Mathematical Analysis of the Global Dynamics of a Model for HIV Infection of CD4+ T Cells

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Abstract: We analyse a mathematical model that describes HIV infection of CD4+ T cells. We are interested in the effect of a small addition of infection on an equilibrium state. Using Rene Descartes' theory of solutions, we show that if the so called basic reproduction number Ro<1, the infection will eventually die out but if Ro >1, then the infection will lead to full blown AIDS, In either case Ro is important in the eventual growth of the disease.

Keywords : basic reproduction number, equilibrium state, AIDS, mathematical model, full blown, Rene Descartes' theory, growth of the disease

1.0 Introduction

The Human Immunodeficiency Virus (HIV) mainly targets a host's CD$+T cells. Chronic HIV infection causes gradual depletion of the $CD4^+$ T cells pool, and thus progressively compromises the host's immune response to opportunistic infections leading to Acquire Immune Deficiency Syndrome (AIDS). For this reason, the count of $CD4^+$ T cells is a primary indicator used to measure progression of HIV infection. In a normal person, the level of $CD4^+$ T cells in peripheral blood is regulated at a level between 800 and 1200 mm^{-3}. Several mathematicians have proposed models to describe the vivo dynamics of T cell and HIV interaction see [1, 4, 5, 6, 7 and 3]. In particular Wang and Li [7] proposed the following model

$$\frac{dT}{dt} = s - \alpha T - rT\left(1 - \frac{T + T^*}{T_{\max}}\right) - kVT \quad (1.1)$$

$$\frac{dT^*}{dt} = kVT - \beta T^* \quad (1.2)$$

$$\frac{dV}{dt} = N\beta T^* - \gamma V \quad (1.3)$$

Where

s: constant production rate at which the body produces $CD4^+$ T cells from precursor in the bone marrow and thymus,

α: natural turnover rate of uninfected T cells,

r: rate at which T cells multiply through mitosis,

T: concentration of the susceptible $CD4^+$ T cells,

T_{max}: maximum level of CD4+T cell concentration in the body,

T^*: the concentration of infected CD4+ T cells by HIV viruses,

V: free HIV virus particle in the blood,

β: natural turnover rate of infected T cells,

γ: natural turnover rate of virus particles,

kVT: describes the incident of HIV infection of healthy $CD4^+$ T cells where k>0 is the infection rate,

N: virus particle produced by infected CD4+ T cell during its life time.

Perelson and Nelson [5] replaced equation (1.1) by

$$\frac{dT}{dt} = s - \alpha T - rT\left(1 - \frac{T^*}{T_{\max}}\right) - kVT$$

And retained (1.2) and (1.3). This is due to the fact that the global dynamics of (1.1)-(1.3) and (1.1), (1.2) and (1.4) have not been fully established in literature. So the research goes on . It on this basis that we are proposing the following model:

2.0 Mathematical Formulation

A model of HIV infection similar to (1.1) but using a logistic growth $rT\left(1 - \frac{T^*}{T_{\max}}\right)$ for infection $CD4^+$T cells is proposed in this paper. Thus the model is

$$\frac{dT}{dt} = s - \alpha T - rT\left(1 - \frac{T^*}{T_{\max}}\right) - kVT$$

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$$\frac{dT^*}{dt} = kVT - \beta T^* \qquad (2.1)$$
$$\frac{dV}{dt} = N\beta T^* - \gamma V$$

3.0 Method of Solution

3.1 Equilibria points

Let $X = \frac{s}{\alpha - r} - T$, *then* (2.1) *becomes*

$$\frac{dX}{dt} = -(\alpha - r)X + \frac{rsT^*}{(\alpha - r)T_{\max}} - \frac{rXT^*}{T_{\max}} + \frac{kVs}{(\alpha - r)} - kVT$$

$$\frac{dT^*}{dt} = kV\frac{s}{\alpha - r} - kVX - \beta T^* \qquad (3.1)$$
$$\frac{dV}{dt} = N\beta T^* - \gamma V$$

