

GLOBAL STABILITY AND PERIODIC SOLUTION OF A VIRAL DYNAMIC
MODEL

Erhan COŞKUN*, Mehmet MERDAN**

*Karadeniz Teknik Üniversitesi, Fen-Edebiyat Fakültesi, Matematik Bölümü,
61000-Trabzon, Türkiye

**Karadeniz Teknik Üniversitesi, Gümüşhane Mühendislik Fakültesi, İnşaat
Mühendisliği Bölümü, 29000-Gümüşhane, Türkiye
e-mail: erhan@ktu.edu.tr, merdan@ktu.edu.tr

Received: 16 August 2007, Accepted: 18 October 2007

Abstract: In this paper, we consider the classical viral dynamic mathematical model. Global dynamics of the model is rigorously established. We prove that, if the basic reproduction $R_0 \leq 1$ number, the HIV infection is cleared from the T-cell population; if $R_0 > 1$, the HIV infection persists. For an open set of parameter values, the chronic-infection equilibrium E_1^* can be unstable and periodic solutions may exist. We establish parameter regions for which E_1^* is globally stable.

Key words: Global stability, HIV infection; CD4+ T cells; Periodic solution

Mathematics Subject Classifications (2000): 65L10, 34B05

BİR VİRAL DİNAMİK MODELİN GLOBAL KARARLILIĞI VE PERİYODİK
ÇÖZÜMÜ

Özet: Bu makalede klasik viral dinamik modeli ele aldık. Modelin global dinamikleri oluşturuldu. Eğer temel üretim sayısı $R_0 \leq 1$ olur ise HIV enfeksiyonu T hücre nüfusundan çıkartılır, eğer $R_0 > 1$ olursa HIV enfeksiyonu çıkartılamaz. Parametre değerlerinin açık bir kümesi için kronik enfeksiyon dengesi E_1^* kararsızdır ve periyodik çözüm oluşabilir. E_1^* in global kararlı olduğu parametre bölgeleri oluşturuldu.

Anahtar kelimeler: Global Kararlılık, HIV enfeksiyon, CD4+ T hücreler, Periyodik çözüm

1. INTRODUCTION

There has been much interest recently dimensional models of viral population dynamics in host cells (CULSHAW & RUAN 2000, DE BOER & PERELSON 1995; HO ET AL 1995; KIRSCHNER 1996; MCLEAN 1994; NELSON & PERELSON 2002; NELSON ET AL 2004, NOWAK & MAY 2000), with most attention focussed on HIV (PERELSON & NELSON 2000). The goal of such modelling is not only to understand the nature of various diseases and their time courses, but also to develop efficient regimes for drug treatments, including the highly successful combination therapies (CALLAWAY & PERELSON 2002; PERELSON ET AL 1997; PHILLIPS ET AL

1997; WEIN ET AL 1997, TAN & WU 1998) used a Monte Carlo simulation to estimate the probability of clearing an initial inoculum of virus. Using a Monte Carlo model of inhost HIV infection, some scientists investigated the variability in T-cell count and viral load (HEFFERNAN & WAHL 2005). Stochastic models have also proven to be useful, especially in determining probabilities of detection of the virus (LE CORFEC ET AL 1999, TAN & WU 1998; KAMINA ET AL 2001; TUCKWELL 2004). Computed solutions for the four-component model were similar and have been described in (TUCKWELL & WAN 2000).

The virus causing AIDS (Acquired Immune Deficiency Syndrome) was first discovered in 1983 by Dr. Luc Montaigner, and then was kept being followed by the scientists at Paris Pasteur Institute. These scientists found this virus in the lymph nodes of the patient. Almost synchronously with these investigations, some other scientists met with this virus as well. And it was called as HIV (Human Immuno Deficiency Virus) by International Virus Classification Committee.

