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Mathematical analysis of the global dynamics of a model for HIV infection of CD4 $^+$ T cells

T. O Oluyo, R. O Ayeni and O. O Ayandokun
Department of Pure and Applied Mathematics
***Ladoke Akintola University of Technology, Ogbomoso*.**
e-mail:- ayodeletayous@yahoo.com, +2348034376150

Abstract

We analyze 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 R_0 < 1, the infection will eventually die out, but if R_o > 1, then the infection will lead to full blown AIDS. In either case R_o is important in the eventual growth of the disease.

1.0 Introduction

The Human Immunodeficiency Virus (HIV) mainly targets a host's CD4$^+$T cells. Chronic HIV infection causes gradual depletion of the CD4$^+$ T cell pool, and thus progressively compromises the host's immune response to opportunistic infections, leading to a Acquired 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 1200mm^{-3}. Several mathematicians have proposed models to describe the in 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

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

$$\frac{dT^*}{dt} = kVT - \beta T^* \tag{1.2}$$

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

where

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

α: natural turn over 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 the HIV viruses,

V: free HIV virus particles in the blood,

β: natural turn over rates infected T cells,

γ: natural turn over rates of virus particles,

Kvt: describes the incidence of the HIV infection of health $CD4^+$ T cells where $k>0$ is the infection rate, *N*: virus particles produced by infected $CD4^+$T cell during its life time. Perelson and Nelson [5] replaced equation (1.1) by

$$\frac{dT}{dt} = s - \alpha T + rT\left(1 - \frac{T}{T_{\max}}\right) - kVT \qquad (1.4)$$

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 is 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

$$\left.\begin{aligned} \frac{dT}{dt} &= s - \alpha T + rT\left(1 - \frac{T^*}{T_{\max}}\right) - kVT \\ \frac{dT^*}{dt} &= kKT - \beta T^* \\ \frac{dV}{dt} &= N\beta T^* - \gamma V \end{aligned}\right\} \qquad (2.1)$$

3.0 Method of solution

3.1 Equilibria points

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

$$\begin{aligned} \frac{dX}{dt} &= -(\alpha - r)X + \frac{rsT^*}{(\alpha - r)T_{\max}} - \frac{rXT^*}{T_{\max}} + \frac{kVs}{(\alpha - r)} - kVX \\ \frac{dT^*}{dt} &= KV\,\frac{s}{(\alpha - r)} - kVX\ - \beta T^* \\ \frac{dV}{dt} &= N\beta T^* - \gamma V \end{aligned} \qquad (3.1)$$

In matrix notation (3.1) becomes

$$\begin{pmatrix} \frac{dX}{dt} \\ \frac{dT^*}{dt} \\ \frac{dV}{dt} \end{pmatrix} = \begin{pmatrix} -(\alpha - r) & \frac{rs}{(\alpha - r)T_{\max}} & \frac{ks}{(\alpha - r)} \\ 0 & -\beta & \frac{ks}{(\alpha - r)} \\ 0 & N\beta & -\gamma \end{pmatrix} \begin{pmatrix} X \\ T^* \\ V \end{pmatrix} + \begin{pmatrix} -\frac{rXT^*}{T_{\max}} - kVX \\ -kVX \\ 0 \end{pmatrix} \qquad (3.2)$$

We now find the equilibrium points by setting $\frac{dX}{dt} = \frac{dT^*}{dt} = \frac{dV}{dt} = 0$ and solving the three simultaneous equations. The system of equations yield two equilibria points

A_0= (0, 0, 0) and $A^* = \left(\frac{\text{ksN} - \gamma\alpha + \gamma r}{\text{kN}(\alpha - \text{r})}, \frac{(\text{ksN} - \gamma\alpha + \gamma r)\text{T}_{\max}}{\gamma r + \text{kT}_{\max}\text{N}\beta}, \frac{(\text{ksN} - \gamma\alpha + \gamma r)\text{T}_{\max}\text{N}\beta}{(\gamma r + \text{kT}_{\max}\text{N}\beta)\gamma} \right)$.

A_0 is infection free, while A^* is the infection equilibrium. The basic reproduction parameter R_0 is defined by $R_0 = \frac{Nks}{\gamma(\alpha - r)}$.

3.2 Nature of the equilibrium points

We shall need the following theorems in the analysis of the nature of the equilibriums 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 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, $t \geq 0$. Then the zero solution of 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 equal to the number of variations in sign of the polynomial or less than this by an even number.

We are now in a position to propose the following theorems:

Theorem **3.1**

The zero solution of the infected-free equilibrium is asymptotically stable if $R_0 < 1$ and if $r < \alpha$ .Otherwise the zero solution is unstable.

