Stability Analysis of Two Mathematical Models of Dynamics of CTLS in the Antiretroviral Therapy for HIV Infection, By Painleve Property Analysis

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Abstract

It is confirmed that Cytotoxic T-Lymphocyte (CTL) play crucial role in the controlling of proliferation of HIV virus in a HIV infected patient.. In search of possible steady states of viral load and $CD4^+$T cells density, few mathematical models of dynamics of CTLs during antiretroviral therapy of HIV infection are reported recently. Stability analysis of two of these mathematical models of dynamics of CTLs are studied using Painleve property analysis (PPA) method. Their results are compared with clinical data and PPA that of another standard model of dynamics of $CD4^+$ T cells and justified the results.

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Keyword:

Cytotoxic T Lymphocyte, Antiretroviral Therapy, Painleve Property, Dynamics, $CD4^+$ T cell, Parameters, Virus, Leukocyte ,Lymphocyte, immunodeficiency, Infection, Cytokines, Resonances, Stability.

I. Introduction

Like any other virus, human immunodeficiency virus (HIV) is intra cellular parasite depends on the host cell for their survival and replication [01], [02],[03],[05] . Main target of HIV virus is specific type of leukocyte called T cells and its depletion deteriorate of immunity. Like any other lymphocytes T cell is produced in the bone marrow then moving to thymus and getting fully developed into immune competent then join with blood for optimise the immune system of the body[01],[02],[03],[05]. There are two types of lymphocytes B and T cells , B cells carry antibody molecules and that release into blood whenever virus ,bacteria etc enter the body. T cells are two types, $CD8^+$ T cell and $CD4^+$ T cells, where $CD8^+$T cells are killing the HIV viruses and T cells release virus specific cytotoxic T lymphocytes (CTL) that helps $CD8^+$ T cells either killing or blocking the multiplication of the HIV virus . So $CD4^+$T cells are called as helper cells [01] –[13].

HIV virus is a retrovirus and its genome is RNA, when it get into host cell ,that RNA genome modified to DNA by reverse transcription process and actively stay inside the host cell and control the replication of cell by mitosis [01]-[13]. The main target cell of the HIV virus is the $CD4^+$T cells then manipulate the genetic mechanism of $CD4^+$T cells to make RNA copies of the viral genome, after that infected $CD4^+$T cell starts producing HIV virus cells by mitosis that cause depletion of $CD4^+$T cell population and so deterioration of immunity [[01]-[05]. In Healthy human body the number of $CD4^+$T cells is around 1000clls/mm^3,when depleted to below 200cells/mm^3 due to HIV virus that person considered as AIDS patient [01]-[03],[05]. The count of CD4$^+$T cells is the only way to identify the progression HIV infection [01]-[05].

Uninfected CD4$^+$T cells producing CTLs that helps CD8$^+$T cells for controlling viral load, either by binding then killing the HIV virus or prevent the mitosis process of infected CD4$^+$T cells [01]-[03],[05]-[13]. The proliferation of CD4$^+$T cells and CTLs responses are the main objects of antiretroviral therapy of HIV infection. When antiretroviral drug administered to a HIV infected patient , CTLs reponses is stimulated and it acts against the infected CD4$^+$T cells [01]-[13].

There are more than twenty antiretroviral drugs are available , their different combinations are using in the antiretroviral therapy of HIV infection. In highly active antiretroviral therapy (HAART) [01,[16].[17]. Reverse Transcriptose Inhibitor (RTI) drugs and Protease Inhibitor (PI) drugs together are administered in order to prevent the decline of CD4$^+$T cells count below 500cells/mm^3 for reconstitution of immune system and improving CTLs count and reducing viral load [01],[12]-[16],[17] . But, continuous HAART therapies found as ineffective [01],[16],[17] due to drug resistance development and mutation of HIV viruses, even after administration of Interleukin-7 (IL-7) for stimulation of CD4$^+$T cells count [16],[17] . High viral load stimulate high CTLs response whereas, low viral load stimulate low CTL response . Hence strong CTL response reduce viral load, but the resultant low viral load leads to low CTL response [01],[13] . That way CTL response and viral load are oscillating even when under antiretroviral therapy and so complete eradication of HIV virus is impossible with present day antiretroviral therapy [01]-[03],[05], ,[13],[16],[17] .

