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OPTIMAL CONTROL AND HOPF BIFURCATION ANALYSIS OF DELAY DEPENDENT HIV PROTEASE INHIBITOR MODEL

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Abstract. In this article, HIV protease inhibitor model with three intracellular delays is considered and the stability analysis for the case of $\bar{\tau} = 0$ where, $\bar{\tau} = \tau + \tau_2$ and $\tau_1 \neq 0$ for the same model is examined. τ_1, the delay corresponding to the loss of target cells is viewed as a bifurcation parameter, a limit cycle bifurcation about the infected steady state is scrutinized. Further, a mathematical model of HIV protease inhibitor model using control terms is presented and analysed mathematically.

1. Introduction

One of the primary reasons for studying infectious diseases is to improve control and ultimately to eradicate the infection from the population. Models can be a powerful tool in this approach, allowing us to optimize the use of limited resources or simply to target control measures more efficiently. In spite of the improvement in sanitation, developments of antibiotics and vaccines, infectious diseases still contribute significantly to deaths worldwide. While the earlier recognized diseases like cholera or the plague still sometimes create problems in underdeveloped countries erupting occasionally in epidemics, in the developed countries hazardous diseases are emerging like AIDS (1981), hepatitis C or E (1989-1990).

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Although the correlates of immune protection in HIV infection remain largely unknown, our knowledge of viral replication dynamics and virus-specific immune responses has grown. Concurrent with these advances, there has been an abundance of mathematical models that attempt to describe these phenomena. Consequently, many mathematical models have been developed to describe the relationships between the Human Immunodeficiency Virus (HIV), etiological agent for AIDS, and $CD4^{+}T$ cells which are the target for the virus [1, 2, 12, 21, 22]. These models are utilized to explore optimal chemotherapy treatment to avoid an excessive use of drugs [13, 14, 15, 17, 26].

Delay differential equations (DDEs), are the subject of active research for more than 60 years and has been studied by many different mathematicians. Delay differential equations are equations which have a delayed argument [16, 27]. These equations constitute a large and important class of dynamical systems. Time delays are natural components of the dynamic processes of biology, ecology, physiology, economics, epidemiology and mechanics and so a realistic model of these processes must include time delays. Delay differential equations arise in situations where some hereditary function appears in the ordinary differential equation. Detailed studies of the real world compel us to take account of the fact that the rate of change of physical systems depends not only on their present state, but also on their past history [3].

In many real world phenomena, the initial conditions or boundary conditions are not enough to predict the future behaviour of the function. Hence to deal with such complexities, it is necessary to have some knowledge of the earlier behaviour of the function.

In the mathematical theory of bifurcations, a Hopf bifurcation is a critical point where a system's stability switches and a periodic solution arises [10, 18, 25]. More accurately, it is a local bifurcation in which a fixed point of a dynamical system loses stability, as a pair of complex conjugate eigenvalues - of the linearisation around the fixed point - crosses the complex plane imaginary axis. Under reasonably generic assumptions about the dynamical system, a small-amplitude limit cycle branches from the fixed point.

A Hopf bifurcation is also known as a PoincarAndronovHopf bifurcation, named after Henri Poincar, Aleksandr Andronov and Eberhard Hopf. Optimal control theory is another area of mathematics that is used extensively in controlling the spread of infectious diseases. Optimal control has a long history of being applied to problems in biomedicine, particularly, to models for cancer chemotherapy. It is a powerful mathematical tool that can be used to make decisions involving complex biological situation [19]. It is often used in the control of the spread of most diseases for which either vaccine or treatment is available.

For example, [8] applied optimal control theory to a set of epidemiological models in their attempt to find the most effective control strategy to minimize the number of individuals who become infected in the course of an epidemic using both treatment and vaccination as control measures. Also, the work by [15] used optimal control theory to determine the optimal treatment strategy for the administration of antiretroviral drug (Reverse Transcriptase Inhibitors) in HIV positive individuals. In [6], also used optimal control theory to determine the condition for the elimination of tumor cells in an individuals under treatment for Cancer.

2. Basic HIV model

The simplest mathematical model to study virus dynamics [23] describes the changes in the density of susceptible target cells (T), infected cells (T^*) and free viruses (V) with differential equations. Target cells constantly enter the system at rate s. These cells die at a natural death rate d_T and become infected at rate k. Upon infection, cells move into the T^* class and have a potentially increased death rate δ. Infected cells produce viruses at rate N. Viruses are removed from the system at rate c. Flow diagrams are a useful tool to illustrate these dynamics. By either solving the system of equations analytically when possible or using numerical methods, we can predict the behavior of densities of viruses and target cells. Stafford et al. [24] used this model to estimate the model parameters by fitting the model to viral load data of 10 HIV patients. The basic HIV model is as follows:

$$\begin{aligned} \frac{dT}{dt} &= s - d_T T - kTV, \\ \frac{dT^*}{dt} &= kTV - \delta T^*, \\ \frac{dV}{dt} &= N\delta T^* - cV. \end{aligned} \tag{2.1}$$

2.1. **The model with protease inhibitors.** In [23], the authors constructed the HIV - 1 model with protease inhibitor therapy together with three intracelluar delay. An analysis about the model is done in the same article. The protease inhibitor model is as follows:

$$\begin{aligned} \dot{T}(t) &= s - d_T T(t) - kT(t)V_I(t), \\ \dot{T^*}(t) &= kT(t)V_I(t) - \delta T^*(t), \\ \dot{V_I}(t) &= N\delta(1-\epsilon_p)T^*(t) - cV_I(t), \\ \dot{V_{NI}}(t) &= N\delta\epsilon_p T^*(t) - cV_{NI}(t), \end{aligned} \tag{2.2}$$

where ϵ_p is the efficacy of the protease inhibitor scaled such that $\epsilon_p = 1$ corresponds to a completely effective drug that results only in the production of non-infectious virions V_{NI}. The parameters used here are described in Table 1.

Table 1:

In Vitro Model Parameters

Notation	Description
s	Rate at which new target cells are generated
d_T	Specific death rate of target cells
k	Constant rate that characterizing target cell infection.
δ	Over all death rate of target cells
N	New virus particles
c	Clearance rate of virion

The model (2.2), is oblivious of intracellular delay and without any proof it comes to an assumption that the infected cells becomes productive promptly. To conquer this limitations we considered the protease inhibitor model with delay. Thus arrives a sub - section here.

