD4^+$T-cells, natural homeostatic proliferation takes place at a very slower rate in healthy and latently infected $CD4^+$T-cells than that of selective mitotic division in Tax-expressing infected cells. Therefore due to this we overlook the effects of passive homeostatic proliferation of the healthy and latently infected $CD4^+$T-cells to make the model simple. The fractional order model is as follows;

$$\left.\begin{aligned} D^{\alpha}x_1(t) &= \lambda - \beta x_1(t)x_3(t) - \mu_1 x_1(t), \\ D^{\alpha}x_2(t) &= \sigma\beta x_1(t)x_3(t) + \varepsilon r x_3(t) - \tau x_2(t) - \mu_2 x_2(t), \\ D^{\alpha}x_3(t) &= \tau x_2(t) + (1-\varepsilon) r x_3(t) - \mu_3 x_3(t), \end{aligned}\right\} \quad \ldots\ldots\ldots\ldots\ldots\ldots (2.1)$$

Where

$x_1(t)$, $x_2(t)$ and $x_3(t)$- represent the number of healthy $CD4^+$T-cells, the number of the latently infected $CD4^+$T-cells and the number of Tax-expressing infected $CD4^+$T-cells at time t respectively.

λ- is the constant birth rate of healthy $CD4^+$T-cells.

μ_1 ,μ_2 and μ_3- represent the natural death rate of healthy$CD4^+$T-cells, resting infected $CD4^+$T-cells and Tax-expressing infecting $CD4^+$T-cells, respectively.

β-is the transmission coefficient among $CD4^+$T-cells.

σ- is the fraction of newly infected cells from infectious transmission that survive the immune attack and subsequently silence Tax expression hence becoming latently infected $\sigma \in (0,1)$.

(1-σ)-is the fraction of newly infected cells from infectious transmission that die off due to immune attack.

τ – is the proportion of latently infected cells expressing Tax hence becoming actively infected.

r -is the rate of mitotic transmission of HTLV-1 involving selective clonal expansion of the Tax-expressing $CD4^+$T-cell.

ε-is the fraction of newly infected cells via mitotic transmission that hides Tax expression hence becoming latently infected. $\varepsilon \in (0,1)$.

(1-ε)- is the fraction of newly infected cells via mitotic transmission that express Tax hence remaining in the Tax-expressing infected $CD4^+$T-cell compartment.

3.0 FRACTIONAL ORDER MODEL ANALYSIS

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The caputo version of fractional order derivative is employed in this paper

The fractional derivative of a function g defined in Caputo way is

$$D^{\alpha}g(x) = I^{n-\alpha}D^{n}g(x) = \frac{1}{\Gamma(n-\alpha)}\int_0^x (x-t)^{n-\alpha-1}g^{n}(t)dt, \quad t > 0,\ n-1 < \alpha < n \text{ and } n \in N$$

3.1 The Existence of a Unique Solution

The following Lemma is considered so as to prove that the solution is unique.

Lemma 3.1.1 [16]. Supposing function $g : R^{+} \times R^{3} \rightarrow R^{3}$ in vector form conforms to the conditions (1) to (4) as stated below:

(1) g(t,X(t)) is a function which is measurable with Lebesgue measure in relation to on $\in R^{+}$;

(2) g(t,X(t)) is a function which is continuous in relation to X(t) on R^{3} ;

(3) Partial differential of $g(t, X)$ with respect to x is continuous in relation to X(t) on R^{3}.

(4) $\|g(t,X)-g(t,Y)\|$ is less or equal to $L \| X-Y \|$, for all $t \in R^{+}$, $X,Y \in R^{3}$.

Therefore

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

$X(0) = X_0$, with $0 < \alpha \leq 1$ have a unique solution.

Theorem 3.1.2 The model (2.1) has a solution $X(t) = [x_1(t),x_2(t),x_3(t)]^{T}$ at t is greater or equal to zero and the solution is unique and will stay in $\mathbf{R}_{+}^{3}$.

Proof: Proving first that for all $[x_1(0), x_2(0), x_3(0)]$ belonging to R_{+}^{3}, model (2.1) has a solution which is unique. It is clear that the vector function g of model (2.1) satisfies the first, second and third conditions of Lemma 3.1.1.