The main unanswered question is ,how to maintain an equilibrium among CD4$^+$T cells count, CTLs proliferation rate and viral load, even if no possibility of complete eradication of HIV viral load in a antiretroviral therapy. For that many mathematical models are suggested [01], [07] – [27] ,[34]. In this study the stability analysis of two of those mathematical models [01],[13] are reporting in search of equilibrium conditions, using Painleve property analysis (PPA) of nonlinear dynamical systems [28], [29], then comparing that results with same type study [27] of another mathematical model [12],[15],[25],[34] [22],[26,].

II. Two Mathematical Models of CTLs Dynamics

<u>CTLs Model 01 ,</u> [13]

$$\frac{dU}{dt}=\alpha_1-\alpha_2U-\alpha_3UV, \qquad (2.01)$$

$$\frac{dI}{dt}=\alpha_3UV-\alpha_4I-\alpha_5IC, \qquad (2.02)$$

$$\frac{dV}{dt}=\alpha_6I-\alpha_7V\ , \qquad (2.03)$$

$$\frac{dC}{dt}=\alpha_8IC-\alpha_9C, \qquad (2.04)$$

Where U is the uninfected cell population density, I is the infected cell population density, V is the free virus load and C is the CTLs population density.

Where the parameters represent

α_1 =rate at which uninfected cells production ,

α_2=rate at which uninfected cells decline.

α_3 =rate at which free virus infecting uninfected cell,

α_4=rate at which infected cells decline,

α_5=rate constant of CTL mediated killing of infected CD4$^+$ T cell,

α_6=rate at which infected cell produce new virus cell,

α_7=rate at which free virus declines,

α_8=CTL responsiveness

α_9=declining rate of uninfected $CD4^+$ by infecting that by virus.

Recently a modified form of above model is reported [01], that is considering as model 02.

CTLs Model 02

Second mathematical model of CTLs dynamics [01],

$$\frac{dU}{dt}=\beta_1-\beta_2U-\beta_3UV, \quad (2.05)$$

$$\frac{dI}{dt}=\beta_3UV-\beta_4I-\beta_5IC, \quad (2.06)$$

$$\frac{dV}{dt}=\beta_6I-\frac{\beta}{(\beta_{10}+V)}-\beta_9V, \quad (2.07)$$

$$\frac{dC}{dt}=\frac{\beta_{11}IC}{(1+V)}-\beta_8C. \quad (2.08)$$

Where the parameters represent

β_1=rate of productoin of cell at born marrow,

β_2=natural death rate of cel,

β_3=rate of virus infecting cells

β_5=destroy of infected cell by CTLs

β_6=rate of free virus produced by infected cell,

β_8=rate of natural death of CTLs,

β_9=destruction of virus by CTLs

β_{10}=half saturation constant of external virus source,

β_{11}=the proliferation rate of CTLs due to antigen due to presence of virus.

Any mathematical model of CTLs dynamics has to explain why the rapid increasing of HIV viral load and that correlated to slow declaim of $CD4^+$ T cells over many years. Also, to explain the reason for a patient with low $CD4^+$ T cells count and large viral load can have almost same amount of HIV specific CTLs densities when a patient with high $CD4^+$T cells count and low viral load . Also, how to maintain a constant equilibrium state of co-existence of CTLs response ,low viral load and count of $CD4^+$T cells at least above 500/mm^3 for a long period.

In this study using Painleve Property Analysis (PPA) {28],[29] the possibility of existence of equilibrium or stability of CTLs dynamics studied corresponding to two of the above well known mathematical models. Results are compared with the stability analysis of modified Pereleson mathematical model's dynamics [22],[26] ,[27].