2.2. **Protease inhibitor model with intracellular delays.** In article [23], a model of HIV-1 infection with a protease inhibitor therapy and three delays was constructed. This model involves the concentrations of uninfected target cells, T, infected cells that are producing virus, T^*, and virus, V. After protease inhibitors are given, virus is classified as either infectious, V_I, i.e., not influenced by the protease inhibitor, or as non-infectious, V_{NI}, due to the action of the protease inhibitor which prevents virion maturation into infectious particles. The model is

$$\begin{aligned} \dot{T}(t) &= s - d_T T(t) - kT(t)V_I(t), \\ \dot{T^*}(t) &= kT(t)V_I(t) - \delta T^*(t), \\ \dot{V_I}(t) &= N\delta(1-\epsilon_p)T^*(t) - cV_I(t), \\ \dot{V_{NI}}(t) &= N\delta\epsilon_p T^*(t) - cV_{NI}(t), \end{aligned} \tag{2.3}$$

where ϵ_p is the efficacy of the protease inhibitor scaled such that $\epsilon_p = 1$ corresponds to a completely effective drug that results only in the production of non-infectious virions V_{NI}. The parameters used here are described same as the above Table 1.

Next, we consider the delay model

$$\begin{aligned}
\dot{T}(t) &= s - d_T T(t) - ke^{-m\tau_1} T(t-\tau_1) V_I(t-\tau_1), \\
\dot{T^*}(t) &= ke^{-m\tau} T(t-\tau) V_I(t-\tau) - \delta T^*(t), \\
\dot{V_I}(t) &= N\delta(1-\epsilon_p) e^{-\nu\tau_2} T^*(t-\tau_2) - cV_I(t), \\
\dot{V_{NI}}(t) &= N\delta\epsilon_p e^{-\nu\tau_2} T^*(t-\tau_2) - cV_{NI}(t),
\end{aligned} \tag{2.4}$$

where τ is the total intracellular delay, τ_1 is the delay corresponding to the loss of target cells by infection, considered in [5], and τ_2 is the delay representing the time necessary for a newly infected virus to become mature and then infectious.

The steady states of the system (2.4) has been computed in [23]. The system (2.4) has two steady states the infection free steady state

$$S_v = (\hat{T}, \hat{T}^*, \hat{V}_I, \hat{V}_{NI}) = (s/d_T, 0, 0, 0)$$

and the infected steady state

$$\begin{aligned}
S_i &= (\bar{T}, \bar{T}^*, \bar{V}_I, \bar{V}_{NI}), \\
&= \left(\frac{s}{d_T R_p}, \frac{d_T c e^{m\tau_1} e^{\upsilon\tau_2}}{(1-\epsilon_p) skN} (R_p - 1), \frac{d_T}{k} e^{m\tau_1} (R_p - 1), \frac{d_T \epsilon_p e^{m\tau_1}}{(1-\epsilon_p)k} (R_p - 1) \right).
\end{aligned}$$

Also, the local stability analysis of the system (2.4) about the steady states are examined in [23]. Also, the sensitivity analysis of the system and further extension of the model by considering the nature factor humoral immunity was studied in [4].

3. Estimation of model parameters using discretization

In this section, our aim is to estimate all parameters of HIV-1 infection protease inhibitor model (2.3). Clinically all the variables in model (2.3), can be measured. Since the cost of quantifying the infected cells is much higher, we are going to omit variable T^*, initially. For this, let $x_1 = T$, $x_2 = V_I$ and $x_3 = V_{NI}$. After some calculations, model (2.3) can be changed to:

$$\dot{x}_1 = \alpha_1 + \alpha_2 x_1 + \alpha_3 x_1 x_2, \tag{3.1}$$

$$\ddot{x}_2 = \alpha_4 \dot{x}_2 + \alpha_5 x_2 + \alpha_6 x_1 x_2, \tag{3.2}$$

$$\ddot{x}_3 = \alpha_4 \dot{x}_2 + \alpha_5 x_3 + \alpha_7 x_1 x_2 \tag{3.3}$$

where,

$$\alpha = \begin{bmatrix} \alpha_1 \\ \alpha_2 \\ \alpha_3 \\ \alpha_4 \\ \alpha_5 \\ \alpha_6 \\ \alpha_7 \end{bmatrix} = \begin{bmatrix} s \\ -d_T \\ -k \\ -c-\delta \\ c\delta \\ N\delta k(1-\epsilon_p) \\ N\delta k\epsilon_p \end{bmatrix}.$$

The vector α defines a one-to-one map for $k \neq 0$, $\delta \neq c$ and $\epsilon_p \neq 1$. Therefore the identification of the original parameters of model (2.3) is equivalent to the identification of α. In this model, it is known that $k \neq 0$ and $\delta < c$ [28], also $\epsilon_p \neq 1$ is assumed [23]. In this case we can define the inverse map as follows:

$$\begin{bmatrix} s \\ d_T \\ k \\ c \\ \delta \\ N \\ \epsilon_p \end{bmatrix} = \begin{bmatrix} \alpha_1 \\ -\alpha_2 \\ -\alpha_3 \\ \dfrac{-\alpha_4 + \sqrt{\alpha_4^2 - 4\alpha_5}}{2} \\ \dfrac{-\alpha_4 - \sqrt{\alpha_4^2 - 4\alpha_5}}{2} \\ \dfrac{2(\alpha_6+\alpha_7)}{\alpha_3(\alpha_4 + \sqrt{\alpha_4^2 - 4\alpha_5})} \\ \dfrac{\alpha_7}{\alpha_6+\alpha_7} \end{bmatrix}.$$

Since there are three unknown parameters in each of equation (3.1) and (3.2), it is necessary to generate at least two other equations based on each of them. This will be achieved by differentiating (3.1) and (3.2) more times, and produce upper derivatives of x_1 and x_2. So one can conclude that at least four measurements of x_1, target cell count and five measurements of x_2, viral load, are needed for a complete determination of the model (2.3) parameter.

We have calculated that

$$\alpha_1 + \alpha_2 x_1^i + \alpha_3 x_1^i x_2^i = \frac{x_1^{i+1} - x_1^i}{d_{i+1}},\ i = 0, 1, 2, \tag{3.4}$$

$$\frac{x_2^{i+1}-x_2^i}{d_{i+2}}\alpha_4+\alpha_5x_2+\alpha_6x_1x_2=\frac{1}{d_{i+1}}\left(\frac{x_2^{i+2}-x_2^{i+1}}{d_{i+2}}-\frac{x_2^{i+1}-x_2^i}{d_{i+1}}\right), i=0,1,2, \quad (3.5)$$

and

$$\frac{x_2^{i+1}-x_2^i}{d_{i+2}}\alpha_4+\alpha_5x_3+\alpha_7x_1x_2=\frac{1}{d_{i+1}}\left(\frac{x_3^{i+2}-x_3^{i+1}}{d_{i+2}}-\frac{x_3^{i+1}-x_3^i}{d_{i+1}}\right), i=0,1,2. \quad (3.6)$$

We can also write the above equations in matrix forms as follows:

$$\begin{bmatrix} 1 & x_1^0 & x_1^0x_2^0 \\ 1 & x_1^1 & x_1^1x_2^1 \\ 1 & x_1^2 & x_1^2x_2^2 \end{bmatrix} \begin{bmatrix} \alpha_1 \\ \alpha_2 \\ \alpha_3 \end{bmatrix} = \begin{bmatrix} \dfrac{x^1-x^0}{d_1} \\ \dfrac{x^2-x^1}{d_2} \\ \dfrac{x^3-x^2}{d_3} \end{bmatrix}. \quad (3.7)$$

Similarly, equations (3.5) and (3.6) can be written in matrix form. Thus, the variables $\alpha_i, i=1,2,\cdots,7$ and then from (2.3), all the basic parameters can be estimated.