Then proving that model (2.1) satisfies the fourth condition of Lemma 3.1.1. Therefore model (2.1) turns out to be

$D^{\alpha}X(t) = A_1X(t) + x_1A_2X(t) + A_3$, where

$$A_1 = \begin{pmatrix} -\mu_1 & 0 & 0 \\ 0 & -(\tau+\mu_2) & 0 \\ 0 & \tau & -\mu_3 \end{pmatrix}, \quad A_2 = \begin{pmatrix} 1 & -\beta & o \\ 0 & \sigma\beta & \varepsilon s \\ 0 & 0 & (1-\varepsilon)r \end{pmatrix} \text{ and } A_3 = \begin{pmatrix} \lambda \\ 0 \\ 0 \end{pmatrix}$$

Let $g(t,X(t)) = A_1X(t) + x_1A_2X(t) + A_3$, therefore

$\|g(t,X(t))-g(t,Y(t))\|$

$= \| A_1(X(t)-Y(t)) + x_1A_2X(t)-x_1A_2Y(t) + x_1A_2Y(t)-y_1A_2Y(t) \|$

$\leq (\| A_1\| + \| x_1\|\| A_2\| + \| A_2\|\| Y(t) \|) \|X(t)-Y(t) \|$

$= L \|X(t)-Y(t) \|$,

Whereby $\|X(t) \|$ is equal to $\Sigma_{i=1}^{3}\ \sum_{i=1}^{3} \sup_t | x_i(t) |$

And L is equal to $\| A_1\| + \| A_2\| (\| x_1\| + \| Y(t) \|)$.

Model (2.1) has a solution which is unique based on Lemma 3.1.1

3.2 The Existence of Non – Negative Solutions

The following two Lemmas are considered so as to prove that the solution is positive.

Lemma 3.2.1 [17]:

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

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Therefore, $g(z) = g(a) + \frac{1}{\Gamma(\alpha)} D^{\alpha}g(\xi)(z-a)^{\alpha}$,

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

Lemma 3.2.2 [17]:

Assuming g(z) belongs to C[a,b] as well as $D^{\alpha}g(z)$ belongs to C [a,b] for $0 < \alpha \leq 1$ therefore;

- g(z) is always non decreasing for every z belonging to [a,b] provided that $D^{\alpha} g(z)$ is greater or equal to zero, for all z ∈ [a, b].
- g(z) is always non increasing for every z belonging to [a,b] provided that $D^{\alpha} g(z)$ is less or equal to zero, for all z ∈ [a, b].

We then prove that the solution of model (2.1) is positive at all times.

Based on model (2.1) we have

$D^{\alpha}x_1(t)|_{x_1=0} = \lambda \geq 0$,

$D^{\alpha}x_2(t)|_{x_2=0} = (\sigma\beta x_1 + \varepsilon r)x_3(t) \geq 0$,

$D^{\alpha}x_3(t)|_{x_3=0} = \tau x_2 \geq 0$.

The solution will stay in R_+^3 based on Lemma 3.2.1 and also lemma 3.2.2. This is because from the two lemmas we know that if the solutions of model (2.1) when t is equal to zero is non-negative (i.e initial conditions are not negative), the solutions of model (2.1) when t is greater than zero is also non- negative and the solution will stay in R_+^3.

3.3 The Existence of Equilibrium Points

In this section, we deliberate on the existence of equilibrium points of the mathematical model (2.1). The basic reproductive ratio of mathematical model (2.1) which represents the mean figure of newly infected cells as a result of an infection by an actively infected $CD4^+$T-cell at the start of the infectious process is stated as shown below

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

R_0 comprises of two segments corresponding to;

- Average number of secondary infection caused by horizontal transmission $R_{01} = \frac{\sigma\beta\lambda\tau}{(\tau+\mu_2)\mu_1\mu_3}$
- Average number of secondary infection caused by mitotic transmission $R_{02} = \frac{\tau\varepsilon r}{(\tau+\mu_2)\mu_3} + \frac{(1-\varepsilon)r}{\mu_3}$.

Assumption of the model:

- $r < \frac{(\tau+\mu_2)\mu_3}{\tau+\mu_2(1-\varepsilon)}$ (to maintain the boundedness of the solution of the model). This demands that the average number of the secondary infection caused by amitotic transmission must on no account be above one i.e $\frac{\tau\varepsilon r}{(\tau+\mu_2)\mu_3} + \frac{(1-\varepsilon)r}{\mu_3} < 1$. Failure for this inequality to hold, then the number of infected cell may rise to infinity

Two relevant equilibrium points are obtained from model (2.1) when calculation is done directly.