It is impossible for a HIV virus to keep living like a normal cell so as not to have any organ and enzyme. They have to penetrate in to a living cell in order to maintain vital activities such as propagation. Therefore, HIV virus invades CD4+T-cells existing in blood. This virus melts the membrane of the cell when it clings to the cell. In the beginning, after words, it pours its own nucleic acid (RNA and DNA) from this puncture. Penetrated nucleic acid into cell of virus immediately seizes the power and starts to use the cell for its own account. Firstly it has the copies of its nucleic acid and directly then its protein covers synthesized. And, combining these, it gets to reveal hundreds of viruses. After a certain time, the viruses inside the cell come out by blowing up the cell and attack new ones. Thus, CD4+T cells are damaged extensively. As long as these cells are damaged, the immunity system of the person weakens and he is caught to opportunist infections more quickly. The amount of HIV virus in man's blood can be determined by doing mischallenous tests. And one of these is determination of viral load. Viral load is the amount of HIV virus in the blood of man. The person having high amount of viral load evolves AIDS more swiftly than the person who has low viral load. CD4+T cells are also named as leukocytes or T helper cells. These with other cells in the human immunity system fight against diseases. HIV uses cells in order to propagate. The number of CD4+T cells of a healthy person is 800-1200/mm³

2. VIRAL DYNAMICAL MODEL

On the behaviour of solution of viral dynamic model is examined at the study (TUCKWELL HC & WAN FYM 2004). The components of the basic three-component model are uninfected CD4+ T-cells, infected such cells and free virus particles are denoted respectively by $x(t)$, $y(t)$ and $v(t)$. These quantities satisfy

$$\begin{cases} \frac{dx}{dt} = s - \mu x - \beta xv \\ \frac{dy}{dt} = \beta xv - \alpha y \\ \frac{dv}{dt} = cy - \gamma v \end{cases} \quad (1)$$

Here

s is the (assumed constant) rate of production of CD4+ T-cells,

μ is their per capita death rate,

βxy is the rate of infection of CD4+ T-cells by virus,

α is the per capita rate of disappearance of infected cells,

c is the rate of production of virions by infected cells and

γ is the death rate of virus particles

Typical parameter values are, with time in days and particle (cell) densities in numbers per cubic millimeter:

$$s_0 = 0.272, \mu_0 = 0.00136, \beta_0 = 0.00027, \alpha_0 = 0.33, c_0 = 50, \gamma_0 = 2$$

This was done with the standard parameter values given above and initial values $x(0) = 200$, $y(0) = 0$ and $v(0) = 1$ for the three-component model.

In this case at the study (TUCKWELL HC & WAN FYM 2004) the simple mathematical model of population dynamics of HIV-1 virus in the beginning was deal with. Although this kind of differential equation systems has numerical solutions, there were few theoretical results duo to nonlinearities. That's why some theoretical results were given. Furthermore, quantitative analysis of equilibrium points was accomplished.

2.1 EQUILIBRIA, STABILITY AND PERIODIC SOLUTION OF VIRAL INFECTION

The possible non-negative equilibria of system (1) are $E_0^*(x_0, 0, 0)$, $E_1^*(x_1, y_1, v_1)$, where

$$\begin{aligned} x_0 &= \frac{s}{\mu}, \\ x_1 &= \frac{\alpha\gamma}{\beta c}, \\ y_1 &= \frac{s}{\alpha} - \frac{\mu\gamma}{\beta c}, \\ v_1 &= \frac{sc}{\alpha\gamma} - \frac{\mu}{\beta}. \end{aligned}$$

Now, we will begin the analysis of the stability of the equilibria of system (1). Let $E^*(x^1, y^1, v^1)$ be any arbitrary equilibrium. The Jacobian matrix of (1) at E^*

$$J(E^*(x^1, y^1, v^1)) = \begin{bmatrix} -\mu - \beta v^1 & 0 & -\beta x^1 \\ \beta v^1 & -\alpha & \beta x^1 \\ 0 & c & -\gamma \end{bmatrix}. \quad (2)$$

Then the characteristic equation about E^* is given by

$$\left| J(E^*(x^1, y^1, v^1)) - \lambda I \right| = \begin{vmatrix} -\mu - \beta v^1 - \lambda & 0 & -\beta x^1 \\ \beta v^1 & -\alpha - \lambda & \beta x^1 \\ 0 & c & -\gamma - \lambda \end{vmatrix} \quad (3)$$

For equilibrium $E_0^*(x_0, 0, 0)$, (3) reduces to

$$(\mu + \lambda) [\lambda^2 + (\alpha + \gamma)\lambda + \alpha\gamma - c\beta x_0] = 0 \quad (4)$$

Hence, $E_0^*(x_0, 0, 0)$ is asymptotically stable for $x_0 < \alpha\gamma / c\beta$, is a saddle with $\dim W^s(E_0^*) = 2$, $\dim W^u(E_0^*) = 1$, for $x_0 > \alpha\gamma / c\beta$.