In matrix notation (3.1) becomes

$$\begin{pmatrix} \frac{dX}{dt} \\ \frac{dT^*}{dt} \\ \frac{dV}{dt} \end{pmatrix} = \begin{pmatrix} -(\alpha - r) & \frac{rs}{(\alpha - r)T_{\max}} & \frac{ks}{(\alpha - r)} \\ 0 & -\beta & \frac{ks}{(\alpha - r)} \\ 0 & N\beta & -\gamma \end{pmatrix} \begin{pmatrix} X \\ T^* \\ V \end{pmatrix} + \begin{pmatrix} -\frac{rXT^*}{T_{\max}} - kVX \\ -kVX \\ 0 \end{pmatrix}$$

We now find equilibrium point by setting

$\frac{dX}{dt} = \frac{dT^*}{dt} = \frac{dV}{dt} = 0$, ad solving the three simultaneous equations. The system of equations yield two equilibria points

$A_o = (0,0,0)$ *and*

$$A^* = \begin{pmatrix} \frac{ksN - \gamma\alpha + \gamma r}{kN(\alpha - r)}, \\ \frac{(ksN - \gamma\alpha + \gamma r)T_{\max}}{\gamma r + kT_{\max}N\beta}, \\ \frac{(ksN - \gamma\alpha + \gamma r)T_{\max}N\beta}{(\gamma r + kT_{\max}N\beta)\gamma} \end{pmatrix}$$

A_o is infection free, while A^* is the infection equilibrium. The basic reproduction parameter R_o is defined by $R_o = \frac{Nks}{\gamma(\alpha - r)}$

3.2 Nature of equilibrium points

We shall need the following theorems in the analysis of the nature of the equilibria points. The two theorems are already in the literature but we shall state and prove new theorems that could be derived from the theorems.

Theorem (Perron [1])

Let $\dot{x} = Ax + f(x,t)$ where the matrix A has all eigenvalues with negative real parts. Let f be real and continuous for small

$\|x\|$ *and* $t \geq 0$ *and* $f(x,t) = 0\|x\|$ *as* $\|x\| \to 0$ uniformly in t, t≥0.Then the zero solution of $\dot{x} = Ax + f(x,t)$ is uniformly asymptotically stable,

Theorem (Descartes' rule of sign [2])

The number of positive zeros of polynomial with real coefficients is either equals to the number of variations in sign of the polynomial or less than this by an even umber.

We are now in position to proceed to the theorem

Theorem 3.1

The zero solution of the infected free equilibrium is asymptotically stable if $R_o<1$ and if $r<\alpha$. Otherwise the zero solution is unstable.

Theorem 3.2

The zero solution of the infected – free equilibrium is unstable if $R_o > 1$.

Theorem 3.3

If then the equilibrium point A* is uniformly asymptotically stable

Theorem 3.4

$$Let\ r_1 = \beta + \frac{r\gamma}{kNT_{\max}} + \gamma + \frac{ksN}{\gamma}$$

$$r_2 = \frac{ksN}{\gamma}\left(\beta + \frac{r\gamma}{kNT_{\max}} + \gamma\right) + \left(\beta + \frac{r\gamma}{kNT_{\max}}\right)\gamma$$
$$- \frac{\gamma r\left(\beta T_{\max}(\alpha - r) + rs\right)}{T_{\max}\left(r\gamma + k\beta NT_{\max}\right)}$$

$$r_3 = ksN\left(\beta + \frac{r\gamma}{kNT_{\max}}\right) -$$
$$\frac{\gamma\left(\beta T_{\max}(\alpha - r) + rs\right)}{r\gamma + k\beta NT_{\max}}\left(\frac{r\gamma}{T_{\max}} + k\beta N\right)$$

$Let\ \alpha = r.\ If\ \beta\alpha T_{\max} + sr > \beta rT_{\max}$ and r1>0, r2>0,r3>0, then the equilibrium point A*is uniformly asymptotically stable.