(i) Model (2.1) has an infection-free equilibrium (IFE) when $R_0 < 1$

IFE $(E_0) = (x_0, 0, 0)$, where $x_0 = \frac{\lambda}{\mu_1}$

implying that the infected $CD4^+$cells are cleared

(ii) There exists an endemic equilibrium (EE) for model (2.1) when $R_0 > 1$,

EE $(E_1) = (x_1^*, x_2^*, x_3^*)$, where,

$x_1^* = \frac{\lambda}{\beta x_3^* + \mu_1}$, $x_2^* = \frac{[\mu_3 - (1-\varepsilon)r]x_3^*}{\tau}$ and $x_3^* = \frac{\mu_1}{\beta}(R_0 - 1)\frac{(\tau+\mu_2)\mu_3}{(\tau+\mu_2)\mu_3 - \tau r - \mu_2(1-\varepsilon)r}$

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3.4 The Global Stability of the Equilibrium Points

In this section, the conditions that are appropriate for the globally asymptotical stability of fractional system which generalize the result for ordinary differential equations are first given. Secondly we shall determine the global asymptotical stability of E_0 and E_1 of model (2.1).

Suppose Ω is an open subset of N dimensional R space (R^n).Let us take into consideration the autonomous system below

$D^\alpha x(t) = g(x)$. ………………………………….. (3.1)

Considering V belongs to $C^1(\Omega, R^n)$,we express the order α of the derivative of V (x) alongside the solutions of equation (3d) as the form below

$D^\alpha V|_{(5)} = I^{1-\alpha} DV|_{(5)} = I^{1-\alpha}\left(\frac{dV}{dx} \quad \frac{dx}{dt}\right)$, where $0 < \alpha \leq$ ……….. (3.2)

We put forward the following important two lemmas so as to give conditions that are appropriate for the globally asymptotical stability of infection-free and the endemic equilibria.

Lemma 3.4.1 [18] Assuming D is a set which is closed and bounded with respect to $D^\alpha x(t) =$ g(x). Every solution of $D^\alpha x(t) = g(x)$ begins from a point in D and stays in D at all times.

Let V: D → R be a function having first partial derivatives which are continuous such that $D^\alpha V|(5) \leq 0$ \$ Let E be a set of all points in D where $D^\alpha V|_{(5)} = 0$ i.e $E = \{x \in D | D^\alpha V|_{(5)} = 0\}$.

Let M be the largest invariant set in E i.e $M = \{x \in E | D^\alpha x(t) = g(x)\}$. Therefore each solution of function x of t beginning in D approaches M as t tends to infinity. For example, if M is equals to zero, therefore x tends to zero, as t tends to infinity.

Lemma 3.4.2 [19] supposing function x of t belongs to a set of all positive real numbers and is continuous as well as derivable. Therefore, for any time instant $t \geq t_0$, x*

$D_t^\alpha\left(x(t) - x^* - x^* \frac{\ln x(t)}{x^*}\right) \leq \left(1 - \frac{x^*}{x(t)}\right) D_t^\alpha x(t)$, x*belongs to a set of all positive real numbers, for all α belonging to (0,1).

A. Global asymptotical stability of Infection-free Equilibrium

In this section we investigate the stability of Infection free equilibrium (IFE)

Theorem 3.4.3 The infection-free equilibrium E_0 is globally asymptotically stable whenever $R_0 < 1$.

Proof: Defining the function of Lyapunov V_1 of t in the way below

$$V_1(t) = x_1(t) - x_0 - x_0 \frac{\ln x_1(t)}{x_0} + \frac{\tau}{(\tau + \mu_2)} x_2(t) + x_3(t).$$

Computing the time derivative of the function $V_1$of t alongside solutions of mathematical model (2.1), we get

$$D^\alpha V_1(t) \leq \left(1 - \frac{x_0}{x_1(t)}\right)[x_0 - \mu_1 x_1(t) - \beta x_1(t) x_3(t)]$$

$$+ \frac{\tau}{(\tau + \mu_2)}[\sigma\beta x_1 x_3 + \varepsilon r x_3 - \tau x_2 - \mu_2 x_2]$$

$$+ [\tau x_2 + (1 - \varepsilon) r x_3 - \mu_3 x_3]$$

$$D^\alpha V_1(t) = -\mu_1 \frac{(x_1(t) - x_0)^2}{x_1(t)} + \mu_3 x_3(t)(R_0 - 1).$$

Notice that $D^\alpha V_1(t) = 0$ as long as $x_1(t) = x_0$ and $x_3(t) = 0$. By the second equation of model (2.1), we also have $x_2(t) = 0$. Therefore, by the invariance principle introduced in [20], equilibrium E_0 turns out to be globally asymptotically stable.