III.Painleve Property Analysis of Ordinary differential equations By ARS Algorithm

In the context of deterministic dynamical systems , chaos has measured by an extreme sensitivity of the solutions to the choice of initial conditions. Equations whose solutions are free from any chaotic behaviour are called ‘ completely Integrable’ , that are characterized by regular or predictable behaviour for all values of initial conditions and for all time. Whereas, in ‘Non-integrable ‘ systems, their regions in the phase space of their dependent variables the motion is irregular and chaotic. This type of study initiated by Sonya Kowaleveskaya [28],[29] in the context of rotating bodies , is the first attempt in dynamical systems associated with singularities.

There are two types singularities [28]’[29], first one called fixed singularity in which their location of singularity determined by the equation itself, second type is the movable singularity where its locations depends on the initial conditions. Fixed singularity type is absent in linear equations, but in nonlinear ordinary differential equations (ODEs) both types of singularities are possible.

Painleve’ found three types of second order nonlinear ODEs with only movable singularities are poles. Then Gambier added three more such types in 1916 and concluded no their cases arising in second order nonlinear ordinary differential equations [28],[29] this property is called Painleve’ Property (PP) . An algorithm developed by Ablowitz, Ramani and Segur called ARS algorithm [28] for nonlinear ordinary first order differential equations that admits movable branch points, either algebraic or logarithamic . ARS algorithm is using to study the stability by PP analysis of two models of CTLs dynamics (2.01)-(2.04) and (2.05)- (2.08)..

Let us consider a system of ordinary differential equations (ODEs) of the form

$$\frac{dwi}{dt} = F_i(w^1,w^2,......w^n), \; i = 1,2,..n \qquad (301)$$

Then we are searching for dominant behaviour of the solutions in the neighbourhood of a movable singularity of the form

$$w^i = \alpha_i \tau^{\rho_i} \;, \text{ where } \tau = (t_0 - t) \quad . \qquad (3.02)$$

Then there are three steps for the ARS algorithm;

Step 01

Substitute equation (3.02) in (3.01) and find all possible values ρ_i, for which two or more leading ordered terms in each equation balance each other, and the rest can be ignored for each such choice of the ρ_i . Also find all possible values of α_i .

Step 02

In step 02 , keep only the leading ordered balancing terms of step 01 and ignore rest and substitute

$$w^i = \alpha_i \tau^{\rho_i} (1 + \gamma_i \tau^r) \quad . \qquad (3.03)$$

All product terms of γ_i are to be omitted, then system reduced to

$$Q(r) .\gamma = 0, \quad \text{where } \gamma = (\gamma_1 \gamma_2, ... \gamma_n). \qquad (3.04),$$

Where Q(r) is an n x n matrix in which r entering only in its diagonal elements, almost linearly. Then find the roots of the determinant of

$$\text{Det } Q(r) = 0 . \qquad (3.05)$$

These values of r are called resonances. Resonance determines the number of arbitrary constants exist in the system of ODEs (3.01). Resonance $r = -1$ is related to the location of the one free constant , namely t_0 the point of the singularity and that always appear in the roots of (3.05).

The resonance $r = 0$ corresponds to the coefficient of one of the the leading ordered terms being arbitrary. Any resonance with real valued and $r > 0$ but not an integer indicates at $t = t_0$ is a movable singularity.

We have to evaluate all possible distinct $(n - 1)$ nonnegative and real valued integer resonances. Less than $(n - 1)$ nonnegative and real valued distinct integer resonances implies system has no PP property.

If R is the largest positive and integer valued resonance r , then substitute in the Laurent series expansions

$$w^i = \alpha_i \tau^{\rho_i} + \sum_{m=1}^{R} \alpha_i^m \tau^{\rho_{i+m}} \qquad (3.06)$$

and verify the compactibility conditions if necessary for finding all free constants required integrability conditions.

IV. Painleve Property Analysis of CTLs Dynamics of Nowak and Bangham Mathemaical Model [01].

For the PPA of (2.01)-(2.04) there are three choices of 'dominating terms'.