4. Bifurcation analysis

In dynamical systems, a bifurcation occurs when a small smooth change, made to the parameter values (the bifurcation parameters) of a system causes a sudden "qualitative" or topological change in its behavior. Before moving into the concept of observing, the conditions for Hopf-bifurcation [11] are satisfied by yielding the required periodic solutions that is $\left(\frac{dRe(\mathbf{P})}{d\tau_1}\right)\Big|_{\tau_1=\tau_1^*} > 0$, we go in depth about the basic concepts of the infected steady state analysis of the model (2.4). In [23], the local stability of the model [23] is studied when $\bar{\tau} \neq 0$ (where $\bar{\tau}=\tau+\tau_2$) and $\tau_1=0$. Theorem with the case, $\bar{\tau}$ vanishes and $\tau_1>0$ is left unstudied in [23].

Definition 4.1. System (2.3) is said to satisfy the Poincare-Bendixson property if any nonempty compact Γ limit set of (2.3) that contains no equilibria is a closed orbit.

Definition 4.2. The autonomous system (2.3) is said to be competitive in Γ, if for some diagonal matrix $\mathfrak{M}=diag(\delta_1,\delta_2,\cdots,\delta_n)$ where each $j=(1,2,...,n)$ is either 1 or -1, $\mathfrak{M}\frac{\partial f}{\partial X}\mathfrak{M}$ has non positive off diagonal elements for all $X\in\Gamma$.

Theorem 4.3. *System* (2.3) *is a competitive system.*

Proof. By looking at the Jacobian of the matrix of the system (2.3) and choosing the matrix $\mathfrak{M}$ as

$$\mathfrak{M} = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & -1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}.$$

We see that system (2.3), is competitive in Γ, with respect to the partial order defined by the orthant $K = \{(T, T^*, V_I, V_{NI}) \in \mathbb{R}^4 : T \geq 0, T^* \geq 0, V_I \geq 0 \ \& \ V_{NI} \geq 0\}$. By simple calculation, we obtain that

$$\mathfrak{M} = \begin{bmatrix} -d_T - kV_I & 0 & -kT & 0 \\ kV_I & -\delta & kT & 0 \\ 0 & N\delta(1-\epsilon_p) & -c & 0 \\ 0 & N\delta\epsilon_p & 0 & -c \end{bmatrix}.$$

The system (2.4) satisfies the Poincare - Bendixson Property, since Γ is convex and system (2.4) is competitive in Γ. □

Now, considering that we have proved the following theorem.

Theorem 4.4.

(i) *If $\bar{\tau}$ vanishes and $\tau_1 > 0$, then the system* (2.4) *is locally asymptotically stable at the infected steady state S_i when $\tau_1 < \tau_1^*$.*

(ii) *Suppose $R_p > 1$, the following result can be obtained. The infected steady state S_i is stable when $\tau_1 \in [0, \tau_1^*)$ and unstable when $\tau_1 > \tau_1^*$. τ_1 is the Hopf Bifurcation value, which means that periodic solutions will bifurcate from this infected steady state as τ_1 passes through the critical value τ_1^**

Proof. Linearising the system of equation (2.4), about the infected steady state S_i and determining the characteristic equation by solving the following determinant,

$$\begin{vmatrix} -d_T - d_T e^{\lambda\tau_1}(R_p - 1) - \lambda & 0 & -\dfrac{ske^{m\tau_1}e^{-\lambda\tau_1}}{d_T R_p} & 0 \\ d_T e^{-m\tau}e^{-m\tau_1}e^{-\lambda\tau}(R_p - 1) & -\delta - \lambda & \dfrac{ce^{-\lambda\tau}e^{\nu\tau_2}}{N(1-\epsilon_p)} & 0 \\ 0 & N\delta(1-\epsilon_p)e^{-\nu\tau_2}e^{-\lambda\tau_2} & -c - \lambda & 0 \\ 0 & N\delta\epsilon_p e^{-\nu\tau_2}e^{-\lambda\tau_2} & 0 & -c - \lambda \end{vmatrix} = 0.$$

Thus the characteristic equation for the infected stead state is

$$\begin{aligned}&(\lambda+c)(\lambda+d_T)\left((\lambda+\delta)(\lambda+c)\delta ce^{-\lambda\bar{\tau}}\right)\\&-d_T(R_p-1)(\lambda+c)(\lambda+\delta)(\lambda+c)e^{-\lambda\tau_1}=0,\end{aligned}\tag{4.1}$$

where $\bar{\tau}=\tau+\tau_2$. For $\tau_1>0$ and $\bar{\tau}=0$ in the (4.1), we get the following equation

$$(\lambda^4+k_1\lambda^3+k_2\lambda^2+k_3\lambda+k_4)-(m_1\lambda^3+m_2\lambda^2+m_3\lambda+m_4)e^{-\lambda\tau_1}=0,\tag{4.2}$$

where,

$$\begin{aligned}k_1&=2c+d_T+\delta,\\k_2&=c^2+2cd_T+2c\delta+d_T\delta,\\k_3&=c^2d_T+c^2\delta+2c\delta d_T,\\k_4&=d_T\delta c^2,\\m_1&=\frac{d_T(R_p-1)}{\delta c},\\m_2&=\frac{d_T(R_p-1)}{\delta c}(2c+\delta),\\m_3&=\frac{d_T(R_p-1)}{\delta c}(c^2+2c\delta),\\m_4&=d_Tc(R_p-1)\delta c.\end{aligned}$$

Suppose if equation (4.2), has imaginary roots, say $\lambda=i\omega^*$ ($\omega^*>0$) is a root of (4.2), then we have

$$\begin{aligned}&((i\omega^*)^4+k_1(i\omega^*)^3+k_2(i\omega^*)^2+k_3(i\omega^*)+k_4)\\&-(m_1(i\omega^*)^3+m_2(i\omega^*)^2+m_3(i\omega^*)+m_4)e^{-i\omega^*\tau_1}=0.\end{aligned}\tag{4.3}$$

Separating the real and imaginary parts of equation (4.3), we have

$$\omega^{*4}-k_2\omega^{*2}+k_4=(m_1\omega^{*3}-m_3\omega^*)\sin(\omega^*\tau_1)-(m_2\omega^{*2}-m_4)\cos(\omega^*\tau_1)\tag{4.4}$$

and

$$k_3\omega^*-k_1\omega^{*3}=(m_1\omega^{*3}-m_3\omega^*)\cos(\omega^*\tau_1)+(m_2\omega^{*2}-m_4)\sin(\omega^*\tau_1).\tag{4.5}$$