B. Global asymptotical stability of Endemic Equilibrium.

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Theorem 3.4.4 The endemic equilibrium (EE) is globally asymptotically stable whenever $R_0>1$

Proof: Defining the function of Lyapunov V_2 of t in the way below

$$V_2(t) = x_1(t)-x_1^*-x_1^* \frac{\ln x_1(t)}{x_1^*} + \frac{\tau x_2^*}{\sigma\beta x_1^* x_3^*}[x_2(t)-x_2^*-x_2^* \frac{\ln x_2(t)}{x_2^*}]$$

$$+ [(x_3(t)-x_3^* -x_3^* \frac{\ln x_3(t)}{x_3^*}].$$

Computing the derivative of the function V_2 of t alongside solutions of mathematical model (2.1), we get

$$D^{\alpha}V_2(t) \le (1-\frac{x_1^*}{x_1(t)})[\mu_1 x_1^* + \beta x_1^* x_3^* - \mu_1 x_1(t) - \beta x_1(t)x_3(t)]$$

$$+ \frac{\tau x_2^*}{\sigma\beta x_1^* x_3^*}(1-\frac{x_2^*}{x_2(t)})[\sigma\beta x_1 x_3 + \varepsilon r x_3 - \tau x_2 - \mu_2 x_2]$$

$$+ (1-\frac{x_3^*}{x_3(t)})[\tau x_2 + (1-\varepsilon) r x_3 - \mu_3 x_3]$$

$$= -\mu_1 \frac{(x_1(t)-x_1^*)^2}{x_1(t)} + \beta x_1^* x_3^*[2 - \frac{x_1^*}{x_1(t)} - \frac{x_1(t)x_3(t)}{x_1^* x_3^*}]$$

$$+ \tau x_2^*[2 - \frac{x_3^*}{x_3(t)} - \frac{x_2^* x_1(t) x_3(t)}{x_1^* x_3^* x_2(t)}]$$

When $R_0 > 1$, notice that $D^{\alpha}V_2(t) \le 0$ and $D^{\alpha}V_2(t) = 0$ as long as $x_1(t)$ is equal to x_1^*, $x_2(t)$ is equal to x_2^* and $x_3(t)$is equal to x_3^*.

By the invariance principle introduced by La Salle, E_1 turns out to be globally asymptotically stable.

3.5. Numerical Technique

To find solutions to the system (2.1), we will employ a numerical technique that was developed and introduced in [21, 22] to find solutions of fractional-order nonlinear differential equations (FDE's). In [21] it was shown that the fractional derivative defined in Caputo way of a function g of t with α as the order which satisfy $0 < \alpha < 1$ may be expressed as

$$D^{\alpha}g(t) = \frac{1}{\Gamma(2-\alpha)}\{ \frac{g^{(1)}(t)}{t^{\alpha-1}}$$

as follows

$$\left.\begin{aligned} &\frac{d}{dt}B_k(g) = -(k-1)t^{k-2}g(t),\ k\ [1 + \sum_{k=1}^{\infty} \frac{\Gamma(k-1+\alpha)}{\Gamma(\alpha-1)k!}] \\ &-[\frac{\alpha-1}{t^{\alpha}}\ g(t) + \sum_{k=2}^{\infty} \frac{\Gamma(k-1+\alpha)}{\Gamma(\alpha-1)(k-1)!}(\frac{g(t)}{t^{\alpha}} + \frac{\mathbf{B_k(g)(t)}}{t^{k-1+\alpha}})]\}, \end{aligned}\right\} \quad \ldots\ldots\ldots\ldots\ldots\ldots (3.3)$$

Where,

$$B_k(g)(t) = -(k-1)\int_0^t \tau^{k-2} g(\tau)d\tau,\ k=2,3,4\cdots, \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.4)$$

And having the properties $= 2,3,4\cdots$. …… (3.5)

We approximate $D^{\alpha}g(t)$ by using M terms in sums appearing in (3.3) as follows:

$$\left.\begin{aligned} &D^{\alpha}g(t) = \frac{1}{\Gamma(2-\alpha)}\{ \frac{g^{(1)}(t)}{t^{\alpha-1}}[1 + \sum_{k=1}^{M} \frac{\Gamma(k-1+\alpha)}{\Gamma(\alpha-1)k!}] \\ &-[\frac{\alpha-1}{t^{\alpha}}\ g(t) + \sum_{k=2}^{M} \frac{\Gamma(k-1+\alpha)}{\Gamma(\alpha-1)(k-1)!}(\frac{g(t)}{t^{\alpha}} + \frac{\mathbf{B_k(g)(t)}}{t^{k-1+\alpha}})]\}, \end{aligned}\right\} \quad \ldots\ldots\ldots\ldots\ldots\ldots (3.6)$$