Case 01.

$$\frac{dU}{dt} = -a_3 UV, \qquad (4.01)$$

$$\frac{dI}{dt} = a_3 UV, \qquad (4.02)$$

$$\frac{dV}{dt} = a_6 I, \qquad (4.03)$$

$$\frac{dC}{dt} = a_8 IC. \qquad (4.04)$$

Substitute,

$$U = \alpha\tau^p,\ I = \beta\tau^q,\ V = \lambda\tau^s,\ C = \delta\tau^w, \qquad (4.05)$$

in (4.01) gives

$$s = -1 \text{ and } p = -a_3\lambda, \qquad (4.06)$$

from (4.02),

$$s = -1,\ q = p = -a_3\lambda,\ \alpha = -\beta, \qquad (4.07)$$

from (4.03).

$$s = -1,\ q = -2,\ \lambda = a_6\alpha = a_6\beta,\ p = -2, \qquad (4.08)$$

from (4.04),

$$q = -1. \qquad (4.09)$$

In (4.08) and (4.09) there are two values of q as -1 and -2 ,is a contradiction. So Case01 is discarded.

Case 02.

$$\frac{dU}{dt} = -a_3 UV, \qquad (4.10)$$

$$\frac{dI}{dt} = -a_5 IC, \qquad (4.11)$$

$\frac{dV}{dt}$=a_6I, (4.12)

$\frac{dC}{dt}$=a_8IC. (4.13)

Substituting (4.05) .

From (4.10),

s=−1, p=−a_3λ , (4.14)

from (4.11),

q=−a_5δ , ω=−1 , (4.15)

from (4.12),

q=−2 , λ=−a_6β, (4.16)

from (4.13),

q=−1. (4.17)

Values of q in (4.16) and (4.17) show contradiction, hence Case 02 discarded.

Case 03,

$\frac{dU}{dt}$=−a_3UV, (4.18)

$\frac{dI}{dt}$=−a_5UV, (4.19)

$\frac{dV}{dt}$=a_6I, (4.20)

$\frac{dC}{dt}$=a_8IC . (4.21)

Substitute (3.05), yield

from (4.18) and (4.21)

s=−1, q=−2 , λ=−a_6β , (4.22)

from (4.21),

$\lambda s\tau^{s-1}=a_7\lambda\tau^{s}$. (4.23)

Contradiction s−1=s, arises in the values of s in (4.23), hence Case 03 discarded.

All the above cases having contradictions moreover, no more further choices of ‘leading order terms ‘ possible implies PPA is to be terminated at this stage. Hence concluding that the system of equations (2.01)-(2.04) of CTLs Model 01 having no Painleve property (PP) , and so system may not yield a stable dynamics.

V. Painleve Property Analysis of CTLs Dynamics of Model 02

For the PPA analysis of (2.05) –(2.08) , there are eight choices of ‘leading order terms ‘ .

Case 01

$\frac{dU}{dt}$=$-a_3$UV, (5.01)

$\frac{dI}{dt}$=a_3UV, (5.02)

a_{10} $\frac{dV}{dt}$=a_6VI, (5.03)

$\frac{dC}{dt}$=a_{11}IC. (5.04)

Substitute,

U=$\alpha\tau^{p}$, I=$\beta\tau^{q}$, V=$\lambda\tau^{s}$, and C=$\delta\tau^{\omega}$, (5.05)

(5.01) yields ,

s=-1, p=$-a_3\lambda$, (5.06)

(5.02) yields,

s=-1, p=q=-1, β=$-$α, λ=$1/a_3$, (5.07) (5.03) yields,

s=-1, p=q=-1, α=$-$β=$\frac{a_{10}}{a_6}$, (4.08)

(5.04) yields

a_{11} =β=ω=1, α=-1 . (5.09)

The value of δ is unknown , still proceeding to the next step in search of finding resonances r .