Theorem 3.5

Let $r_4>$, $r_5>r_6>o$, then the infection equilibrium A* is asymptotically stable

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$$r_4 = \beta + \frac{r\gamma}{kNT_{\max}} + \gamma + \frac{ksN}{\gamma}$$

$$r_5 = \frac{ksN}{\gamma}\left(\beta + \frac{r\gamma}{kNT_{\max}} + \gamma\right) + \left(\beta + \frac{r\gamma}{kNT_{\max}}\right)\gamma - \frac{\gamma r\left(\beta T_{\max}(\alpha - r) + rs\right)}{T_{\max}\left(r\gamma + k\beta NT_{\max}\right)}$$

$$r_3 = ksN\left(\beta + \frac{r\gamma}{kNT_{\max}}\right) - \frac{\gamma\left(\beta T_{\max}(\alpha - r) + rs\right)}{r\gamma + k\beta NT_{\max}}\left(\frac{r\gamma}{T_{\max}} + k\beta N\right)$$

Theorem 3.6

If $R_o > 1$ *and* $\left(\beta kNT_{\max} + r\gamma\right)^2 > krN\left(\beta T_{\max}(\alpha - r) + rs\right)$

then A^* *is locally asymptotically stable*

We now prove the theorems.

Proof of Theorem 3.1

By (2.1), the Jacobian matrix at A_o

$$J(A_o) = \begin{pmatrix} -(\alpha - r) & \frac{rs}{(\alpha - r)T_{\max}} & \frac{ks}{(\alpha - r)} \\ 0 & -\beta & \frac{ks}{(\alpha - r)} \\ 0 & N\beta & -\gamma \end{pmatrix}$$

So the eigenvalues are given by

$$\left(-(\alpha - r) - \lambda\right)\left(\lambda^2 + (\beta + \gamma)\lambda + \beta\gamma - \frac{ksN\beta}{(\alpha - r)}\right) = 0 \; i.e$$

$$\left(-(\alpha - r) - \lambda\right)\left(\lambda^2 + (\beta + \gamma)\lambda + \beta\gamma(R_o - 1)\right) = 0$$

$$\lambda_1 = -(\alpha - r) \; and \; \lambda^2 + (\beta + \gamma)\lambda + \beta\gamma(R_o - 1) = 0$$

Now $\beta > 0, \gamma > 0, \mathrm{r} > 0$. *So if* $R_o < 1$, the number of variation in sign is zero. Hence all eigenvalues are negative. Therefore A_o is uniformly asymptotical stable.

Proof of Theorem 3.2

If Ro>1, from the proof of theorem 1,

$\lambda^2 + (\beta + \gamma)\lambda + \beta\gamma(R_o - 1) > 0 \;\; \beta > 0, \gamma > 0, \mathrm{r} > 0$

implies that the number of variations in sign is 1. So J (A_o) has a positive root. Hence A_o is unstable.

Proof of Theorem 3.3

The Jacobian of the matrix of (2.1) at A* translated to the origin is

$$J(A^*) = \begin{pmatrix} \frac{ksN}{\gamma} & \frac{r\gamma}{kNT_{\max}} & \frac{\gamma}{N} \\ \frac{k\beta T_{\max}\left(-ksN + \alpha\gamma - r\gamma\right)}{\left(r\gamma - k\beta NT_{\max}\right)\gamma} & -\beta & \frac{\gamma}{N} \\ 0 & N\beta & -\gamma \end{pmatrix}$$

so if $\frac{kN\left(\beta T_{\max}(\alpha - r) + sr\right)}{\left(r\gamma + k\beta NT_{\max}\right)} = 0$ then the eigenvalues are $\lambda_1 = -\frac{kNs}{\gamma}, \lambda_2 = -\beta - \frac{r\gamma}{kNT_{\max}}, \lambda_3 = -\gamma$. The results follow since all the eigenvalues are negative.

Proof of Theorem 3.4

If α=r, r_i >0,i=1,2,3 and if $\beta\alpha T_{\max} + sr > \beta r T_{\max}$, then $J(A^*)$ translate to the origin is

$$\begin{pmatrix} -\frac{ksN}{\gamma} & \frac{r\gamma}{kNT_{\max}} & \frac{\gamma}{N} \\ \frac{ksNr}{\gamma r + k\beta NT_{\max}} & -\beta - \frac{r\gamma}{kNT_{\max}} & 0 \\ 0 & N\beta & -\gamma \end{pmatrix}$$

The eigenvalues is obtained by satisfy $\lambda^3 + \lambda^2 r_1 + \lambda r_2 + r_3 = 0$. The number of variation in signs is zero. Clearly λ=0 is not a solution if we replace λ by -λ. The number of variation in sign is 3. Hence all the eigenvalues have negative real parts. Hence A^* is uniformly asymptotically stable.