Equation (3.6) can be modified in the form as follows:

$$D^{\alpha}g(t) \simeq Q(\alpha,t,M)f^{(1)}(t) + Y(\alpha,t,M)g(t) + \sum_{k=2}^{M} A(\alpha,t,k)\frac{B_k(g)(t)}{t^{k-1+\alpha}}, \ldots\ldots\ldots\ldots (3.7)$$

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Where,

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

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

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

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

We set

$H_1(t) = x_1(t)$,

$H_{M+1}(t) = x_2(t)$,

$H_{2M+1}(t) = x_3(t)$,

$H_k(t) = B_k(x_1)(t)$,

$H_{M+k}(t) = B_k(x_2)(t)$,

$H_{2M+k}(t) = B_k(x_3)(t)$, $\quad k = 2,3,4\cdots$.

Model (2.1) can be modified in the form as follows

$$\left.\begin{aligned}
&Q(\alpha,t,M)H_1'(t) + Y(\alpha,t,M)H_1(t) + \sum_{k=2}^{M} A(\alpha,t,k)\frac{H_k(t)}{t^{k-1+\alpha}} \\
&= \lambda - \beta H_1(t)H_{2M+1}(t) - \mu_1 H_1(t) , \\
&Q(\alpha,t,M)H_{M+1}'(t) + Y(\alpha,t,M)H_{M+1}(t) + \sum_{k=2}^{M} A(\alpha,t,p)\frac{H_{M+k}(t)}{t^{k-1+\alpha}} \\
&= \sigma\beta H_1(t)H_{2M+1}(t) + \varepsilon r H_{2M+1}(t) - \tau H_{M+1}(t) - \mu_2 H_{M+1}(t), \\
&Q(\alpha,t,M)H_{2M+1}'(t) + Y(\alpha,t,M)H_{2M+1}(t) + \sum_{k=2}^{M} A(\alpha,t,k)\frac{H_{2M+k}(t)}{t^{k-1+\alpha}} \\
&= \tau H_{M+1}(t) + (1-\varepsilon) r H_{2M+1}(t) - \mu_3 H_{2M+1}(t),
\end{aligned}\right\} \quad \ldots\ldots\ldots\ldots (3.8)$$

Where, $H_k(t) = -(k-1)\int_0^t \tau^{-2} H_1(\tau)d\tau$,

$$\left.\begin{aligned}
&H_{M+k}(t) = -(k-1)\int_0^t \tau^{k-2} H_{M+1}(\tau)d\tau, \\
&H_{2M+k}(t) = -(k-1)\int_0^t \tau^{k-2} H_{2M+1}(\tau)d\tau, \qquad k = 2,3,4\cdots M.
\end{aligned}\right\} \quad \ldots\ldots\ldots\ldots\ldots (3.9)$$

Equations (3.8) and (3.9) can now be rewritten in the form as follows

$$\left.\begin{aligned}
&H_1'(t) = \frac{1}{Q(\alpha,t,M)}[\lambda - \beta H_1(t)H_{2M+1}(t) - \mu_1 H_1(t) \\
&- Y(\alpha,t,M)H_1(t) - \sum_{k=2}^{M} A(\alpha,t,k)\frac{H_k(t)}{t^{k-1+\alpha}}] , \\
&H_k'(t) = -(k-1)t^{k-2}H_1(t),\ k = 2,3,4\cdots M, \\
&H_{M+1}'(t) = \frac{1}{Q(\alpha,t,M)}[\sigma\beta H_1(t)H_{2M+1}(t) + \varepsilon r H_{2M+1}(t) - \tau H_{M+1}(t) - \mu_2 H_{M+1}(t)
\end{aligned}\right\} \quad \ldots\ldots\ldots (3.10)$$

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$-Y(\alpha,t,M)H_{M+1}(t) - \sum_{k=2}^{M} A(\alpha,t,k)\frac{H_{M+k}(t)}{t^{k-1+\alpha}}]$,

$H'_{M+k}(t) = -(k-1)t^{k-2}H_{M+1}(t)$, $k = 2,3,4\cdots M$,

$H'_{2M+1}(t) = \frac{1}{Q(\alpha,t,M)}[\tau H_{M+1}(t)+(1-\varepsilon)rH_{2M+1}(t) - \mu_3 H_{2M+1}(t)$