Substitute,

U=$\alpha\tau^{p}(1+\gamma\tau^{r})$, V=$\beta\tau^{q}(1+\theta\tau^{r})$, I=$\lambda\tau^{s}(1+\eta\tau^{r})$, C=$\delta\tau^{\omega}(1+o\tau^{r})$,(4.10)

in (5.01) -(5.04) of Case 01 get,

p=q=s=-1, ω=$a_{11\lambda=}a_{11}\beta=-a_{11}\alpha$, (5.10)

and

rγ+θ=0, (5.11)

γ+θ$-$(r$-$1)η=0, (5.12)

a_{10}(θ+η)+(r$-$1)θ=0, (5.13)

ωη$-$ rσ=0. (5.14)

The matrices form of (5.11) – (5.14) is ,

$$\begin{pmatrix} r & 0 & 1 & 0 \\ 1 & (1-r) & 1 & 0 \\ 0 & a_{10} & a_{10}(r-1) & 0 \\ 0 & \omega & 0 & -r \end{pmatrix}\begin{pmatrix}\gamma \\ \eta \\ \theta \\ \sigma\end{pmatrix}=\begin{pmatrix}0 \\ 0 \\ 0 \\ 0\end{pmatrix}. \qquad (5.15)$$

The solution of (5.15) gives,

r=0, r==+1, r=(1−a_{10}) . (5.16)

Only three values of resonances r, instead of four values . Hence Case 01 discarded.

Case 02

$\frac{dU}{dt}$=−a_3UV, (5.17)

$\frac{dI}{dt}$=−a_5IC, (5.18)

a_{10} $\frac{dV}{dt}$=a_6VI, (5.19)

$\frac{dC}{dt}$=a_{11}IC. (5.20)

Substitute (5.05) in Case 02 equations (5.17)-(5.20),gives

s=q=ω=−1, p=−$\frac{a_3}{\lambda}$, δ=$\frac{1}{a_5}$, λ=$\frac{\beta}{\alpha}$ and β=−$\frac{1}{a_{11}}$. (5.21)

For finding resonance , substitute all values of (5.21) in(5.10) of the Case 02 equations (5.17) – (5.20) get,

σr−θ =0 , (5.22)

rγ−pη=0, (5.23)

rθ+σ=0, (5.24)

and

rη−θ=0. (5.25)

Respective resonances are,

r(r−p)=0,

or

r=0 and r=p. (5.26)

Only two distinct roots instead of four, so Case 02 discarded.

Case 03

Substitute , (5.05) in Case 3 equations,

$\frac{dU}{dt}$=−a_3UV, (5.27)

$\frac{dI}{dt}$=−a_5IC, (5.28)

a_{10} $\frac{dV}{dt}$=a_6VI, (5.29)

$\frac{dC}{dt}$=a_{11}IC, (5.30)

we get

s=q=ω=−1, p=$-a_3\lambda$, δ=$\frac{1}{a_5}$, β=$-\frac{1}{a_{10}}$, $a_6=a_{10}{}^2$. (5.31)

For finding resonances, substitute in (5.10) we get,

rγ+a_3λη=0, (5.32)

rθ+σ=0, (5.33)

rη+θ=0, (5.34)

and

rσ+θ=0. (5.35)

Gives the resonance values as,

r=0, r=1,and r=−1. (5.36)

Only three roots instead of four roots. Hence Case 03 is discarded .

<u>Case 04.</u>

$\frac{dU}{dt}=-a_3$UV, (5.37)

$\frac{dI}{dt}=a_3$UV, (5.38)

$a_{10}\frac{dV}{dt}=-\mathrm{a}_9V^2$, (5.39)

$\frac{dC}{dt}=a_{11}$IC. (5.40)

Substitute (5.05) then get,

p=q=s=−, β=$-a_3$, λ=$\frac{1}{a_3}$. (5.41)

Keeping other constants as unknown ,proceed to seek for values of resonances. Substitute values in (5.10), get

rγ+a_3λη=0, (5.42)

(r−1)θ+$\frac{\alpha}{a_3}$(γ+η)=0, (5.43)

rη+(2a_{10}−1)η=0, (5.44)

and

rσ−$a_{11}a_3$θ=0. (5.45)

Then the resonances equation is

r(r−1)(r+2a_{10}−1)=0. (5.46)

Implies , only three roots instead of four, so Cae 04 discarded.

