

Stability Analysis of Dynamics of Mathematical Model Of HIV Infection of CD4⁺ T Cells, By Painleve Property Analysis

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Abstract:

Studied the possible conditions for the long term stability of a mathematical model developed by Rabeeca Kulshaw et al of the dynamics of HIV infection of CD4⁺ T cells during antiviral drugs administering to HIV infected patients . Long term stability conditions are found by using Painleve' property analysis , during antiviral therapy in terms of the parameters of the models and control parameters of the possible oscillations or irregularity behaviour that leads to chaos in the system are also reported. Results are compared with earlier reported clinical data.

Keywords : Stability, Infection, Painleve' property, Parameters, Therapy, Oscillation, Chaos, Leukocytes, Immunity, Antiviral, Thymus, Nonlinear, Differential equation. Resonances, Algorithm.

I. INTRODUCTION

Main target of human immunodeficiency virus (HIV) is the selective depletion of a specific type of leukocyte called CD4⁺ T cells ,also called as Helper T cells . The depletion of CD4⁺ T cells cause the deterioration of immunity of the body. In healthy body the number of CD4⁺ T cells are around 1000-1200 cells/mm³, like any other lymphocytes this is produced in the bone marrow then moving to thymus and getting fully matured into immune competent CD4⁺ T cells and optimize the immune system of the body [01].

Generally, combination of two or more antiviral drugs therapy is used to control the HIV infection that regulate the count of CD4⁺ T cells are at least above 500cells/mm³ . If that fails even after few cycles then cycle of Interleukin-7 (IL-7) is to be administered . The efficiency of these antiviral therapy for a long term regulation of the CD4⁺T cell's count and its relation to other parameters of the body are still under study.

Interaction between HIV virus and the CD4⁺ T cells during the antiviral therapy is first mathematically modelled by Ho et al [02] in 1995 and then Perelson et al [03] in 1996. After that many different types of studies reported, both stochastic and deterministic models [04] – [08].

In this study, Rabeeca Kulshaw et al [08] mathematical model is adopted to study the long term stability of the dynamics using Painleve' property analysis of nonlinear dynamical systems [09] and searching for the connection between parameters of the mathematical model and the stability conditions for keeping the CD4⁺ T cells count at least above 500 cells/mm³ . The mathematical model of Rabeeca Kulshaw et al [08] is a special case of an earlier study of Perelson et al [03] , in which the initial and advanced stages of HIV infections are separately considered.

Whereas, in Rabeeca Kulshaw et al [08] study, both initial and advanced stages of HIV infection combined together and so four coupled nonlinear ordinary differential equations (NODEs) of Perelson et al model [03] reduced to only three NODEs.

Perelson et al model for advanced stage of HIV infection in which CD4⁺T cells are actively infected is containing four coupled nonlinear ordinary differential equations [03],

$$\frac{dT}{dt} = a_1 - a_2T + a_3T[1 - (T + T^* + T^{**})/T_0] - a_4VT, \quad (1.01)$$

$$\frac{dT^*}{dt} = a_4VT - a_2T^* - a_5T^*, \quad (1.02)$$

$$\frac{dT^{**}}{dt} = a_5T^* - a_6T^{**}, \quad (1.03)$$

and

$$\frac{dV}{dt} = N a_6T^{**} - a_4VT - a_7V. \quad (1.04)$$

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 the concentration of free HIV virus particles.

Where $a_1, a_2, a_3, a_4, a_5, a_7$ are nonzero parameters, T_0 is the maximum number of $CD4^+$ T cells concentration possible in the healthy body, it is 1000 cells/mm³, N is the number of free virus produced by Metosis of the HIV infected $CD4^+$ T cells.

From the clinical data [03], following are the physical meaning of parameters and their values in the initial stage of HIV infection :

Parameters	Physical meaning of parameters	Initial values
a_1	Rate of supply of $CD4^+$ T cells from Precursors	$10 \text{ day}^{-1}\text{mm}^{-3}$
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 $CD4^+$ Tcells becoming infected by free HIV virus	$2.4 \times 10^{-5} \text{ day}^{-1} \text{mm}^{-1}$

a_5	Rate of latently infected cells that convert to actively infected	$3 \times 10^{-3} \text{ day}^{-1}$
a_6	Death rate of actively infected $CD4^+$ T cell	0.24 day^{-1}
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}

(1.07)

Rabeeca Kulshaw et al [08] model is the following

$$\frac{dT}{dt} = a_1 - a_2 T + a_3 T [1 - T(T + T^*)/T_0] - a_4 VT, \quad (1.08)$$

$$\frac{dT^*}{dt} = a_4 VT - a_6 T^*, \quad (1.09)$$

and

$$\frac{dV}{dt} = N a_6 T^* - a_7 V - a_4 VT. \quad (1.10)$$

II. PAINLEVE PROPERTY ANALYSIS (PPA) OF NONLINEAR ORDINARY DIFFERENTIAL EQUATIONS, 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 [09] in the context of rotating bodies, is the first attempt in dynamical systems associated with singularities.

There are two types singularities, 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 [10], this property is called Painleve’ Property (PP). An algorithm developed by Ablowitz, Ramani and Segur called ARS algorithm [09] for nonlinear ordinary first order differential equations that admits movable branch points, either algebraic or logarithmic. ARS algorithm is using to study the stability by PP analysis of (3.08) and (3.10).