Theorem **3.2**

The zero solution of the infected-free equilibrium is unstable if $R_0 \succ 1$

Theorem **3.3**

If $\beta\alpha T_{\max} + sr = \beta r T_{\max}$, then the equilibrium point A^* is uniformly asymptotically stable.

Theorem **3.4**

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

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

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

Let $\alpha = r$ .If $\beta\alpha T_{\max} + sr > \beta r T_{\max}$ and if $r_1 > 0$, $r_2 > 0$, $r_3 > 0$, then the equilibrium point A is uniformly asymptotically stable.*

Theorem 3.5

Let $r_4 > 0$, $r_5 > 0$ and $r_6 > 0$, *then the infection equilibrium A^* is asymptotically stable.*

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

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

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

***Theorem* 3.6**

If $R_o > 1$ and $(\gamma r + \beta kNT_{\max})^2 > rkN(\beta T_{\max}(\alpha - r) + sr)$ *then A* is locally asymp-*

ptotically stable.

We now prove the theorems.

***Proof of Theorem* 3.1**

By (2.1), the Jacobian matrix at A_0,

$$J(A_0) = \begin{pmatrix} -(\alpha - r) & \frac{rs}{(\alpha - r)T_{\max}} & \frac{ks}{(\alpha - r)} \\ 0 & -\beta & \frac{ks}{(\alpha - r)} \\ 0 & N\beta & -\gamma \end{pmatrix}$$

So the eigenvalues are given by $(-(\alpha - r) - \lambda)\left(\lambda^2 + (\beta + \gamma)\lambda + \beta\gamma - \frac{ksN\beta}{(\alpha - r)}\right) = 0$, i.e

$$(-(\alpha - r) - \lambda)\left(\lambda^2 + \lambda(\beta + \gamma) - \beta\gamma(R_0 - 1)\right) = 0$$

$$\lambda_1 = -(\alpha - r) \text{ and } \lambda^2 + \lambda(\beta + \gamma) - \beta\gamma(R_0 - 1) = 0$$

Now $\beta > 0$, $\gamma > 0$,r >0. So if $R_0 < 1$, the number of variations in sign is zero. Hence all eigenvalues are negative. Therefore A_0 is uniformly asymptotically.

***Proof of Theorem* 3.2**

If $R_0 > 1$, the from the proof of theorem 1, $\left(\lambda^2 + \lambda(\beta + \gamma) - \beta\gamma(R_0 - 1)\right) > 0$, $\beta > 0$, $\gamma > 0$,r >0 implies that the number of variations in sign is 1. So J (A_0) has a positive root. Hence A_0 is unstable.

***Proof of Theorem* 3.3** ■

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

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

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

***Proof of Theorem* 3.4:**

If $\alpha = r$. $r_i > 0$,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 eigenvalue is obtained by satisfy $\lambda^3 + \lambda^2 r_1 + \lambda r_2 + r_3 = 0$. The number of variations in sign 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 $r_6 > 0$, then as in theorem 3.4 all the eigenvalues are negative and then A^* is asymptotically stable.

***Proof of Theorem* 3.6**

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

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

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

So $r_5 > 0$ if $\gamma(\beta kNT_{\max} + r\gamma)^2 - kN\gamma r(\beta T_{\max}(\alpha - r) + rs) > 0$,

But $(\beta kNT_{\max} + r\gamma)^2 > kN\gamma r(\beta T_{\max}(\alpha - r) + rs) > 0$. Hence $r_5 > 0$.

Also $r_6 = kNs\left(\beta + \dfrac{r\gamma}{kNT_{\max}}\right) - \dfrac{\gamma(\beta T_{\max}(\alpha - r) + rs)}{\gamma r + k\beta NT_{\max}}\left(\dfrac{\gamma r}{T_{\max}} + kN\beta\right) = s\beta kN - \beta\gamma(\alpha - r)$. Now $R_0 > 1$ implies $skN > \gamma(\alpha - r)$. Therefore $r_3 > 0$. Hence A^* is locally asymptotically stable.