Since x_0 and x_1 satisfy

$$\begin{aligned} s - \mu x_0 &= 0, \\ s - \mu x_1 - \beta x_1 v_1 &= 0, \\ s - \mu x_1 &= x_1 \left(\frac{\beta s c}{\alpha \gamma} - \mu \right), \\ x_1 > \frac{s}{\mu}, s - \mu x_1 > 0 &\Rightarrow x_1 > x_0, \\ x_1 < \frac{s}{\mu}, s - \mu x_1 < 0 &\Rightarrow x_1 < x_0, \end{aligned}$$

Hence, if $x_1 > \frac{s}{\mu}$, then $x_1 > x_0 = \frac{s}{\mu}$, and $E_0^*(x_0, 0, 0)$ is unstable, at the same time,

the positive equilibrium $E_1^*(x^1, y^1, v^1)$ exists. Further, if $x_1 < \frac{s}{\mu}$, then $x_1 < x_0 = \frac{s}{\mu}$,

and

$E_0^*(x_0, 0, 0)$ is locally asymptotically stable, meanwhile, the positive equilibrium $E_1^*(x^1, y^1, v^1)$. $y^1 < 0, v^1 < 0$ is not feasible. Let

$$R_0 = \frac{s}{\mu},$$

denote the basic reproduction number. When $R_0 > 1$, the uninfected steady-state E_0^* is stable and the infected steady-state E_1^* does not exist (unphysical). When $R_0 < 1$, E_0^* becomes unstable and E_1^* exists.

For equilibrium $E_1^*(x^1, y^1, v^1)$, (1) reduces to

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0, \quad (5)$$

where

$$a_1 = \alpha + \gamma + \frac{\beta sc}{\gamma\alpha} > 0,$$

$$a_2 = (\alpha + \gamma) \frac{\beta sc}{\gamma\alpha} > 0,$$

$$a_3 = \beta sc - 3\mu\gamma\alpha > 0,$$

We also have

$$a_1a_2 - a_3 = (\alpha + \gamma)^2 \left(\frac{\beta sc}{\gamma\alpha} \right) + (\alpha + \gamma) \left(\frac{\beta sc}{\gamma\alpha} \right)^2 - \beta sc + 3\mu\gamma\alpha > 0.$$

By Routh–Hurwitz criterion, we have the following Theorem 2.1.

Theorem 2.1. Suppose that,

$$(i) R_0 > 1$$

$$(ii) a_1a_2 - a_3 = (\alpha + \gamma)^2 \left(\frac{\beta sc}{\gamma\alpha} \right) + (\alpha + \gamma) \left(\frac{\beta sc}{\gamma\alpha} \right)^2 - \beta sc + 3\mu\gamma\alpha > 0, .$$

Then the positive equilibrium $E_1^*(x^1, y^1, v^1)$ is asymptotically stable.

For the parameter values

$s_0 = 0.272$, $\mu_0 = 0.00136$, $\beta_0 = 0.00027$, $\alpha_0 = 0.33$, $c_0 = 50$, $\gamma_0 = 2$ this parameter existence in the literature, the conditions of Theorem 2.1 are satisfied. The infected steady state $E_1^*(122220, 0.6228, 15.5690)$ is asymptotically stable. Numerical simulations show that trajectories of system (1) approach to the steady state.

Theorem 2.2. There is $M > 0$ such that, for any positive solution $(x(t), y(t), v(t))$ of system (1),

$$y(t) < M, v(t) < M, \text{ for all large } t.$$

Proof. Set

$K_1(t) = x(t) + y(t)$. Calculating the derivative of $K_1(t)$ along the solutions of system (1), we find

$$\begin{aligned} K_1'(t) &= s - \mu x(t) - \alpha y(t) \\ &\leq -\mu K_1(t) + s \\ K_1'(t) + \mu K_1(t) &\leq s \end{aligned}$$

Furthermore,

$$K_1(t) \leq \frac{s}{\mu} + \left(K_1(0) - \frac{s}{\mu} \right) e^{-\mu t}$$

Hence, we obtain the boundedness of $K_1(t)$, that is, there exist $t_2 > 0$ ve $M_1 > 0$, such that