$-Y(\alpha,t,M)H_{2M+1}(t) - \sum_{k=2}^{M} A(\alpha,t,k)\frac{H_{2M+k}(t)}{t^{k-1+\alpha}}]$,

$H'_{2M+k}(t) = -(k-1)t^{k-2}H_{2M+1}(t)$, $k = 2,3,4\cdots M$,

Having initial conditions as follows:

$$\left.\begin{aligned} &H_1(\psi) = x_1(0),\\ &H_k(\psi) = -\frac{k-1}{2}\Delta t^{k-1}x_1(0),\\ &H_{M+1}(\psi) = x_2(0),\\ &H_{M+k}(\psi) = -\frac{k-1}{2}\Delta t^{k-1}x_2(0),\\ &H_{2M+1}(\psi) = x_3(0),\\ &H_{2M+k}(\psi) = -\frac{k-1}{2}\Delta t^{k-1}x_3(0), \qquad k = 2,3,4\cdots M. \end{aligned}\right\} \quad \ldots\ldots\ldots (3.11)$$

In chapter four, we consider the numerical solution of system of ordinary differential equation (3.10) having initial conditions (3.11) by using the famous and widely used Runge-Kutta method of fourth order.

4.0. NUMERICAL SIMULATIONS

Numerical simulations for the system (2.1) were conducted to confirm the validity of the results attained. All the differential equations are solved by using Runge-Kutta method of fourth order.

Each parameter is assumed to be non-negative in cubic millimeters per day in entire numerical runs. Approximations of values of parameter were done using both theoretical and experimental techniques in $CD4^+$ lymphocyte kinetics studied in [23].

Table 4.1Appropriate values of parameter

Parameter	Range of value per day	Descriptions	Source
λ	15 to 25 cells per mm^3	Rate at which healthy $CD4^+$ cells are produced	[23]
β	0.0005 to 0.003 cells per mm^3	Infectious transmissibility coefficient	[23]
r	0.04 to 0.4	Rate at which actively infected cells expressing Tax selectively proliferate	[23]
σ	0 to 1	Portion of proviral cells from infectious transmission that are alive	[23]
ε	0 to 1	Portion of proviral cells from mitotic transmission that are alive	[23]
τ	0.0003 to 0.03	Rate of spontaneous Tax expression	[23]
μ_1	0.01 to 0.05	Rate at which healthy cells die naturally	[23]
μ_2	0.01 to 0.05	Rate at which latently infected cells die naturally	[23]
μ_3	0.01 to 0.05	Rate at which actively infected cells die naturally	[23]