Squaring and adding equations (4.4) and (4.5), We obtain the following equation

$$\begin{aligned}&\omega^{*8}+(k_1^2m_1^2-2k_2)\omega^{*6}+(k_2^2-m_2^2+2k_4+2m_1m_3-2k_1k_3)\omega^{*4}\\&+(2m_1m_4-m_3^2+2k_2k_4)\omega^{*2}+k_4^2+m_4^2=0.\end{aligned}\tag{4.6}$$

Substituting $\omega^{*2}=h$, in (4.6), we procure the following equation

$$F(h)=h^4+B_1h^3+B_2h^2+B_3h+B_4=0,\tag{4.7}$$

where,

$$\begin{aligned} B_1 &= k_1^2 - m_1^2 - 2k_2, \\ B_2 &= k_2^2 - A_2^2 + 2k_4 + 2m_1m_2 - 2k_1k_3, \\ B_3 &= 2m_1m_4 - m_3^2, \\ B_4 &= k_4^2 - m_4^2. \end{aligned}$$

Derivative of equation (4.7) with respect to h, is given below

$$\dot{F}(h) = 4h^3 + 3B_1h^2 + 2B_2h + B_3 = 0. \tag{4.8}$$

Since $R_p > 1$, (if $R_p < 1$, then the infected steady state is negative, which makes no sense and for $R_p = 1$, the infected steady state is same as the viral free steady state), the co- efficients of the above equation (4.8) are all positive and $\dot{F}(h) > 0$.

Now, we assume that $B_4 < 0$, by using Descartes rule of signs, equation (4.7) has positive root h and from this we come to know that equation (4.6) has a couple of purely imaginary roots $i\omega^*$. From equations (4.4) and (4.5), we examine

$$\begin{aligned} \tau_1^* = \frac{1}{\omega^*}\arccos\Bigg(&\frac{(\omega^{*4} - k_2\omega^{*2} + k_4)(m_4 - m_2\omega^{*2})}{(m_1\omega^{*3} - m_3\omega^*)^2 + (m_4 - m_2\omega^{*2})^2} \\ &+ \frac{(k_3\omega^* - k_1\omega^{*3})(m_1\omega^{*3} - m_3\omega^*)}{(m_1\omega^{*3} - m_3\omega^*)^2 + (m_4 - m_2\omega^{*2})^2}\Bigg) + \frac{2j\pi}{\omega^*}, \end{aligned}$$

where $j = 0, 1, 2, \cdots$. From the above examination, we conclude that all the roots of characteristic equation have negative real parts for any $\tau_1 \in [0, \tau_1^*)$. Here, we verify the sign $\left(\frac{dRe(\lambda)}{d\tau_1}\right)\Big|_{\tau_1=\tau_1^*}$, where sign is the signum function and $Re(\lambda)$ is the real part of P. Further, using a quantity of mathematical calculations, we are about to say that the infected steady state of model (2.4), is stable for $\tau_1 < \tau_1^*$ and Hopf bifurcation occurs when $\tau_1 = \tau_1^*$.

Here the τ_1 is the key parameter in the model that plays an effective role to define HIV-1 dynamics behaviour, so we consider τ_1 as a bifurcation parameter, to find conditions for preservation of instability or stability of the system. When τ, τ_1 and τ_2 are zero, the system (2.4) as follow,

$$\begin{aligned} \dot{T}(t) &= s - d_TT(t) - kT(t)V_I(t), \\ \dot{T^*}(t) &= kT(t)V_I(t) - \delta T^*(t), \\ \dot{V_I}(t) &= N\delta(1-\epsilon_p)T^*(t) - cV_I(t), \\ \dot{V_{NI}}(t) &= N\delta\epsilon_pT^*(t) - cV_{NI}(t). \end{aligned} \tag{4.9}$$

Let us define $\Gamma = \{(T, T^*, V_I V_{NI}) \in \mathbb{R}^4 : 0 < T(t) \leq A_1, 0 < T^*(t) \leq A_1, 0 < V_I(t) \leq A_2, 0 < V_{NI} \leq A_3\}$. Obviously Γ is convex. From Definition (4.2) and Theorem 4.3, we examined that there are no trivial periodic orbits observed for the system (2.4). Here, we will show that a positive delay τ_1 is able to destabilize the infected steady state of the model (2.4) and for $\tau_1 > 0$, we discuss the existence of bifurcating periodic solutions. We observe that the conditions for Hopf Bifurcation [11] are satisfied yielding the required periodic solutions that is $\left(\frac{dRe(\lambda)}{d\tau_1}\right)\Big|_{\tau_1=\tau_1^*} > 0$.

For the purely imaginary roots of $\lambda = i\omega_0^*$ in the characteristic equation of the infected steady state (4.2), for $\bar{\tau} = 0$ and $\tau_1 > 0$, we have

$$|P(i\omega_0^*)| = |Q(i\omega_0^*)|,$$

where, $P(\lambda) = \lambda^4 + k_1\lambda^3 + k_2\lambda^2 + k_3\lambda + k_4$ and $Q(\lambda) = m_1\lambda^3 + m_2\lambda^2 + m_3\lambda + m_4$. Differentiating (4.2) with respect to τ_1, we have the following,

$$\begin{aligned}
&\{(4\lambda^3 + 3k_1\lambda^2 + 2k_2\lambda + k_3) - e^{-\lambda\tau_1}(3m_1\lambda^2 + 2m_2\lambda + m_3) \\
&+ \tau_1 e^{-\lambda\tau_1}(m_1\lambda^3 + m_2\lambda^2 + m_3\lambda + m_4)\}\frac{d\lambda}{d\tau_1} \\
&= \lambda e^{-\lambda\tau_1}(m_1\lambda^3 + m_2\lambda^2 + m_3\lambda + m_4),
\end{aligned}$$