$K_1(t) < M_1$, for $t > t_2$. Then $I(t)$ has an ultimately above bound. It follows from the third equation of Eq. (1) that $y(t)$ has an ultimately above bound, say, their maximum is a M . Then the assertion of Theorem 2.2 now follows and the proof is complete. This shows that system (4) is dissipative. \square

Define

$$\Omega = \left\{ (x(t), y(t), v(t)) : 0 \leq x(t) \leq x_0, 0 \leq y(t), v(t) \leq M \right\}.$$

It is easy to see that, for system (1),

$$x' \geq s - \mu x,$$

which implies that

$$\liminf_{t \rightarrow \infty} x(t) \geq \frac{\alpha\gamma}{\beta c} \equiv m$$

Theorem 2.3. If $R_0 > 1$, then $E_0^*(x_0, 0, 0)$ is globally asymptotically stable.

Proof. From the last two equations of Eq. (1), for $t > t_1$, we have

$$\begin{aligned} y' &= \beta x_0 v - \alpha y \\ v' &= cy - \gamma v \end{aligned} \tag{6}$$

Since $R_0 > 1$, we have $s > \mu$

$$x(t) = \frac{s}{\mu} + \left(x(0) - \frac{s}{\mu} \right) e^{-\mu t}$$

This clearly shows that $\lim_{t \rightarrow \infty} x(t) = x_0$. This proves the theorem.

Theorem 2.4. If $R_0 > 1$, then system (2) is permanent.

Proof. If $R_0 > 1$, we have $x_0 > \frac{\alpha\gamma}{\beta c}$. We begin by verifying weak persistence of (1). If it is not weakly persistence, it follows from the proof of Theorem 2.1 that there is a positive orbit $(x(t), y(t), v(t))$ of (1) such that

$$\lim_{t \rightarrow \infty} x(t) = x_0, \quad \lim_{t \rightarrow \infty} y(t) = 0, \quad \lim_{t \rightarrow \infty} v(t) = 0.$$

Then choose $t_0 > 0$ large enough such that if $t \geq t_0$, we have

$$\begin{cases} y'(t) \geq \beta \hat{x}v(t) - \alpha y(t), \\ v'(t) = cy(t) - \gamma v(t). \end{cases}$$

Let us consider the matrix A_ε

$$A_\varepsilon = \begin{pmatrix} -\alpha & \beta\hat{x} \\ c & -\gamma \end{pmatrix} \quad (8)$$

Since A_ε admits positive off-diagonal element, the Perron–Frobenius theorem implies that there is positive eigenvector $v = (v_1, v_2)$ for the maximum eigenvalue α' of A_ε .

Let us consider

$$\begin{cases} z_1' = \beta\hat{x}z_1(t) - \alpha z_1(t), \\ z_2' = cz_1(t) - \gamma z_2(t). \end{cases} \quad (9)$$

Let $z(t) = (z_1(t), z_2(t))$ be a solution of (9) through (lv_1, lv_2) at $t = t_0$, where $l > 0$ satisfies $lv_1 < y(t_0)$, $lv_2 < v(t_0)$. Since the semi flow of (9) is monotone and $A_\varepsilon v > 0$, it follows that $z_i(t)$ is strictly increasing and $z_i(t) \rightarrow +\infty$, as $t \rightarrow \infty$, contradicting the eventual boundedness of positive solution of (2). Thus, no positive orbit of (2) tends to $(x_0, 0, 0)$, at t tends to infinity. This shows that (2) is weakly persistent. Then an application of the techniques of paper (PERELSON AS & NEUMANN A & MARKOWITZ M & LEONARD J & HO D 1996) concludes the permanence of (2). The proof of Theorem 2.4 is completed.

Theorem 2.5. Assume D is convex and bounded. Suppose system

$$X' = F(X), \quad X \in D \quad (10)$$

is competitive and permanent and has the property of stability of periodic orbit. If $\overline{X_0}$ is the only equilibrium point in $\text{int}D$ and if it is locally asymptotically stable, then it is globally asymptotically stable in $\text{int}D$.

By looking at its Jacobian matrix and choosing the matrix H as

$$H = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & -1 \end{pmatrix}$$

we see that system (2) is competitive in Ω , with respect to the partial order defined by the

$$\text{orthant } K_1 = \{(x, y, v) \in R^3 : x \leq 0, y \geq 0, v \geq 0\}$$

Theorem 2.6. If $R_0 > 1$, then the positive equilibrium E^* of (1) is globally asymptotically stable.