Proof of Theorem 3.5

The eigenvalues of $J(A^*)$ translated to the origin satisfy $\lambda^3 + \lambda^2 r_4 + \lambda r_5 + r_6 = 0$. If r_4>0,r_5>0 and r_6>, then as in theorem (3.4) all eigenvalues are negative and then A^* is asymptotically stable,

Proof of Theorem 3.6

If $R_o > 1$ *and* $\left(\gamma r + \beta kNT_{\max}\right)^2 > rkN\left(\beta T_{\max}(\alpha - r) + sr\right)$. The eigenvalues are given by

$\lambda^3 + \lambda^2 r_4 + \lambda r_5 + r_6 = 0$. Clearly r_4>0

Now r_5= $\frac{ksN}{\gamma}\left(\beta + \frac{r\gamma}{kNT_{\max}} + \gamma\right) + \left(\beta + \frac{r\gamma}{kNT_{\max}}\right)\gamma - \frac{\gamma r\left(\beta T_{\max}(\alpha - r) + rs\right)}{T_{\max}\left(\gamma r + k\beta NT_{\max}\right)}$

So r_5>0

$\gamma\left(\beta kNT_{\max} + r\gamma\right)^2 - kN\gamma r\left(\beta T_{\max}(\alpha - r) + rs\right) > 0,$

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But $\gamma\left(\beta kNT_{\max}+r\gamma\right)^2+kN\gamma r^2\beta T_{\max}\left(1+s\right)>kN\gamma r\beta T_{\max}\alpha$, hence $r_5>0$

$$kNs\left(\beta+\frac{r\gamma}{kNT_{\max}}\right)-$$

Also $r_6=\left(\frac{\gamma\left(\beta T_{\max}\left(\alpha-r\right)+rs\right)}{\gamma r+k\beta NT_{\max}}\right)\left(\frac{r\gamma}{T_{\max}}+kN\beta\right)$

$$=skN\beta-\beta\gamma\alpha+\beta\gamma r.$$

Now Ro>1 implies that $skN+\gamma r>\gamma\alpha$

Therefore r6>o. Hence A^* is locally asymptotically stable.

4.0. Numerical Solution

4.1 Numerical Solution of infection free equilibrium

4.2 Numerical Solution of infection equilibrium

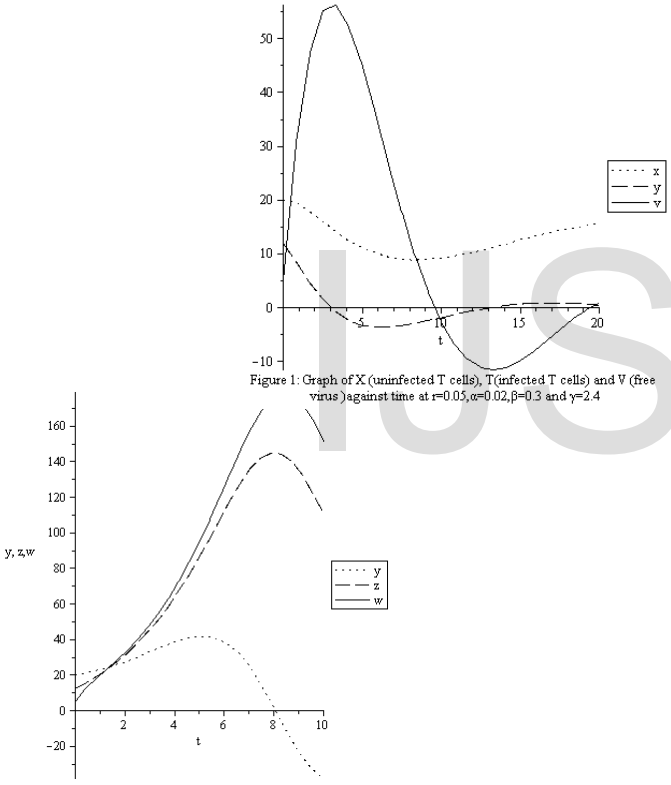

Figure 1: Graph of X (uninfected T cells), T(infected T cells) and V (free virus)against time at r=0.05,α=0.02,β=0.3 and γ=2.4