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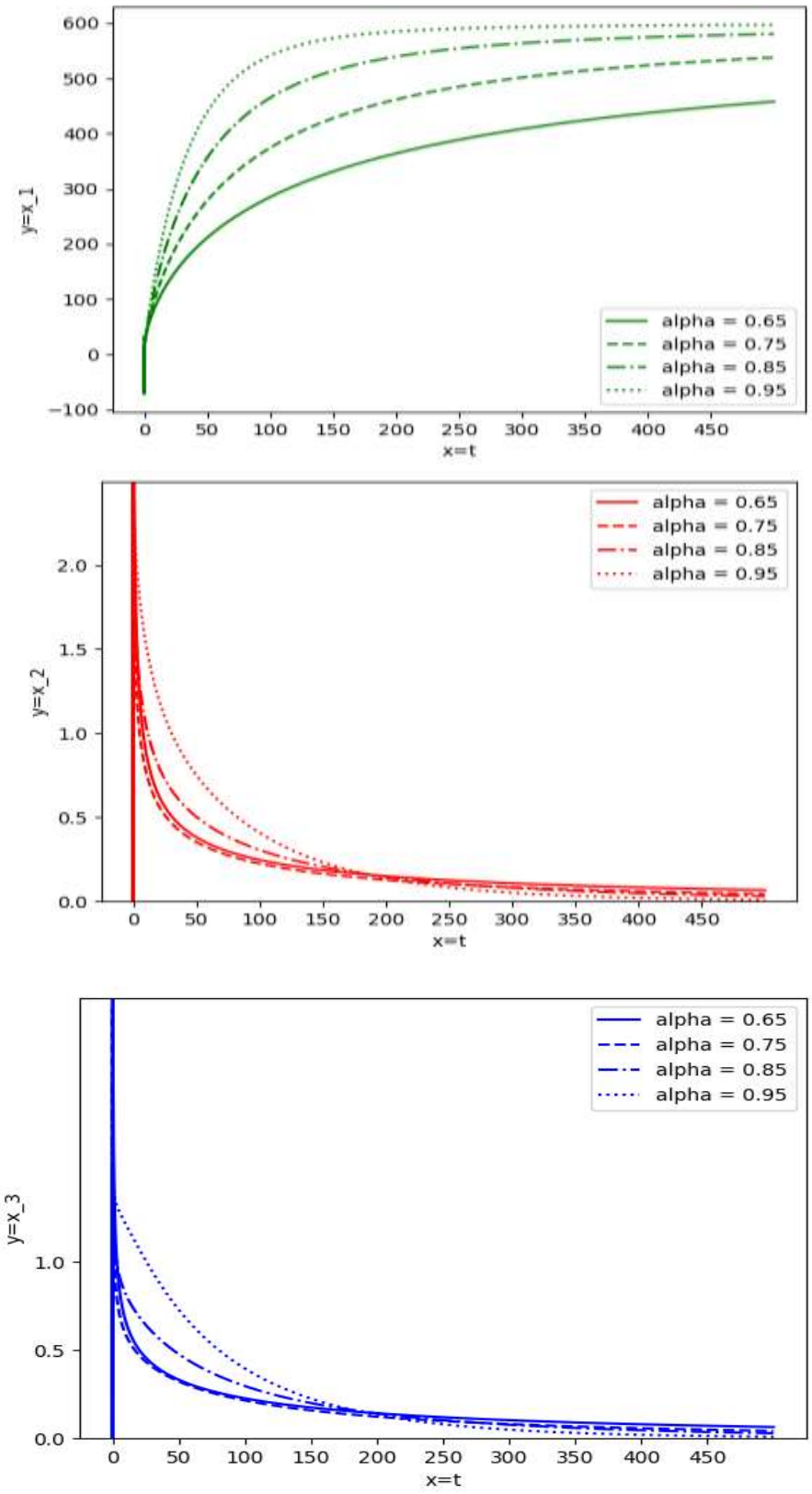

Figure 4.2: The above graphs display the approximate results of system (2.1). Approximation of the results were done at $\psi = \Delta t = 0.01$. The parameter values are $\alpha = 0.65, 0.75, 0.85, 0.95$, $\lambda = 20$, $\beta = 0.001$, $\sigma = 0.01$, $\varepsilon = 0.9$, $r = 0.05$, $\tau = 0.03$, $\mu_1 = 1/30$, $\mu_2 = 1/30$, $\mu_3 = 0.05$, and $M = 10$ and the initial conditions $x_1(0) = 10$, $x_2(0) = 2.5$, $x_3(0) = 1.5$. By direct computation, $R_0 = 0.5832 < 1$, therefore disease-free equilibrium $E_0 = (600, 0, 0)$ is globally asymptotically stable as demonstrated in the graphs. From the figure it can be seen that as alpha increases the trajectories of the solutions of the model near the integer-order ordinary differential equation.