4.0 Numerical solution

4.1 Numerical solution of infection free equilibrium

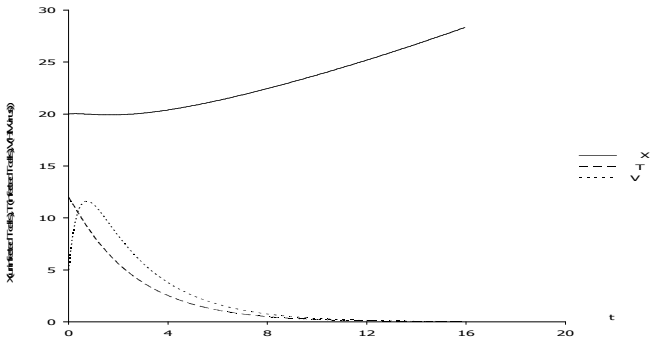

Figure 1: Graph of *X* (uninfected T cells), T (infected T cells) and V (HIV virus) against time at *r* =0.05, α = 0.02, β = 0.3 and γ = 2.4

4.2 Numerical solution of infection equilibrium

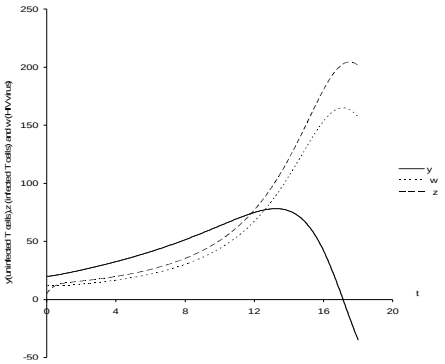

Figure 2: Graph of *y* (uninfected T cells), *z* (infected T cells) and w (HIV virus) against time at $r = 0.05$, $\alpha = 0.02$, $\beta = 0.3$ and $\gamma = 2.4$

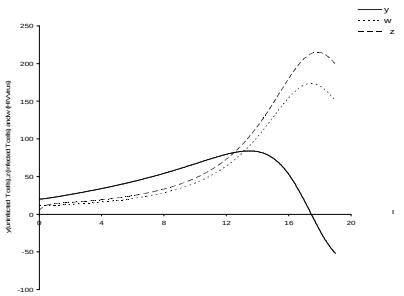

Figure 3: Graph of *y* (uninfected T cells), *z* (infected T cells) and *w* (HIV virus) against time at $r = 0.08$, $\alpha = 0.02$, $\beta = 0.3$ and $\gamma = 2.4$

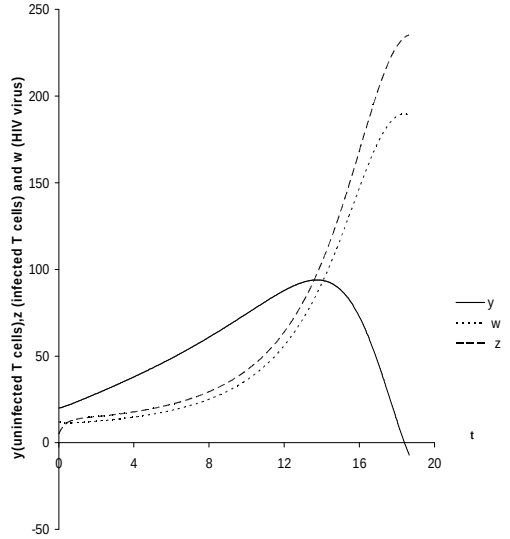

Figure 4: Graph of *y* (uninfected T cells), *z* (infected T cells) and w (HIV virus) against time at $r = 3$, $\alpha = 0.02$, $\beta = 0.3$ and $\gamma = 2.4$

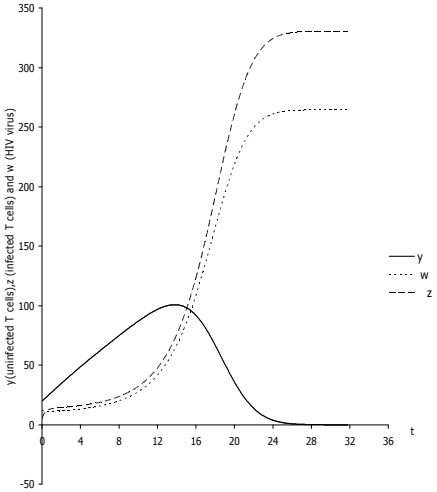

Figure 5: Graph of *y* (uninfected T cells), *z* (infected T cells) and w (HIV virus) against time at $r = 10$, $\alpha = 0.02$, $\beta = 0.3$ and $\gamma = 2.4$

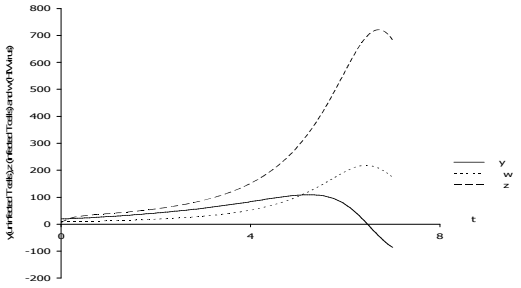

Figure 6: Graph of *y* (uninfected T cells), *z* (infected T cells) and w (HIV virus) against time at $r = 0.05$, $\alpha = 0.1$, $\beta = 1.1$ and $\gamma = 3.2$