Figure 2: Graph of y(uninfected T cells), z(infected T cells), w(HIV virus) against time at r=0.05,α=0.02, β=0.3,γ=2.4

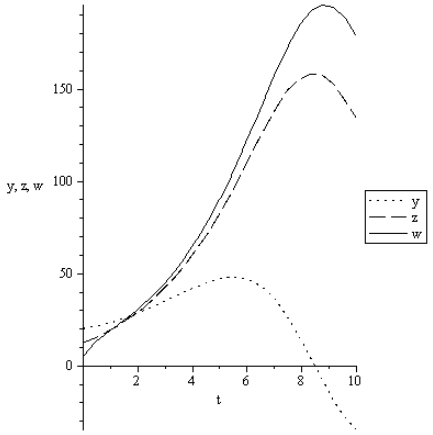

Figure3:Graph of y(uninfected T cells), z(infected T cells),w(HIV virus) against time at r=0.8, α=0.02,β=0.3,γ=2.4

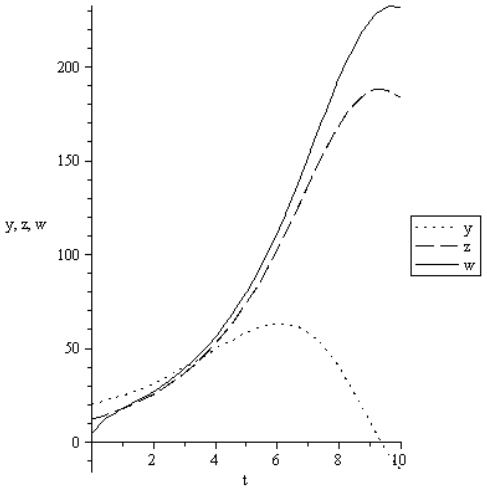

Figure 4: Graph of y(uninfected T cells), z(infected T cells), w(HIV virus) against time at r=0.05,α=0.02, β=0.3,γ=2.4

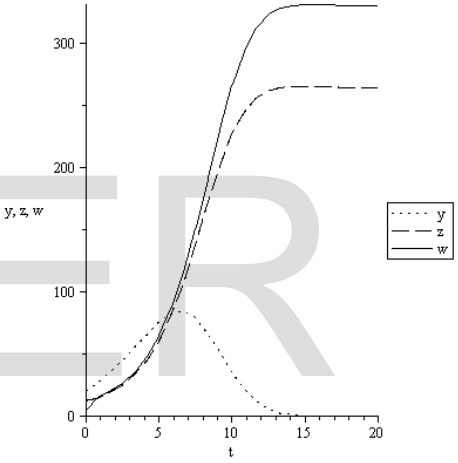

Figure 5:Graph of y(uninfected T cells), z(infected T cells),w(HIV virus) against time at r=0.8, α=0.02, β=0.3,γ=2.4

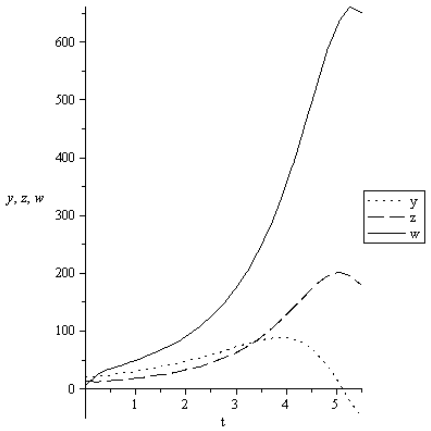

Figure 8: Graph of y(uninfected T cells), z(infected T cells), w(HIV virus) against time at r=3,α=0.1, β=1.1,γ=3.2

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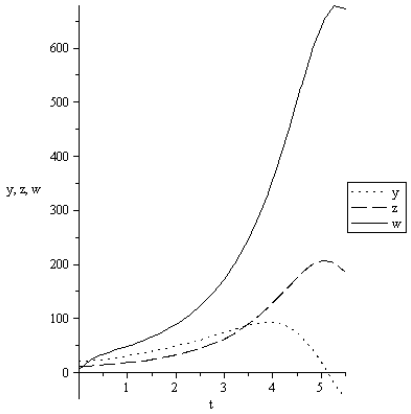