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

$$\frac{dw_i}{dt} = F_i(w^1, w^2, \dots, w^n), \quad i = 1, 2, \dots, n \quad (2.01)$$

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

$$w^i = \alpha_i \tau^{\rho_i}, \quad \text{where } \tau = (t_0 - t). \quad (2.02)$$

Then there are three steps for the ARS algorithm;

Step 01

Substitute equation (2.02) in (2.01) 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

$$w^i = \alpha_i \tau^{\rho_i} (1 + \gamma_i \tau^r). \quad (2.03)$$

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

$$Q(r) \cdot \gamma = 0, \quad \text{where } \gamma = (\gamma_1, \gamma_2, \dots, \gamma_n). \quad (2.04),$$

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

$$\text{Det } Q(r) = 0. \quad (2.05)$$

These values of r are called resonances. Resonance determines the number of arbitrary constants exist in the system of ODEs (2.01). 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 (2.05).

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

$$w^i = \alpha_i \tau^{p_i} + \sum_{m=1}^R \alpha_{i+m} \tau^{p_{i+m}} \quad (2.06)$$

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

III. PAINLEVE' PROPERTY ANALYSIS OF MODELLED EQUATIONS USING ARS ALGORITHM

Culshaw et al mathematical model (1.08) – (1-10) is .

$$\frac{dT}{dt} = a_1 - a_2 T + a_3 T [1 - (T + T^*)/T_0] - a_4 VT, \quad (1.08)$$

$$\frac{dT^*}{dt} = a_4 VT - a_6 T^*, \quad (1.09)$$

and

$$\frac{dV}{dt} = N a_6 T^* - a_7 V - a_4 VT. \quad (1.10)$$

Substitute

$$T = \alpha \tau^p, \quad T^* = \beta \tau^q, \quad V = \lambda \tau^s, \quad \text{where } \tau = (t - t_0), \quad (3.01)$$

in (1.08) – (1.10) and we get following 'leading order balancing

terms are

$$\frac{dT}{dt} = -a_3 T^2/T_0, \quad \frac{dT^*}{dt} = a_4 VT \quad \text{and} \quad \frac{dV}{dt} = -a_4 VT, \quad (3.02)$$

for the following choices

$$\alpha = T_0/a_3, \quad \beta = -\lambda, \quad p = -1, \quad q = -a_4 T_0/a_3 \text{ and } q = s. \quad (3.03)$$

For finding resonance values of r , substitute following equations in the balancing leading order equations (3.02)

$$T = \alpha \tau^p(1 + \gamma \tau^r), \quad T^* = \beta \tau^q(1 + \delta \tau^r) \quad \text{and} \quad V = \lambda \tau^s(1 + \omega \tau^r). \quad (3.04)$$

Gives following set of resonance equations

$$\begin{aligned} \gamma(r+1) &= 0, \\ \gamma \frac{a_4 T_0}{a_3} + \delta \left[r - \frac{a_4 T_0}{a_3} \right] + \eta \frac{a_4 T_0}{a_3} &= 0, \\ \eta r + \gamma \frac{a_4 T_0}{a_3} &. \end{aligned} \quad (3.05)$$

Respective matrix equation is

$$\begin{pmatrix} (r+1) & 0 & 0 \\ \frac{a_4 T_0}{a_3} \left(r - \frac{a_4 T_0}{a_3} \right) & \frac{a_4 T_0}{a_3} & 0 \\ \frac{a_4 T_0}{a_3} & 0 & r \end{pmatrix} \begin{pmatrix} \gamma \\ \delta \\ \eta \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}. \quad (3.06)$$

Implies,

$$\begin{vmatrix} (r+1) & 0 & 0 \\ \frac{a_4 T_0}{a_3} \left(r - \frac{a_4 T_0}{a_3} \right) & \frac{a_4 T_0}{a_3} & 0 \\ \frac{a_4 T_0}{a_3} & 0 & r \end{vmatrix} = 0. \quad (3.07)$$

From (3.07), we get the values of resonances r as ,

$$r = -1, \quad r = 0, \quad \text{and} \quad r = (a_4 T_0/a_3). \quad (3.08)$$

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. So

$$(a_4 T_0/a_3) \geq +1 \quad \text{and must be an integer.} \quad (3.10)$$

$$T_0 \geq \left(\frac{a_3}{a_4} \right), \text{ and must be an integer.} \quad (3.11)$$

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 $2.4 \times 10^{-5} \text{ day}^{-1}$. Hence, the condition for stability (3.11) becomes

$$T_0 \geq \frac{0.03 \text{ day}^{-1}}{2.4 \times 10^{-5} \text{ day}^{-1}}, \quad (3.12)$$

IV. DISCUSSION

According to ARS algorithm , strong PP exists only when the values of p , q , s are all negative and nonzero integers. From (3.03) we have

$$P = -1 \text{ and } q = s = -a_4 T_0 / a_3 , \quad (4.01)$$

by condition of resonance (3.10) we found $a_4 T_0 / a_3 \geq +1$, and so all

above values including s are negative. Also for the condition for strong PP and strong stability all values of (4.01) must be integers .Hence dynamics of HIV infection of $CD4^+$ T cells is stable without any oscillations the required condition (3.11), or

$$T_0 \frac{a_4}{a_3} \geq +1 , \text{ and an integer.} \quad (4.02)$$

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) [04], [05] and its dosage and cycles are to be adjusted according to the stability condition (4.02) . But any variation from condition (4.02) will lead to oscillations that observed in the clinical study [03] .

In the previous study [03] 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 (4.02) as any positive integer , so more than two steady states are possible. 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 .

One of the limitations of the 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 , Lyapunov 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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