Proof. The proof of this theorem is the same as those of Theorem 2.1 and 4.2 in [10]. Since system (1) is competitive, permanent and E^* is locally asymptotically stable if $R_0 > 1$. Furthermore, in accordance with Theorem 2.5 (where we can choose $D = \Omega$), Theorem 2.6 would be established if we show that system (1) has the property of stability of periodic orbits. In the following, we prove it.

Proposition 2.1 System (1) has the property of stability of periodic orbits. System (2.1) has the property of stability of periodic orbits.

Proof. Let $P(t) = (x(t), y(t), v(t))$ be a periodic solution whose orbit Γ is contained in $\text{int}\Omega$. In accordance with the criterion given by (MULDOWNEY JS 1990), for the asymptotic orbital stability of a periodic orbit of a general autonomous system, it is sufficient to prove that the linear nonautonomous system

$$\dot{W}(t) = \left(DF^{[2]}(P(t)) \right) W(t) \quad (11)$$

is asymptotically stable, where $DF^{[2]}$ is the second additive compound matrix of the Jacobian

DF (see Appendix A).

The Jacobian of Eq. (1) is given by

$$DF = \begin{pmatrix} -\mu - \beta v & 0 & -\beta x \\ \beta v & -\alpha & \beta x \\ 0 & c & -\gamma \end{pmatrix}$$

For the solution $P(t)$, Eq. (11) becomes

$$\begin{cases} \dot{W}_1 = -(\mu + \alpha + \beta v)W_1 + \beta x W_2 + \beta x W_3, \\ \dot{W}_2 = cW_1 - (\mu + \gamma + \beta v)W_2, \\ \dot{W}_3 = \beta v W_2 - (\alpha + \gamma)W_3, \end{cases}$$

(12)

To prove that Eq. (12) is asymptotically stable, we will use the following Lyapunov function,

$$U(W_1, W_2, W_3, x, y, v) = \sup \left\{ |W_1|, \frac{y}{v} (|W_2| + |W_3|) \right\}. \quad (13)$$

From Theorem 2.4, we obtain that the orbit of $P(t)$ remains at a positive distance from the

boundary of Ω . Therefore, there exists a constant $c_1 > 0$, such that

$$U(W_1, W_2, W_3, x, y, v) \geq c_1 \sup \{ |W_1|, W_2(t), W_3(t) \} \quad (14)$$

For all (W_1, W_2, W_3) and $(x, y, v) \in P(t)$, we have the following inequalities:

$$\begin{cases} D_+ |W_1| \leq -(\mu + \alpha + \beta v)|W_1| + \beta x (|W_2| + |W_3|), \\ D_+ |W_2| \leq c|W_1| - (\mu + \gamma + \beta v)|W_2|, \\ D_+ |W_3| \leq \beta v |W_2| - (\alpha + \gamma)|W_3|. \end{cases} \quad (15)$$

From (15), we get

$$\begin{aligned} D_+ \frac{y}{v} (|W_2| + |W_3|) &= \left(\frac{y'}{v} - \frac{yv'}{v^2} \right) (|W_2| + |W_3|) + \frac{y}{v} D_+ (|W_2| + |W_3|) \\ &\leq \left(\frac{y'}{y} - \frac{v'}{v} \right) \frac{y}{v} (|W_2| + |W_3|) + c \frac{y}{v} |W_1| - (\gamma + \mu) \frac{y}{v} |W_2| \\ &\quad - (\alpha + \gamma) \frac{y}{v} |W_3|. \end{aligned}$$

Thus, we can obtain

$$D_+ U(t) \leq \sup \{g_1(t), g_2(t)\} U(t), \quad (16)$$

where

$$g_1(t) = -(\mu + \beta v + \alpha) + \frac{\beta xv}{y},$$

$$g_2(t) = \frac{cy}{v} + \frac{y'}{y} - \frac{v'}{v} - G_1,$$

$$G_1 = \min \{ \mu + \gamma, \alpha + \gamma \}.$$

From the second equation of system (1), we have

$$\begin{aligned} g_1(t) &= -(\mu + \beta v + \alpha) + \frac{\beta xv}{y} \\ &\leq -(\mu + \beta v + \alpha) + \frac{\beta xv}{y} = -\mu - \beta v + \frac{y'}{y} \end{aligned}$$