which implies that

$$\begin{aligned}
\left(\frac{d\lambda}{d\tau_1}\right)^{-1} &= \frac{(4\lambda^3 + 3k_1\lambda^2 + 2k_2\lambda + k_3) - e^{-\lambda\tau_1}(3m_1\lambda^2 + 2m_2\lambda + m_3)}{\lambda e^{-\lambda\tau_1}(m_1\lambda^3 + m_2\lambda^2 + m_3\lambda + m_4)} \\
&\quad + \frac{\tau_1 e^{-\lambda\tau_1}(m_1\lambda^3 + m_2\lambda^2 + m_3\lambda + m_4)}{\lambda e^{-\lambda\tau_1}(m_1\lambda^3 + m_2\lambda^2 + m_3\lambda + m_4)} \\
&= \frac{(4\lambda^3 + 3k_1\lambda^2 + 2k_2\lambda + k_3)}{\lambda e^{-\lambda\tau_1}(m_1\lambda^3 + m_2\lambda^2 + m_3\lambda + m_4)} \\
&\quad - \frac{(3m_1\lambda^2 + 2m_2\lambda + m_3)}{\lambda(m_1\lambda^3 + m_2\lambda^2 + m_3\lambda + m_4)} + \frac{\tau_1}{\lambda} \\
&= \frac{(4\lambda^3 + 3k_1\lambda^2 + 2k_2\lambda + k_3)}{\lambda(\lambda^4 + k_1\lambda^3 + k_2\lambda^2 + k_3\lambda + k_4)} \\
&\quad - \frac{(3m_1\lambda^2 + 2m_2\lambda + m_3)}{\lambda(m_1\lambda^3 + m_2\lambda^2 + m_3\lambda + m_4)} + \frac{\tau_1}{\lambda} \\
&= \frac{(3\lambda^4 + 2k_1\lambda^3 + k_2\lambda^2 - k_4)}{\lambda^2(\lambda^4 + k_1\lambda^3 + k_2\lambda^2 + k_3\lambda + k_4)} \\
&\quad - \frac{(2m_1\lambda^3 + m_2\lambda^2 - m_4)}{\lambda^2(m_1\lambda^3 + m_2\lambda^2 + m_3\lambda + m_4)} + \frac{\tau_1}{\lambda}.
\end{aligned}$$

Thus we have

$$\begin{aligned}
\Omega &= sign\left\{Re\left(\frac{(3\lambda^4+2k_1\lambda^3+k_2\lambda^2-k_4)}{\lambda^2(\lambda^4+k_1\lambda^3+k_2\lambda^2+k_3\lambda+k_4)}\right.\right.\\
&\qquad\left.\left.-\frac{(2m_1\lambda^3+m_2\lambda^2-m_4)}{\lambda^2(m_1\lambda^3+m_2\lambda^2+m_3\lambda+m_4)}+\frac{\tau_1}{\lambda}\right)\right\}_{\lambda=i\omega_0^*}\\
&= sign\left\{Re\left(\frac{(3(i\omega_0)^{*4}+2k_1(i\omega_0)^{*3}+k_2(i\omega_0)^{*2}-k_4)}{(i\omega_0)^{*2}((i\omega_0)^{*4}+k_1(i\omega_0)^{*3}+k_2(i\omega_0)^{*2}+k_3i\omega_0^*+k_4)}\right.\right.\\
&\qquad\left.\left.-\frac{(2m_1(i\omega_0)^{*3}+m_2(i\omega_0)^{*2}-m_4)}{(i\omega_0)^{*2}(m_1(i\omega_0)^{*3}+m_2(i\omega_0)^{*2}+m_3i\omega_0^*+m_4)}+\frac{\tau_1}{i\omega_0^*}\right)\right\}\\
&= sign\left\{Re\left(\frac{(3\omega_0^{*4}-k_2\omega_0^{*2}-k_4)-i2k_1\omega_0^{*3}}{\omega_0^{*2}((\omega_0^{*4}+k_2\omega_0^{*2}-k_4)+i(k_1\omega_0^{*3}-k_3\omega_0^*))}\right.\right.\\
&\qquad\left.\left.-\frac{(m_2\omega_0^{*2}+m_4)-i2m_1\omega_0^{*3}}{\omega_0^{*2}((m_4-m_2\omega^{*2})+i(m_3\omega_0^*-m_1\omega_0^{*3}))}+\frac{\tau_1}{i\omega_0^*}\right)\right\}\\
&= \frac{1}{\omega_0^{*2}}sign\left\{\frac{(k_4+k_2\omega_0^{*2}+3\omega_0^{*4})(\omega_0^{*4}+k_2\omega_0^{*2}-k_4)+2k_1\omega_0^{*3}(k_1\omega_0^{*3}-k_3\omega_0^*)}{(\omega_0^{*4}+k_2\omega_0^{*2}-k_4)^2+(k_1\omega_0^{*3}-k_3\omega_0^*)^2}\right.\\
&\qquad\left.+\frac{(m_2\omega_0^{*2}+m_4)(m_2\omega_0^{*2}-m_4)+2m_1\omega_0^{*3}(m3\omega_0^*-m_1\omega_0^{*3})}{(m_4-m_2\omega_0^{*2})^2+(m_3\omega_0^*-m_1\omega_0^{*3})^2}\right\}\\
&= \frac{1}{\omega_0^{*2}}sign\left\{\frac{(k_4+k_2\omega_0^{*2}+3\omega_0^{*4})(\omega_0^{*4}+k_2\omega_0^{*2}-k_4)+2k_1\omega_0^{*3}(k_1\omega_0^{*3}-k_3\omega_0^*)}{(m_4-m_2\omega_0^{*2})^2+(m_3\omega_0^*-m_1\omega_0^{*3})^2}\right.\\
&\qquad\left.+\frac{(m_2\omega_0^{*2}+m_4)(m_2\omega_0^{*2}-m_4)+2m_1\omega_0^{*3}(m3\omega_0^*-m_1\omega_0^{*3})}{(m_4-m_2\omega_0^{*2})^2+(m_3\omega_0^*-m_1\omega_0^{*3})^2}\right\}\\
&= \frac{1}{\omega_0^{*2}}sign\left\{\frac{3\omega_0^{*8}+(2m_1^2-2k_1^2)\omega_0^{*6}+(m_2^2+2k_1k_3-k_1^2-k_4-2m_1m_3)\omega_0^{*4}}{(m_4-m_2\omega_0^{*2})^2+(m_3\omega_0^*-m_1\omega_0^{*3})^2}\right.\\
&\qquad\left.+\frac{(m_1m_2+m_2m_4-k_2k_4)\omega_0^{*2}+k_4^2+m_4^2}{(m_4-m_2\omega_0^{*2})^2+(m_3\omega_0^*-m_1\omega_0^{*3})^2}\right\}
\end{aligned}$$

and this determines a set of possible eigenvalues of ω_0^*. We focused to determine the direction of motion of λ as τ_1 is varied, that is, we examined that

$$\Omega = sign\left\{\left(\frac{dRe(\lambda)}{d\tau_1}\right)\right\}_{\tau_1=i\omega_0^*} = sign\left\{Re\left(\frac{d(\lambda)}{d\tau_1}\right)^{-1}\right\}_{\tau_1=i\omega_0^*}.$$

As $2m_1^2-2k_1^2$, $m_2^2+2k_1k_3-k_1^2-k_4-2m_1m_3$, $m_1m_2+m_2m_4-k_2k_4$ and $k_4^2+m_4^2$ are positive by virtue of equation (4.6), we have $\left(\frac{dRe(\lambda)}{d\tau_1}\right)\Big|_{\omega^*=\omega_0^*,\tau_1=\tau_1^*} > 0$. Thus, the solution curve of the characteristic equation (4.6) crosses the

imaginary axis. This shows that a Hopf Bifurcation occurs at $0 < \tau_1 = \tau_1^*$. By continuity the infected steady state is locally asymptotically stable when $\tau_1 < \tau_1^*$. □

5. Optimal control of HIV protease inhibitor model

We consider the mathematical model for HIV-1 infection with protease inhibitors and intracellular delay. The dynamics of this model are governed by the equations in the system (2.4).