Figure 6: Graph of y(uninfected T cells), z(infected T cells),w(HIV virus) against time at r=0.05,α=0.1, β=1.1,γ=3.2

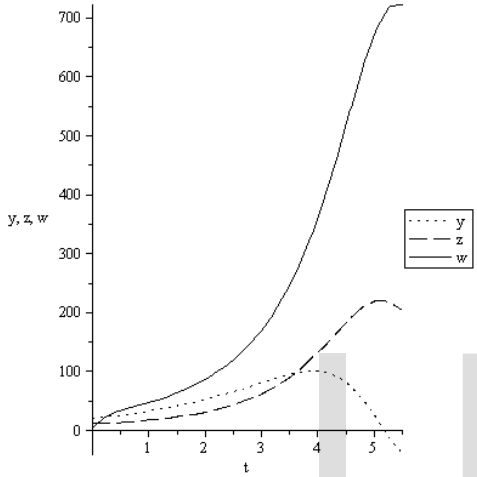

Figure 7:Graph of y(uninfected T cells), z(infected T cells), w(HIV virus) against time at r=0.8,α=0.1, β=1.1,γ=3.2

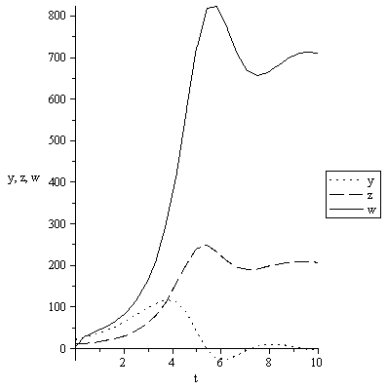

Figure 9: Graph of y(uninfected T cells), z(infected T cells),w(HIV virus) against time at r=10,α=0.1, β=1.1,γ=3.2

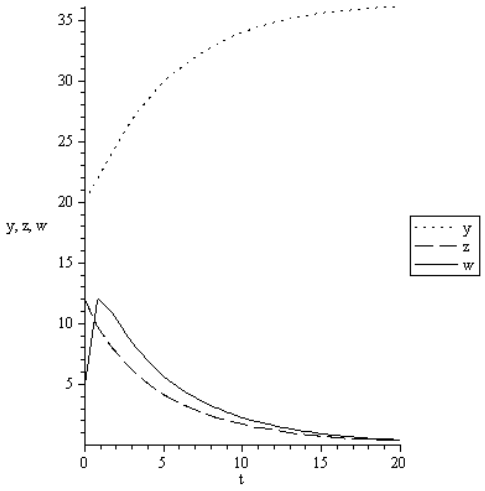

Figure 10: Graph of y(uninfected T cells), z(infected T cells), w(HIV virus) against time at $\beta\alpha T_{\max} + sr = \beta r T_{\max}$ r=0.05,α=0.02,β=0.3,γ=2.4

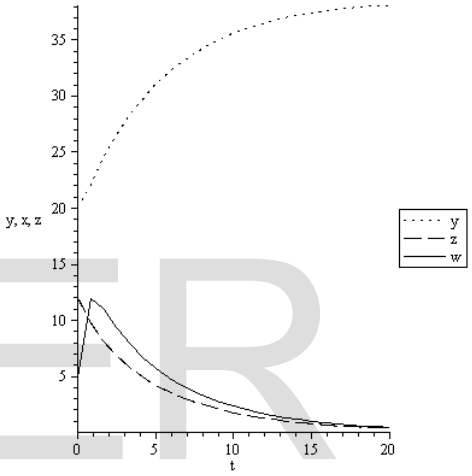

Figure 11:Graph of y(uninfected T cells), z(infected T cells),w(HIV virus) against time at $\beta\alpha T_{\max} + sr = \beta r T_{\max}$ r=0.8, α=0.02,β=0.3,γ=2.4