If $\mu > \alpha$, then $G_1 = \mu + \gamma$, then we get

$$g_2(t) = \frac{y'}{y} - \mu.$$

Hence,

$$\sup \{g_1(t), g_2(t)\} \leq g_2(t) = \frac{y'}{y} - \mu \quad (17)$$

If $\mu < \alpha$, then $G_1 = \alpha + \gamma$, then we get

$$g_2(t) = \frac{y'}{y} - \alpha. \quad (18)$$

Hence,

$$\sup \{g_1(t), g_2(t)\} \leq g_2(t) = \frac{y'}{y} - \alpha$$

Let $m = \min \{ \alpha, \mu \}$. Then from (17) and (18), we have

$$\sup \{g_1(t), g_2(t)\} \leq \frac{y'}{y} - m.$$

Therefore, from (16) and Gronwall's inequality, we obtain

$$U(t) \leq U(0)y(t)e^{-mt} \leq U(0)Me^{-mt}.$$

Thus $\lim_{t \rightarrow \infty} U(t) = 0$. By (14) it turns out that

$$(W_1, W_2, W_3) \rightarrow 0, \text{ as } t \rightarrow \infty$$

This implies that the linear system Eq. (12) is asymptotically stable and therefore the periodic solution is asymptotically orbitally stable. This proves Proposition 2.1. \square

APPENDIX A

In this appendix, we shall give the definition of an additive compound matrix. A survey of properties of additive compound matrices together with their connections to differential equations may be found in (Lİ Y & MULDOWNNEY JS 1995), (MULDOWNNEY JS 1990).

We start by recalling the definition of a k th exterior power or multiplicative compound of a matrix.

Definition A.1. Let A be an $n \times m$ matrix of real or complex numbers. Let $a_{i_1, \dots, i_k, j_1, \dots, j_k}$ be the minor of A determined by the rows (i_1, \dots, i_k) and the columns (j_1, \dots, j_k) , $1 \leq i_1 < i_2 < \dots < i_k \leq n$, $1 \leq j_1 < j_2 < \dots < j_k \leq m$. The k th multiplicative compound matrix $A^{(k)}$ of A is the $\binom{n}{k} \times \binom{m}{k}$ matrix whose entries, written in lexicographic order, are $a_{i_1, \dots, i_k, j_1, \dots, j_k}$.

In particular, when A is an $n \times k$ matrix with columns a_1, a_2, \dots, a_k , $A^{(k)}$ is the exterior product

$$a_1 \wedge a_2 \wedge \dots \wedge a_k.$$

In the case $m = n$, the additive compound matrices are defined in the following way.

Definition A.2. Let A be an $n \times n$ matrix. The k th additive compound $A^{[k]}$ of A is the $\binom{n}{k} \times \binom{n}{k}$ matrix given by

$$A^{[k]} = D(I + hA)^{(k)} \Big|_{h=0}$$

(19)

If $B = A^{[k]}$, then the following formula for $b_{i,j}$ can be deduced from Eq. (19). For any integer $i = 1, \dots, \binom{n}{k}$, let $(i) = (i_1, i_2, \dots, i_k)$ be the i th member in the lexicographic ordering of all k -tuples of integers such that $1 \leq i_1 < i_2 < \dots < i_k \leq n$. Then

$$b_{i,j} = \begin{cases} a_{i_1, i_1} + \dots + a_{i_k, i+k} & \text{if } (i) = (j), \\ (-1)^{r+s} a_{i_s, j_r} & \text{if exactly one entry } i_s \text{ in } (i) \text{ does not occur in } (j) \\ & \text{and } j_r \text{ does not occur in } (i) \\ 0 & \text{if } (i) \text{ differs from } (j) \text{ in two or more entries} \end{cases}$$

In the extreme cases when $k = 1$ and $k = n$, we have $A^{[1]} = A$ and $A^{[n]} = \text{tr}(A)$ and $A[n] = \text{tr}(A)$. For $n = 3$, the matrices $A^{[k]}$ are as follows:

$$A^{[1]} = A, \quad A^{[2]} = \begin{pmatrix} a_{11} + a_{22} & a_{23} & -a_{13} \\ a_{32} & a_{11} + a_{33} & a_{12} \\ -a_{31} & a_{21} & a_{22} + a_{33} \end{pmatrix}, \quad A^{[3]} = a_{11} + a_{22} + a_{33}.$$

3. CONCLUSION

In this paper, we investigate the model of the saturation response of the infection rate, and present a complete mathematical analysis for the global dynamics of a model for the infection of CD4+ T cells. In the model, the CD4+ T-cell population is partitioned into three subclasses: uninfected (susceptible) x , infected cells y , and free virus particles v . The infection is through direct contact with actively infected x cells. After infection, a x cell stays latent for a period of time, then becomes actively infected.