We introduce the controls u_1 and u_2 which measure the efficiency of infected target cells and protease inhibitors. Hence, (2.4) becomes,

$$\begin{aligned} \dot{T}(t) &= s - d_T T(t) - (1-u_1(t))ke^{-m\tau_1}T(t-\tau_1)V_I(t-\tau_1), \\ \dot{T^*}(t) &= (1-u_1(t))ke^{-m\tau}T(t-\tau)V_I(t-\tau) - \delta T^*(t), \\ \dot{V}_I(t) &= (1-u_2(t))N\delta(1-\epsilon_p)e^{-\nu\tau_2}T^*(t-\tau_2) - cV_I(t), \\ \dot{V}_{NI}(t) &= (1-u_2(t))N\delta\epsilon_p e^{-\nu\tau_2}T^*(t-\tau_2) - cV_{NI}(t). \end{aligned} \tag{5.1}$$

The control functions, $u_1(t)$ and $u_2(t)$ are bounded, Lebesgue integrable functions. The control $u_2(t)$ represents the efficiency of drug therapy in inhibiting viral production, such that the virion production rate under therapy are $(1-u_2(t))N\delta(1-\epsilon_p)$ and $(1-u_2(t))N\delta\epsilon_p$ for infectious and non-infectious virus particles respectively.

If $u_2 = 1$, the inhibition is 100% effective, whereas if $u_2 = 0$, there is no inhibition.

The control $u_1(t)$ represents the efficiency of drug therapy in blocking new infection, so that infection rate in the presence of drug is $(1-u_1(t))k$.

Let $C = C([-\tau_{max}, 0], \mathbb{R}^4)$ be the Banach space of continuous functions, from interval $[-\tau_{max}, 0]$ into $\mathbb{R}^4$ with the topology of uniform convergence, where $\tau_{max} = \max\{\tau, \tau_1, \tau_2\}$. It is easy to show that there exists a unique solution $(T(t), T^*(t), V_I(t), V_{NI}(t))$ of system (5.1) with initial data $(T^0, T^{*0}, {V_I}^0, {V_{NI}}^0) \in C$.

In addition, for biological reasons, we assume that the initial data for system (5.1) satisfy

$$T^0(s) \geq 0,\ T^{*0}(s) \geq 0,\ {V_I}^0(s) \geq 0,\ {V_{NI}}^0(s) \geq 0, \quad s \in [-\tau_{max}, 0]. \tag{5.2}$$

5.1. **The optimal control problems.** The problem is to maximize the objective functional

$$J(u_1, u_2) = \int_{t_0}^{t_f} \left\{ T(t) + V_I(t) - \left[\frac{L_1}{2}u_1^2(t) + \frac{L_2}{2}u_2^2(t) \right] \right\}, \tag{5.3}$$

where the parameters $L_1 \geq 0$ and $L_2 \geq 0$ are based on the benefits and costs of the treatment. Our target is to maximize the objective functional defined

in (5.3) by increasing the number of the uninfected cells, maximizing the efficacy of the protease inhibitors which prevents the virus becomes productively infectious, decreasing the viral load, and minimizing the cost of treatment. In other words, we are seeking optimal control pair (u_1^*, u_2^*) such that

$$J(u_1^*, u_2^*) = \max\{J(u_1, u_2) : (u_1, u_2) \in U\}, \tag{5.4}$$

where U is the control set defined by

$$U = \{u = (u_1, u_2) : u_i \text{ measurable}, \ 0 \le u_i(t) \le 1, t \in [0, t_f], i = 1, 2\}. \tag{5.5}$$

5.1.1. **Existence of optimal control pair.** The existence of the optimal control pair can be obtained using a result by Fleming and Rishel [7] and Lukes [20].

Theorem 5.1. *There exists an optimal control pair* $(u_1^*, u_2^*) \in U$ *such that*

$$J(u_1^*, u_2^*) = \max_{(u_1,u_2)\in U} J(u_1, u_2). \tag{5.6}$$

Proof. To use an existence result in [14], we must check the following properties.

(1) The set of controls and corresponding state variables is nonempty.
(2) The control set U is convex and closed.
(3) The right-hand side of the state system is bounded by a linear function in the state and control variables.
(4) The integrand of the objective functional is concave on U.
(5) There exists constants $c_1, c_2 > 0$, and $\beta > 1$ such that the integrand $L(T, V_I, u_1, u_2)$ of the objective functional satisfies

$$L(T, V_I, u_1, u_2) \le c_2 - c_1 \left(|u_1|^2 + |u_2|^2\right)^{\beta/2}. \tag{5.7}$$

In order to verify these conditions, we use a result by Lukes [20] to give the existence of solutions of system (5.3) with bounded coefficients, which gives condition (1). We note that the solutions are bounded. Our control set satisfies condition (2). Since our state system is bilinear in u_1, u_2, the right hand side of system satisfies condition (3), using the boundedness of the solutions. Note that the integrand of our objective functional is concave.

Also we have the last condition needed

$$L(T, V_I, u_1, u_2) \le c_2 - c_1 \left(|u_1|^2 + |u_2|^2\right), \tag{5.8}$$

where c_2 depends on the upper bound on T and V_I, and $c_1 > 0$. Since $M_1, M_2 > 0$, we conclude that there exists an optimal control pair. □

5.2. **Optimality system.** Pontryagins minimum principle with delay given in [9] provides necessary conditions for an optimal control problem. This principle converts (2.4), (5.3) and (5.4) into a problem of maximizing an Hamiltonian H with

$$\begin{aligned}
&H(t,T,T^*,V_I,V_{NI},T_\tau,V_{I(\tau)},T_{\tau_1},V_{I(\tau_1)},T^*_{\tau_2},u_1,u_2,\lambda)\\
&=\frac{L_1}{2}u_1^2+\frac{L_2}{2}u_2^2-T-V_I\\
&\quad+\lambda_1[s-d_TT-(1-u_1)ke^{-m\tau_1}T_{\tau_1}V_{I(\tau_1)}]\\
&\quad+\lambda_2[(1-u_1)ke^{-m\tau}T_\tau V_{I(\tau)}-\delta T^*]\\
&\quad+\lambda_3[(1-u_2)N\delta e^{-\nu\tau_2}(1-\epsilon_p)T^*_{\tau_2}-cV_I]\\
&\quad+\lambda_4[(1-u_2)N\delta e^{-\nu\tau_2}\epsilon_pT^*_{\tau_2}-cV_{NI}].
\end{aligned}$$

By applying Pontryagins minimum principle with delay in state [9], we obtain the following theorem.