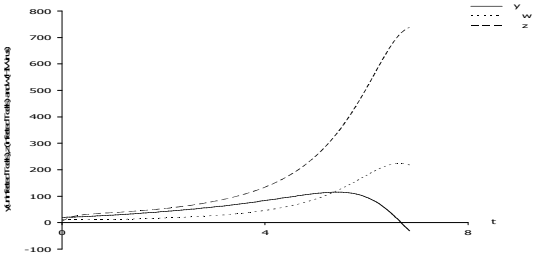

Figure 7: Graph of *y* (uninfected T cells), *z* (infected T cells) and w (HIV virus) against time at $r = 0.8$, $\alpha = 0.1$, $\beta = 1.1$ and $\gamma = 3.2$

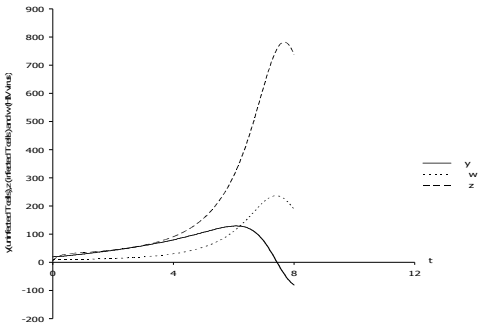

Figure 8: Graph of *y* (uninfected T cells), *z* (infected T cells) and w (HIV virus) against time at r =3, α = 0.1, β = 1.1 and γ = 3.2

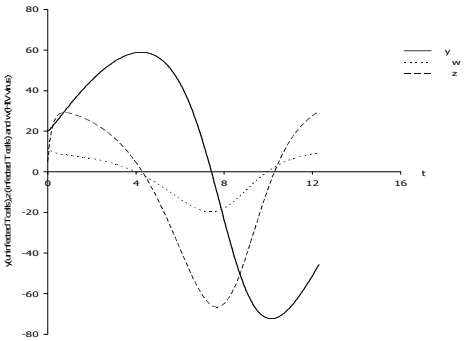

Figure 9: Graph of *y* (uninfected T cells), *z* (infected T cells) and w (HIV virus) against time at r =10, α = 0.1, β = 1.1 and γ = 3.2

4.3 Numerical solution for infection equilibrium at $\beta\alpha T_{\max} + sr = \beta r T_{\max}$

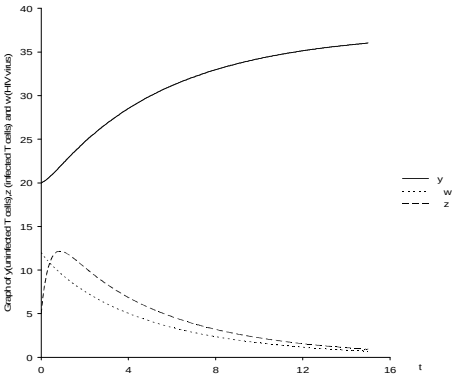

Figure 10: Graph of *y* (uninfected T cells), *z* (infected T cells) and w (HIV virus) against time at $\beta\alpha T_{\max} + sr = \beta r T_{\max}$ r =0.05, α = 0.02, β = 0.3 and γ =2.4

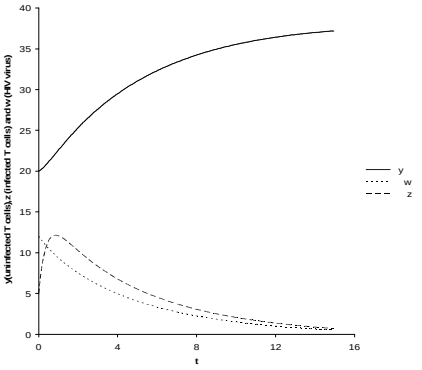

Figure 11: Graph of *y* (uninfected T cells), *z* (infected T cells) and w (HIV virus) against time at $\beta\alpha T_{\max} + sr = \beta r T_{\max}$ r = 0.8, α = 0.02, β = 0.3 and γ =2.4