Our analysis shows that such a difference in the growth term does not alter the qualitative behaviours of solutions. More specifically, models with these two different growth terms have the same basic reproduction number

$$R_0 = \frac{\hat{x}}{\mu}$$

where \hat{x} is the equilibrium of CD4+ T cells in the absence of HIV infection. Furthermore, for

both models, the infection-free equilibrium $E_0^* = (\hat{x}, 0, 0)$ is globally stable if $R_0 \leq 1$, and a unique chronic-infection equilibrium E_1^* exists if $R_0 > 1$. E_1^* can be unstable for an open set of parameter values, and periodic solutions may exist. Quantitatively, both growth forms produce the same level of CD4 count at the chronic-infection equilibrium E_1^* , while the full logistic term leads to a lower level of viral load at the equilibrium E_1^* .

REFERENCES

- BUTLER G, FREEDMAN HI, WALTMAN P, 1986. Uniform persistence system, *Proceedings of the American Mathematical Society*, 96, 425–430.
- HIRSCH, M.W., 1990. System of differential equations which are competitive or cooperative, IV, *SIAM Journal on Mathematical Analysis*, 21, 1225–1234.
- HO D, NEUMANN A, PERELSON A, CHEN W, LEONARD J, MARKOWITZ M, 1995. Rapid turnover of plasma virions and CD4+ lymphocytes in HIV-1 infection, *Nature*, 373, 123–126.
- LI Y, MULDOWNNEY, J. S., 1995. Global stability for the SEIR model in epidemiology, *Mathematical Biosciences*, 125, 155–164.
- MULDOWNNEY JS, 1990. Compound matrices and ordinary differential equations, *Rocky Mountain Journal of Mathematics* 20, 857–872.
- NEUMANN A, LAM N, DAHARI H, GRETCH D, WILEY T, LAYDEN T, PERELSON, A., 1998. Hepatitis C viral dynamics in vivo and antiviral efficacy of the interferon- α therapy, *Science* 282, 103–107.

- NOWAK M.A, BONHOEFFER S, HILL AM, BOEHME R, THOMAS HC, MCDADE H, 1996. *Viral dynamics in hepatitis B virus infection, Proceedings of the National Academy of Sciences, USA, 93, 4398–4402.*
- NOWAK MA, LLOYD AL, VADQUEZ G.M et al., 1997. *Viral dynamics of primary viremia and antitroviral therapy in simian immunodeficiency virus infection, Journal of Virology 71, 7518–7525.*
- PERELSON AS, NEUMANN A, MARKOWITZ M, LEONARD J, HO D, 1996. HIV-1 dynamics in vivo: Virion clearance rate, infected cell life-span, and viral generation time, *Science, 271, 1582.*
- PERELSON AS, ESSUNGER Y, CAO M, VESANEN A, HURLEY K, SAKSELA M., MARKOWITZ D HO 1997. Decay characteristics of HIV-1-infected compartments during combination therapy, *Nature 387, 188.*
- PERELSON, AS, NELSON P, 1999. Mathematical analysis of HIV-1 dynamics in vivo, *SIAM Review, 41 (1), 3–44.*
- TUCKWELL HC, WAN FYM., 2004. On the behaviour of solutions in viral dynamical models, *BioSystems, 73,157-161*
- ZHU HR, SMÍTH HL, 1994. Stable periodic orbits for a class of three-dimensional competitive systems, *Journal of Differential Equations, 110, 143–156.*
- WEI X, GHOSH S, TAYLOR M, JOHNSON V, EMİNİ E, DEUTSCH P, LIFSON J, BONHOEFFER S, NOWAK M, HAHN B, SAAG S, SHAW G., 1995. Viral dynamics in human immunodeficiency virus type 1 infection, *Nature 373, 117.*