Theorem 5.2. *Given optimal controls u_1^*,u_2^* and solutions $\bar{T},\bar{T}^*,\bar{V}_I$ and $\bar{V}_{NI}$ of the corresponding state system* (5.1)*, there exists adjoint variables, $\lambda_1,\lambda_2,\lambda_3$ and λ_4 satisfying the equations*

$$\begin{aligned}
\lambda_1'(t) &= 1+\lambda_1(t)d_T+ke^{-m\tau_1}\chi_{[0,t_f-\tau_1]}(t)\lambda_1(t+\tau_1)(u_1(t+\tau_1)-1)\bar{V}_I(t)\\
&\quad -ke^{-m\tau}\chi_{[0,t_f-\tau]}(t)\lambda_2(t+\tau)(u_1(t+\tau)-1)\bar{V}_I(t),\\
\lambda_2'(t) &= -\chi_{[0,t_f-\tau_2]}(t)[\lambda_3N\delta(1-\epsilon_p)e^{-\nu\tau_2}(u_2(t+\tau_2)-1)\\
&\quad +\lambda_4(t)N\delta\epsilon_pe^{-\nu\tau_2}(u_2(t+\tau_2)-1)],\\
\lambda_3'(t) &= 1+ke^{-m\tau_1}\chi_{[0,t_f-\tau_1]}(t)\lambda_1(t+\tau_1)(u_1(t+\tau_1)-1)\bar{T}(t)\\
&\quad -ke^{-m\tau}\chi_{[0,t_f-\tau]}(t)\lambda_2(t+\tau)(u_1(t+\tau)-1)\bar{T}(t)+c\lambda_3(t),\\
\lambda_4'(t) &= c\lambda_4(t),
\end{aligned}\tag{5.9}$$

with transversality condition

$$\lambda_i(t_f)=0,\ i=1,\cdots,4.$$

Moreover, the optimal control is given by

$$\begin{aligned}
u_1^*(t) &= \min\left(1,\max\left(0,\frac{k}{L_1}\left[\lambda_2(t)e^{-m\tau}\bar{T}(t-\tau)\bar{V}_I(t-\tau)\right.\right.\right.\\
&\qquad\left.\left.\left.-\lambda_1(t)e^{-m\tau_1}\bar{T}(t-\tau_1)\bar{V}_I(t-\tau_1)\right]\right)\right),\\
u_2^*(t) &= \min\left(1,\max\left(0,\frac{N\delta}{L_2}\left[e^{-\nu\tau_2}\bar{T}^*(t-\tau_2)((1-\epsilon_p)\lambda_3(t)+\epsilon_p\lambda_4)\right]\right)\right).
\end{aligned}\tag{5.10}$$

Proof. The adjoint equations and transversality conditions can be obtained by using Pontryagins minimum principle with delay in state [9] such that

$$\begin{aligned}
\lambda_1'(t) &= -\frac{\partial H}{\partial T}(t) - \chi_{[0,t_f-\tau]}(t)\frac{\partial H}{\partial T_\tau}(t+\tau) \\
&\quad -\chi_{[0,t_f-\tau_1]}(t)\frac{\partial H}{\partial T_{\tau_1}}(t+\tau_1), \lambda_1(t_f) = 0, \\
\lambda_2'(t) &= -\frac{\partial H}{\partial T^*}(t) - \chi_{[0,t_f-\tau_2]}(t)\frac{\partial H}{\partial T^*_{\tau_2}}(t+\tau_2), \lambda_2(t_f) = 0, \\
\lambda_3'(t) &= -\frac{\partial H}{\partial V_I}(t) - \chi_{[0,t_f-\tau]}(t)\frac{\partial H}{\partial V_{I(\tau)}}(t+\tau) \\
&\quad -\chi_{[0,t_f-\tau_1]}(t)\frac{\partial H}{\partial V_{I(\tau_1)}}(t+\tau_1), \lambda_3(t_f) = 0, \\
\lambda_4'(t) &= -\frac{\partial H}{\partial V_{NI}}(t), \lambda_4(t_f) = 0. \qquad (5.11)
\end{aligned}$$

The optimal control u_1^* and u_2^* can be solved from the optimality conditions

$$\frac{\partial H}{\partial u_1} = 0, \qquad \frac{\partial H}{\partial u_2} = 0, \qquad (5.12)$$

which implies that

$$\begin{aligned}
\frac{\partial H}{\partial u_1} &= L_1 u_1 + k e^{-m\tau_1}\lambda_1 T(t-\tau)V_I(t-\tau) + k e^{-m\tau}\lambda_2 T(t-\tau_1)V_I(t-\tau_1) \\
&= 0, \\
\frac{\partial H}{\partial u_2} &= L_2 u_2 - \lambda_3 N\delta e^{-\nu\tau_2}(1-\epsilon_p)T^*(t-\tau_2) - \lambda_4 N\delta e^{-\nu\tau_2}\epsilon_p T^*(t-\tau_2) \\
&= 0. \qquad (5.13)
\end{aligned}$$

By the bounds in U of the controls, it is easy to obtain u_1^* and u_2^* in the form of (5.11), respectively.

Suppose if we substitute u_1^* and u_2^* in the system (2.4) and (5.9), we obtain the following optimality system

$$\begin{aligned}
\dot{T}^{\#}(t) &= s - d_T T^{\#}(t) - (1-u_1^*(t))k e^{-m\tau_1}T^{\#}(t-\tau_1)V_I^{\#}(t-\tau_1), \\
\dot{T^*}^{\#}(t) &= (1-u_1^*(t))k e^{-m\tau}T^{\#}(t-\tau)V_I^{\#}(t-\tau) - \delta T^{*\#}(t), \\
\dot{V}_I^{\#}(t) &= (1-u_2^*(t))N\delta(1-\epsilon_p)e^{-\nu\tau_2}T^{*\#}(t-\tau_2) - cV_I^{\#}(t), \\
\dot{V}_{NI}^{\#}(t) &= (1-u_2^*(t))N\delta\epsilon_p e^{-\nu\tau_2}T^{*\#}(t-\tau_2) - cV_{NI}^{\#}(t),
\end{aligned}$$