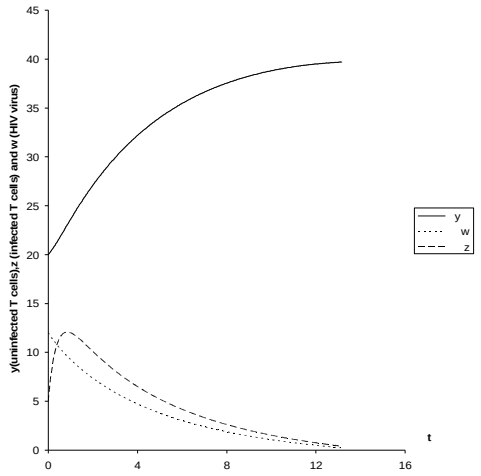

Figure 12: Graph of *y* (uninfected T cells), *z* (infected T cells) and w (HIV virus) against time at $\beta\alpha T_{\max} + sr = \beta r T_{\max}$ r = 3, α = 0.02, β = 0.3 and γ =2.4

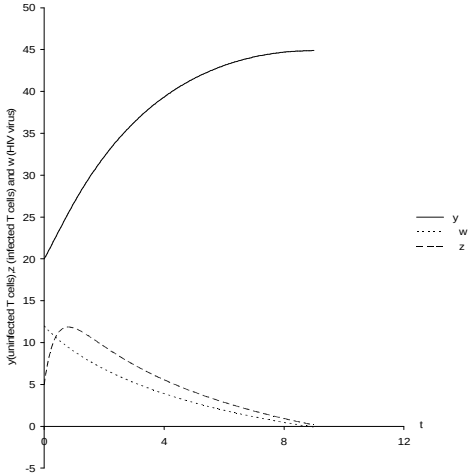

Figure 13: Graph of *y* (uninfected T cells), *z* (infected T cells) and w (HIV virus) against time at $\beta\alpha T_{\max} + sr = \beta r T_{\max}$ r = 10, α = 0.02, β = 0.3 and γ =2.4

5.0 Discussion of result

The infection-free equilibrium of (2.1) is stable if $R_0 < 1$ and r < α.The infection free equilibrium of (2.1) is unstable if $R_0 > 1$.The infection equilibrium (2.1) is asymptotically stable if $\beta\alpha T_{\max} + sr = \beta r T_{\max}$. Also if $\alpha = r$, 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, $(\gamma r + \beta k N T_{\max})^2 > rkN(\beta T_{\max}(\alpha - r) + sr)$ then the infection equilibrium (2.1) is locally and asymptotically stable.

Figure 1 shows the stability of the infection free equilibrium, in figures 2, 3, and 4, at α (turn over rate of uninfected T cells) =0.02, β(turn over rate of infected T cells) = 0.3 and γ (turn over rate of virus particles) =2.4, as r which is the rate at which T cells multiply through mitosis increases the rate at which the virus infects the uninfected T cells increases and the infection T cells increases. The figures show the unstable nature of the infection equilibrium, in figure 5, at a particular time the infected T cells (z) and virus (w) keep on escalating at a constant rate. In figures 6, 7, 8 and 9 as α, βand γ are increased, we observed that the infection rate is likewise increased. The graphs also show the unstable nature of infection equilibrium. While figures 10, 11, 12 and 13 show the asymptotic behavior of the infection equilibrium as $\beta\alpha T_{\max} + sr = \beta r T_{\max}$. In these figures 10-13, as r increases, the earlier the infection T cells (z) and HIV virus (*w*) got eradicated and the 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 lemmas based on Descartes rules of signs. These lemma and theorems allowed us to discuss the nature of stability of the equilibrium points when no numerical values are given to the associated parameters.

We solved existing characteristics equations 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.

Reference

[1] Bonhoeffer, Sebastin., May,Robert M., Shaw,George M. and Nowak,Martins A. (1997): Virus dynamics and drug therapy. Proc.Nati. Acad. Sci. USA Vol 94 pp 6971-6976.

[2] Derrick W.R and Grossman S (1976): Elementary Differential Equations, Addison Wesley, Reading.

[3] Labarre, A.E. Jr. (1961): Elementary Mathematical Analysis. Addison- Wesley Publishing Company, Inc Reading. pp 297-298.

[4] Leenheer P .De and Smith L.H., (2003): Virus dynamics: a global analysis, SIAM J. Appl.Math.63, 1313.

[5] Perelson A.S., Kirschner D.E and Boer R.de (1993): Dynamics of HIV infection of $CD4^+$ T cells.Math.Biosci 114, 81.

[6] Rutherford G and Woo J (1998): Contact tracing and the control of Human immunodeficiency Virus.J.Amer.Med Asso. (259) 3609-3610.

[7] Wang, Liancheng and Li, Michael Y. (2006): Mathematical analysis of the global dynamics of a model for HIV infection of $CD4^+$ T cells, Math. Biosci 200, 44-57.