<u>Case 05</u>

$\frac{dU}{dt}=-a_3 UV$, (5.47)

$\frac{dI}{dt}=a_3 UV$, (5.48)

$a_{10}\frac{dV}{dt}=a_6 VI$, (5.49)

and

$\frac{dC}{dt}=-a_8 VC$. (5.50)

Substitute (5.05),yield

p=q=s=−1, $\omega=-\frac{a_8}{a_3}$, $\delta=\lambda=\frac{1}{a_3}$, $\beta=-\alpha=\frac{a_{10}}{a_6}$. (5.51)

Substitute in (5.10) ,then resonance equation are

$r\gamma+\eta=0$, (5.52)

$(r-1)\theta+\gamma+\eta=0$, (5.53)

$r\eta+\theta=0$, (5.54)

and

$r\sigma+\frac{a_8}{a_3}\eta=0$. (5.55)

Then resonance equation is,

$r(r-1)(r+1)(1-r)=0$. (5.56)

Only three distinct values of resonances r, so Case 05 discarded.

Case 06

$\frac{dU}{dt}=-a_3 UV$, (5.57)

$\frac{dI}{dt}=-a_5 IC$, (5.58)

$a_{10}\frac{dV}{dt}=a_6 VI$, (5.59)

and

$\frac{dC}{dt}=-a_8$ VI . (5.60)

Substitute (5.05) yield,

q=s=ω=−1, $p=\frac{a_3}{a_8}$,$\lambda=\frac{1}{a_8}$, $\beta=-\frac{a_{10}}{a_6}$,$\delta=\frac{1}{a_6}$. (5.61)

Since all parameters of the CTL Model 02 are positive ,but in (5.61) p>0 is a contradiction to the PPA analysis . So Case 06 discarded.

Case 07

$\frac{dU}{dt}=-a_3UV$, (5.62)

$\frac{dI}{dt}=a_3UV$, (5.63)

$a_{10}\frac{dV}{dt}=a_6VI$, (5.64)

and

$V\frac{dC}{dt}=a_{11}$ IC . (5.65)

Substitute (5.05) yield,

q=−1 and −2 , (5.66)

is a contradiction and so Case 07 is discarded

Case 08

$\frac{dU}{dt}=-a_3UV$, (5.67)

$\frac{dI}{dt}=a_5IC$, (5.68)

$a_{10}\frac{dV}{dt}=-a_9V^2$, (5.69)

and

$\frac{dC}{dt}=a_{11}$ IC . (5.70)

Substitute (5.05) yield,

$p=-\frac{a_3a_{10}}{a_9}$, q=s=ω=−1, $\beta=-\frac{1}{a_{11}}$, $\lambda=\frac{a_{10}}{a_9}$, $\delta=-\frac{1}{a_5}$. (5.71)

For the values of resonances substitute in (5.10) ,

$r+\frac{a_3a_{10}}{a_9}\eta=0$, (5.72)

rθ+σ=0, (5.73)

(r+1)η=0, (5.74)

and

rσ+θ=0. (5.75)

Then the values of resonances r ,

$r^3=1$ and r=−1, equal roots. (5.76)

Only two distinct values of resonances and so Case 08 discarded.

Case 09

$$\frac{dU}{dt}=-a_3UV\ , \qquad (5.77)$$

$$\frac{dI}{dt}=-a_5IC\ , \qquad (5.78)$$

$$a_{10}\frac{dV}{dt}=-a_9V^2\ , \qquad (5.79)$$

and

$$\frac{dC}{dt}=-a_8\ VC\ . \qquad (5.80)$$

Substitute (5.05) yield

$$\omega= s=-1,\ p=-\frac{a_3}{a_{10}},\ q=-a_5\ \delta,\ \lambda=\frac{a_{10}}{a_9}\ . \qquad (5.81)$$

Substitute in (5.10) get the resonance equations,

$$r\gamma+\frac{a_3}{a_{10}}\eta=0\ , \qquad (5.82)$$

$$(r+1)\eta=0\ , \qquad (5.83)$$

$$r\sigma+\eta=0, \qquad (5.84)$$

and

$$(r+1+q)\theta+\sigma=0\ . \qquad (5.85)$$

Then values of resonances r are

$$r=0,\ r=-1. \qquad (5.86)$$

No four distinct values of resonances r, so Case 09 discarded.