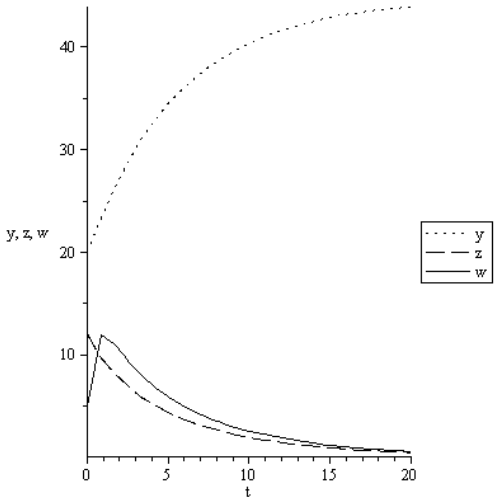

Figure 12: Graph of y(uninfected T cells), z(infected T cells), w(HIV virus) against time at $\beta\alpha T_{\max} + sr = \beta r T_{\max}$,r=3,α=0.02,β=0.3,γ=2.4

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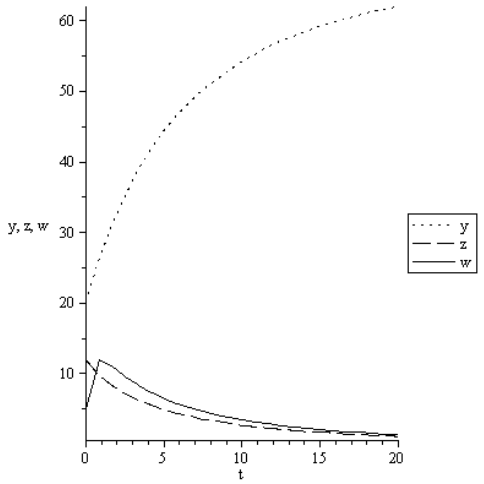

Figure 13:Graph of y(uninfected T cells), z(infected T cells), w(HIV virus) against time at $\beta\alpha T_{\max} + sr = \beta r T_{\max}$,r=10,α=0.02,β=0.3,γ=2.4

5.0 Discussion of Results

The infection free equilibrium of (2.1) is stable if $R_o<1$ and r< α. The infection free equilibrium (2.1) is unstable if $Ro_>1$. The infection equilibrium (2.1) is asymptotically stable if $\beta\alpha T_{\max} + sr = \beta r T_{\max}$. Also if α=r, the zero solution of the infection equilibrium (2.1) is asymptotically stable if $\beta\alpha T_{\max} + sr > \beta r T_{\max}$, $r_1>0,r_2>0,r_3>0$. If $R_o>1$,

$\left(\gamma r + \beta k N T_{\max}\right)^2 > rkN\left(\beta T_{\max}\left(\alpha - r\right) + sr\right)$ then the infection equilibrium (2.1) is locally asymptotically stable.

Figure 1 shows the stability of infection free equilibrium, in figures 2,3 and 4, at α(turnover rate of uninfected T cells) =0.02 , ,β(turnover rate of infected T cells)=0.3 and γ turnover rate of virus particles)=2.4 as r which is the rate at which T cell multiply through mitosis increases the rate at which the virus infect the uninfected T cells increases and the infected T cells increases, The figures shows the instability nature of the infected equilibrium, in figure 5 at a particular time, the infected T cells (z) and virus kept on escalating at a constant rate. In figures 6, 7, 8 and 9 as α , β and γ are increased we observed that the infection rate is increased. The graphs also show the unstability nature of infection equilibrium. While figures 10, 11, 12 1nd 13 show the asymptotic behaviour of infection equilibrium as $\beta\alpha T_{\max} + sr = \beta r T_{\max}$. In these figures 10, 11, 12 and 13 as r increases the earlier the infection T cells (z) and HIV virus (w) got eradicated and uninfected T cells increases.

6.0 Conclusion

In this paper, we modified an existing HIV/AIDS model. We investigated the characteristic equation and discussed the stability of equilibrium points that were not previously considered.

We formulated stability theorems and lemma based on Descartes' rules of signs. These lemma and theorems allow us to discuss the nature of stability of equilibria point when no numerical values were given to the associated parameters.

We solve existing characteristics equation numerically using realistic values for the parameters and we interpreted the graphs that resulted from the numerical solution.

The stability criteria showed that if drugs could be procured to satisfy the criteria, we may be in a position to stem the spread of AIDS.

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