$$
\begin{aligned}
\lambda_1'(t) &= 1+\lambda_1(t)d_T+ke^{-m\tau_1}\chi_{[0,t_f-\tau_1]}(t)\lambda_1(t+\tau_1)(u_1(t+\tau_1)-1)\bar{V}_I(t)\\
&\quad -ke^{-m\tau}\chi_{[0,t_f-\tau]}(t)\lambda_2(t+\tau)(u_1(t+\tau)-1)\bar{V}_I(t),\\
\lambda_2'(t) &= -\chi_{[0,t_f-\tau_2]}(t)[\lambda_3 N\delta(1-\epsilon_p)e^{-\nu\tau_2}(u_2(t+\tau_2)-1)\\
&\quad +\lambda_4(t)N\delta\epsilon_p e^{-\nu\tau_2}(u_2(t+\tau_2)-1)],\\
\lambda_3'(t) &= 1+ke^{-m\tau_1}\chi_{[0,t_f-\tau_1]}(t)\lambda_1(t+\tau_1)(u_1(t+\tau_1)-1)\bar{T}(t)\\
&\quad -ke^{-m\tau}\chi_{[0,t_f-\tau]}(t)\lambda_2(t+\tau)(u_1(t+\tau)-1)\bar{T}(t)+c\lambda_3(t),\\
\lambda_4'(t) &= c\lambda_4(t),\\
u_1^*(t) &= \min\left(1,\max\left(0,\frac{k}{L_1}[\lambda_2(t)e^{-m\tau}\bar{T}(t-\tau)\bar{V}_I(t-\tau)\right.\right.\\
&\qquad \left.\left.-\lambda_1(t)e^{-m\tau_1}\bar{T}(t-\tau_1)\bar{V}_I(t-\tau_1)]\right)\right),\\
u_2^*(t) &= \min\left(1,\max\left(0,\frac{N\delta}{L_2}\left[e^{-\nu\tau_2}\bar{T}^*(t-\tau_2)((1-\epsilon_p)\lambda_3(t)+\epsilon_p\lambda_4)\right]\right)\right),\\
\lambda_i(t_f) &= 0,\ i=1,\cdots,4. \qquad (5.14)
\end{aligned}
$$

□

6. Conclusion

In this article, we pondered HIV protease inhibitor model with three intracellular delays. By a pedantic analysis, we have examined that the model has a threshold dynamics. In [23], the two positive steady states of the model thus considered was derived and named as viral free steady states and infected steady state accordingly. Also, the local stability analysis of model about these steady states are accomplished. But, in the case of infected steady state, an analysis for $\bar{\tau}=0$, where $\bar{\tau}=\tau+\tau_2$ and $\tau_1\neq 0$ is left undone. Thus, in this article we incorporated the study of thus case and by the result, the delay τ_1 as a bifurcation parameter, a sufficient condition is derived for the infected steady state. By this, we have obtained that τ_1, the delay corresponding to the loss of target cells,has effect on the infected steady state of model (2.4), to stabilize the system under a small delay in the loss of target cells and leads to Hopf bifurcation with small level of delay value. In the optimal control section, we gave a delay mathematical model with two controls that describe HIV infection with Protease inhibitor during therapy. Currently, there is no effective therapy for HIV infection and the cost of treatment is beyond reach of many infected patients. Hence, we presented an optimal therapy in order to minimize the cost of treatment, reduce the viral load, and improve the therapy response.

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References

[1] R.M. Anderson, *The role of mathematical models in the study of HIV transmission and the epidemiology of AIDS*, J. Acquired Immune Deficiency Syndromes, **1** (1988), 241-256.

[2] S.H. Bajaria, G. Webb, M. Cloyd and D. Kirschner, *Dynamics of naive and memory CD4+T lymphocytes in HIV-1 disease progression*, J. Acquired Immune Deficiency Syndromes, **30** (2002), 41-58.

[3] R. Bellman and K.L. Cooke, *Differential-Difference Equations*, Academic Press, New York. 1963.

[4] M. Divya and M. Pitchaimani, *An Analysis of the delay dependent HIV -1 Protease Inhibitor model*, Inter. J. Biomath., **11**(3) (2018), 1850031.

[5] N.M. Dixit and A.S. Perelson, *Complex patterns of viral load decay under antiretroviral therapy: influence of pharmacokinetics and intracellular delay*, J. Theor. Biol. **226** (1) (2004), 95109.

[6] K. Fister and J. Donnelly, *Immunotherapy: An optimal control theory approach,* Mathe. Biosciences and Eng., **2** (2005), 499-510.

[7] W.H. Fleming and R.W. Rishel, *Deterministic and Stochastic Optimal Control*, Springer, New York, USA, 1975.

[8] H. Gaff and E. Schaefer, *Optimal control applied to vaccination and treatment strategies for various epidemiological models*, Math. Biosciences and Eng., **6** (2009), 469-492.

[9] L. Gollmann, D. Kern and H. Maurer, *Optimal control problems with delays in state and control variables subject to mixed control-state constraints*, Opti. Cont. Appl. and Methods, **30**(4) (2009), 341-365.

[10] J. Hale and H. Koak, *Dynamics and Bifurcations*, Springer-Verlag, 1991.

[11] J. Hale and S.V. Lunel, *Introduction to Functional Differential Equations*, Springer, NewYork, 1993.

[12] J.M. Hyman and E.A. Stanley, *Using mathematical models to understand the AIDS epidemic*, Math. Bioscience, **90** (1988), 415-473.

[13] H.R. Joshi, *Optimal control of an HIV immunology model*, Opti. Cont. Appl. and Methods, **23** (2002), 199-213.

[14] H.R. Joshi, *Optimal Control Problems in PDE and ODE Systems*, Thesis of Doctorate, University of Tennessee, USA, 2002.

[15] D. Kirschner, S. Lenhart and S. Serbin, *Opti. Cont. of Chemotherapy of HIV*, J. of Math.l Biology, **35** (1997), 775-792.

[16] Y. Kuang, *Delay Differential Equations with Population Dynamics*, Academic press, Boston, 1993.

[17] J.J. Kutch and P. Gurfil, *Optimal control of HIV infection with a continuously-mutating viral population*, Proc. Amer. Cont. Conference Anchorage, 2002.

[18] Y. A. Kuznetsov, *Elements of Applied Bifurcation Theory*, Springer-Verlag, 2004.

[19] S. Lenhart and J. Wortman, *Optimal control applied to biological models,* Taylor and Francis, Boca Raton, 2007.

[20] D. L. Lukes, *Differential Equations: Classical To Controlled*, Math. in Science and Eng., Academic Press, New York, USA, **162**, 1982.

[21] C. McCluskey, *A model of HIV/AIDS with staged progression and amelioration*, Math. Bioscience, **181** (2003), 1-16.
[22] A.S. Perelson, *Modelling viral and immune system dynamics*, Nat. Rev. Immunol., **2** (2002), 2836.
[23] M. Pitchaimani, C. Monica and M. Divya, *Stability analysis for HIV infection delay model with protease inhibitor*, Biosystems, **114**(2) (2013), 118-124.
[24] M.A. Stafford, L. Corey, Y. Cao, E.S. Daar, D.D. Ho and A.S. Perelson, *Modeling plasma virus concentration during primary HIV infection*, J. Theor. Biol. **203** (2000), 285301.
[25] Steven H. Strogatz, *Nonlinear Dynamics and Chaos*, Addison Wesley, 1994.
[26] D. Tully, *Optimizing Chemotherapy in an HIV Model*, College of the Redwoods, Springer, 1999.
[27] W. Wang, *Global behavior of an SEIRS epidermic model with time delay*, Appl. Math. Letters, **15** (2002), 423-428.
[28] X. Xia, *Estimation of HIV/AIDS parameters*, Automatica, **39**(11) (2003), 1983-1988.