Since all the Cases failed to obtain the allowed values of resonances, the CTL Model 02 has no PP.

VI. Conclusion

Since CTLs dynamics both models are of not Painleve types, the dynamics of both models are of unstable types, that observed in the clinical experiments [12]- [26],[34]. Even after repeated administration of IL-7 , count of $CD4^+T$ cells fluctuates after short periods and the retroviral therapy is to be continued to life long period of the HIV infected patient [16],[17]. Moreover, above PPA of both models failed to suggests any possible values of the parameters of the mathematical models for which stable dynamics can be found out. Hence CTLs dynamics both models are unstable for all values of the respective parameters. That means, for a stable dynamics the both model equations have to be modified so a to satisfy the Painleve property.

Pereleson et al [34] reported a Mathematical model for the dynamics of $CD4^+T$ cells without specifically considering the CTLs dynamics ,

$$\frac{dT}{dt} = a_1 - a_2T + a_3T[1 - (T + T^* + T^{**})/T_0] - a_4VT\ , \qquad (6.01)$$

$$\frac{dT*}{dt} = a_4VT - a_2T^* - a_5T^*\ , \qquad (6.02)$$

$$\frac{dT**}{dt} = a_5T^* - a_6T^{**}\ , \qquad (6.03)$$

and

$$\frac{dV}{dt} = N\, a_6 T^{**} - a_4 VT - a_7 V. \qquad (6.04)$$

Above model Culshaw et al [22],[26] modified to three equations by combining T^* and T^{**} together to T^* . Where T denotes the concentration of uninfected $CD4^+T$ cells , T^*denoted concentration of latently infected $CD4^+$ T cells, T^{**}denotes actively infected $CD4^+T$ cells of advanced stage of HIV infection and V is density of viral load . The Culshaw et al mathematical model is

$$\frac{dT}{dt} = a_1 - a_2 T + a_3 T[1 - (T+T^*)/T_0] - a_4 VT\,, \qquad (6.05)$$

$$\frac{dT^*}{dt} = a_4 VT - a_6 T^*\,, \qquad (6.06)$$

and

$$\frac{dV}{dt} = N\, a_6\, T^* - a_7\, V - a_4 VT, \qquad (6.07)$$

where the physical meaning of parameters from clinical data are [34]

Parameters	Physical meaning of parameters	Initial values
a_1	Rate of supply of $CD4^+T$ cells from Precursors	$10\ day^{-1} mm^{-3}$
a_2	Death rate of uninfected and latently infected $CD4^+T$ cells population	$0.02\ day^{-1}$
a_3	Rate of growth of population of $CD4^+T$ cells by Mitosis	$0.03\ day^{-1}$
a_4	Rate constant for $CD4^+T$cells becoming infected by free HIV virus	$2.4\times10^{-5} day^{-1}\ mm^{-1}$
a_5	Rate of latently infected cells that convert to actively infected	$3\times10^{-3} day^{-1}$
a_6	Death rate of actively infected $CD4^+T$ cell	$0.24\ day^{-1}$
$\mathbf{a_7}$	Death rate of free virus	$2.4\ day^{-1}$
N	Number of free virus produced by lysing a $CD4^+T$ cell	Varies
T_0	Maximum $CD4^+T$ cell population level	$1000\ mm^{-3}$

(6.08)

The PPA analysis [27] of above Culshaw et al mathematical model equations (6.05)-(6.07) gives the resonance equations as[27],

$$\gamma(r + 1) = 0, \qquad (6.09)$$

$$\gamma \frac{a_4 T}{a_3} + \delta\left[r - \frac{a_4 T_0}{a_3}\right] + \eta\frac{a_4 T_0}{a_3} = 0, \qquad (6.10)$$