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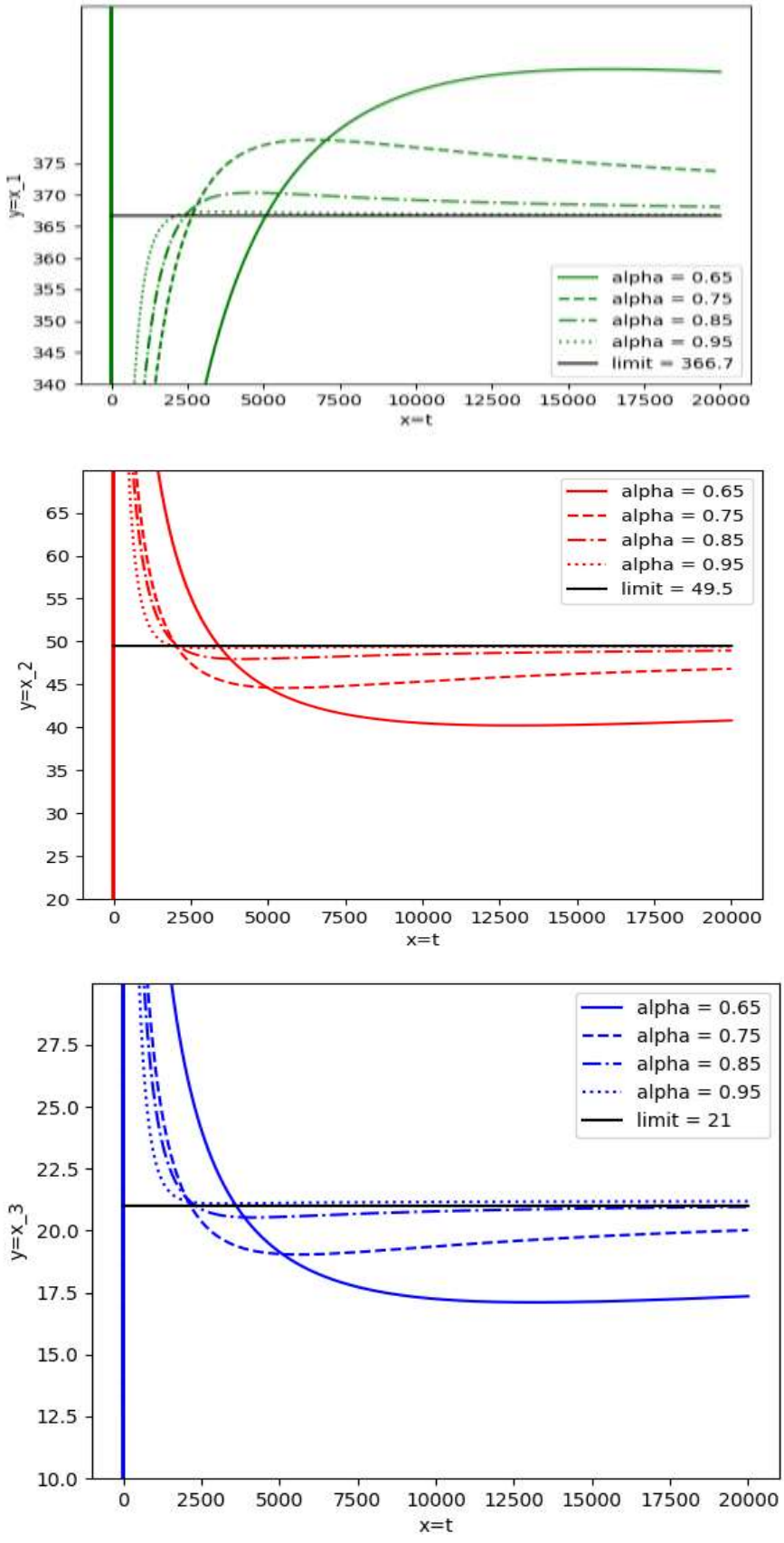

Figure 4.3: The above graphs display the approximate results of system (2.1). Approximation of the results were done at ψ = Δt = 0.8, choosing λ = 20, β = 0.001, σ = 0.1, ε =0.8, r = 0.1, τ = 0.03, μ_1= 1/30,μ_2= 0.02, μ_3= 0.09, and M = 10 and the initial conditions $x_1(0)$ = 1000, $x_2(0)$ = 250, $x_3(0)$ = 150. By direct computation, R_0 = 1.1556 > 1, therefore endemic equilibrium E_1= (366.6258, 49.5091, 21.2182) is globally asymptotically stable as demonstrated in the graphs. From the figure it can be seen that as alpha increases the trajectories of the solutions of the model near the integer-order ordinary differential equation.

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5.0 CONCLUSION

In this research, we have formulated a fractional order HTLV-1 model incorporating mitotic transmission and cell-to-cell transmission of the virus. The suggested model is significant since fractional order systems have memory and the core feature of immune response constitutes memory. We carried out global stability analysis and it showed that infection-free equilibrium is globally asymptotically stable if $R_0 < 1$, meaning the infection will eventually be no more, and when $R_0 > 1$, the endemic equilibrium is globally asymptotically stable, meaning the infection will carry on.

Numerical operations were executed to illustrate the theoretical results. The aftereffect of parameter α which is the order of system of equation (2.1) on the epidemic dynamics was discovered. Figures.4.2 - 4.3 demonstrate that; increase in α cause the curves of the mathematical model to near the integer-order ordinary differential equation.

6.0 RECOMMENDATION

Examining the results found in this research, the convergence rate of the numerical results of mathematical model (2.1) for diverse values of α could be achieved also. Also in majority of biological models, time delay is taken into account for the aim of illustrating the phenomena being studied accurately. In that case, studying global asymptotic stability of equilibria for delayed fractional order HTLV-1 model is going to be a really worthy as well as crucial thesis.

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