$\eta\, r + \quad \gamma\, \frac{a_4 T_0}{a_3}$. (6.11)

Respective matrix equation is

$$\begin{pmatrix} (r+1) & 0 & 0 \\ \frac{a_4 T_0}{a_3} & \left(r - \frac{a_4 T_0}{a_3}\right) & \frac{a_4 T_0}{a_3} \\ \frac{a_0 T_0}{a_3} & 0 & r \end{pmatrix} \begin{pmatrix} \gamma \\ \delta \\ \eta \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix} . \qquad (6.12)$$

From (6.12), we get the values of resonance values r as ,

$r = -1$, $r = 0$, and $r = (a_4 T_0 / a_3)$. (6.13)

Since two values of resonances r are −1,and 0 , so for satisfying PP the third resonance value must be greater than or equal to +1 and an integer. Hence

$(a_4 T_0 / a_3) \geq +1$ and must be an integer. (6.14) $T_0 \geq \left(\frac{a_3}{a_4}\right)$,and must be an integer and above 0 . (6.15)

The parameter T_0 is the maximum allowed value of CD4$^+$ T cells and it is 1000 mm^{-3}, parameter a_3 is the growth rate of CD4$^+$ T cells by mitosis and its value is 0.03 day^{-1} and parameter a_4 is the rate of CD4$^+$ T cells infected by free HIV virus and its value is 2.4×10^{-5}day^{-1} . Hence ,the condition for stability (3.11) becomes

$$T_0 \geq \frac{0.03\ day^{-1}}{2.4\times10^{-5}\ day^{-1}} \quad , \qquad (6.16)$$

Since T_0 is the maximum allowed number of CD$^+$ Tcells, that is constant, so above condition of stability (4.02) depends on the parameters a_3 and a_4 . Where a_3 is the growth rate of CD4$^+$ T cells by mitosis ,that depends on age of the patient . After adult stage production rate of CD4$^+$ T cells decreases . Hence , only alternative is boost the proliferation rate of CD4$^+$Tcells by drugs like Interlokin-7

(IL-7) [17] and its dosage and cycles are to be adjusted according to the stability condition (6.16) . But any variation however small that may be from condition (6.16) will lead to oscillations that observed in the clinical study .

In the previous study [12],[15],25] [22],[26],[34], it is found that the steady state or stability of dynamics depends on population of CD4$^+$ T cells but they observed only two steady state or stability possibilities, in this study we found the stability depends on condition (6.16) as any positive integer , so more than two steady states are possibl, but that depends on allowed values of the parameters a_3 anda_4 . Moreover, these steady states are also depends on the parameter a_4 the rate CD4$^+$ T cells infected by free HIV virus particles, that other studies ignored . The depletion of uninfected CD4$^+$ T cells a_3 and the growth of infected CD4$^+$T cells a_4 depends on viral load and CTLs responses. So these variations indirectly related to CTLs responses and viral load.

Dynamics of CTLs responses and viral load are very much similar to Lotka-Voletera's two species food chain model and so comparison with that dynamics may give a better insight into the CTLs dynamics .Moreover, these dynamics related to the self-organization behavior of biological systems and some faculty of the human brain also controlling these dynamics, that is to be investigated.

One of the limitations of the all known mathematical models is all the dynamics depended on only one independent variable time t , spatial change is ignored. But in real time data the growth, life span and death of $CD4^+$ T cells varies from location to locations in the body, so their interaction with HIV virus also vary considerably when location changes. For that dynamics we may have to model with nonlinear coupled partial differential equations , that very difficult to study. In all previous studies , Lyaponov exponents method is used, but that developed only for nonlinear ODEs for the study of stability.

In fact, there is a method of PP analysis for nonlinear partial differential equation (NPDE) [11] that can be used to find the criteria for long term stability. That method, this author used in NPDE [12] as well as for ODE [13] , that may be another option for getting long term stability.

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