A mathematical model for the control of HIV infection - An optimal control approach

Jayanta Mondal, Priti Kumar Roy, Fahad Al Basir

***Abstract*—** In this research article, we proposed a mathematical model for HIV infection with an aim to control the disease using combined drugs namely reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs). We incorporate two control parameters into the model representing the two drugs and find the optimal treatment strategy using Pontryagin minimum principle that will produce maximum uninfected cells and minimum viral load with a minimum dose of drug therapies to prevent harmful effects associated with excessive use of drugs in the body. Numerical simulation of the nonlinear model has confirmed our analytical studies.

***Keywords*—** HIV-1, CD4 T cells, CTL response cells, Reverse transcriptase inhibitors (RTIs), Protease inhibitors (PIs), Mathematical modeling, Stability theory, Optimal control theory.

I. Introduction

AIDS has developed into a global pandemic since the first patients were identified in 1981. It is reported that 38.6 million people currently live with HIV-1 infection, 4.1 million people have been newly infected and 2.8 million AIDS deaths occurred in 2005. Virus number in the blood is a major indicator of the disease stages. Sometimes these stages are meant to correspond to CD4C T-cell count ranges [1, 2].

Mathematical modeling and analysis of virus dynamics can be helpful to develop treatment strategies for infections and to provide insights on evaluating an effective antiviral drug therapy to clear viruses from the human body [3, 4, 5, 6]. Public awareness through media is equali important to prevent the disease [18]. Several authors have devoted their efforts in studying the dynamics of mathematical models which describe the dynamics of virus population in vivo, including human immunodeficiency virus (HIV) [7].

Mathematical models involving optimal control therapies of HAART and IL-2, include those by Stengel [3]. Blower shows that incidence rates of HIV will fall as more HIV-positive individuals gain access to treatment, but the underlying assumption is that treated individuals would change their behavior and the levels of risky behavior do not increase [9]. Bachar and Dorfmayr showed that treatment without reduction of risky behavior may even increase the proportion of infected individuals [8]. Treatment increases the expected available time for the transmission of HIV [11]. Although HIV is not yet curable, there are antiretroviral drugs that help in boosting the immune system against cell infections. These antiretroviral drugs are categorized into two groups which are reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs). RTIs disrupt the conversion of RNA of the virus to DNA so that new HIV infection of cells is prevented [10]. On the other hand, PIs hinder the production of the virus particles by the actively infected CD4+T cells [12, 17]. (RTIs), Protease inhibitors (PIs) as a combined therapy on HIV infection by proposing a mathematical model. Pontryagin minimum principle is adopted for the cost effectiveness and excess use of the drugs. We finally fulfil the analytical results with numerical simulations.

It is well known now that HAART therapies can effectively control the HIV replication to undetectable levels, unless treatment is disrupted or drug resistance occurs. It is also well known that Reverse Transcriptase Inhibitors (RTI) could block new infection and as a result control HIV infection. Optimal control chemotherapy through RTI is very much needed and the present investigation will shed some light in this direction [13, 19].

In this research article, we have studied the effect of Reverse transcriptase inhibitors (RTIs), Protease inhibitors (PIs) as a combined therapy on HIV infection by proposing a mathematical model. Pontryagin minimum principle is adopted for the cost effectiveness and excess use of the drugs. We finally fulfil the analytical results with numerical simulations.

II. The Mathematical Model

In our model, where $T(t)$ represents the concentration of susceptible $CD4^+T$ cells at time t, $T^*(t)$ represents the concentration of infected $CD4^+T$ cells at time t, $V(t)$ represents the concentration of free HIV Virus at time t and $Z(t)$ represents the concentration of immune

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response $(CTLs)$ at time t. The following system is proposed for HIV infection:

$$\begin{aligned}
\frac{dT}{dt} &= \lambda + r_1 T(1-\frac{T+T^*}{T_m}) - aT - kVT,\\
\frac{dT^*}{dt} &= kVT + r_2 T^*(1-\frac{T+T^*}{T_m}) - dT^*\\
&\quad -\delta T^* Z,\\
\frac{dV}{dt} &= NdT^* + \frac{\alpha V}{b+V} - \varepsilon V,\\
\frac{dZ}{dt} &= \frac{\beta T^* Z}{1+V} - cZ.
\end{aligned} \tag{1}$$

with $T(0)>0, T^*(0)>0, V(0)>0, Z(0)>0$.

Here, λ is denotes the body to believed to produce susceptible $CD4^+T$ cells from precursors in the bone marrow and thymus at a constant rate, susceptible $CD4^+T$ cells have natural turn-over rate a, r_1 be the growth rate of $CD4^+T$ cells, T_m is the carrying capacity of $CD4^+T$ cells.

The parameter k represents the rate of infection of $CD4^+T$ cells with free virus, d is the natural death rate of infected $CD4^+T$ cells r_2 be the growth rate of infected T cells, the clearance rate of infected cells by CTLs is δ, each infected $CD4^+T$ cell is assumed to produce N virus particles during its life time, including any of its daughter cells. The term in the third equation $\frac{\alpha V}{b+V}$ represents growth of virus from other infected cells such as macrophages and infected thymocytes. It should be noted here that the growth rate of external viral source other than T cells is α and half saturation constant of external viral source is b. Clarence rate of virus is denoted by ε and the rate of CTL proliferation in response to antigen due to presence of virus is given by $\frac{\beta T^* Z}{1+T^*}$ from where β is the proliferation rate and the natural death rate of CTLs is c.

A. Equilibrium and stability analysis

In this section, we only consider positive equilibriums of the system and there stability.

1) Equilibria

The system (1) with the initial condition possesses the following positive equilibrium: the disease free equilibrium, $E_0(T_0,0,0,0)$, and the endemic equilibrium, $E^*(T_2,T_2^*,V_2,Z_2)$, where

$$T_0 = \frac{T_m(r-a)+\sqrt{(T_m(r-a))^2+4r\lambda T_m}}{\beta-c}$$

and

$$\begin{aligned}
T_2 &= \frac{-(aT_m - r_1T_m + kV_2)+\eta}{2r_1},\\
\eta &= \sqrt{(aT_m - r_1T_m + kV_2)^2 + 4r_1\lambda}\\
V_2 &= \frac{\varepsilon b-\alpha+\sqrt{(\varepsilon b-\alpha)^2+4\varepsilon NdT_2^*}}{2\varepsilon} \quad (1)\\
Z_2 &= \frac{T_m(\alpha kV_2T_2 - dT_2) + r_2T^*(T_m - T_2 - T_2^*)}{\delta T_m T_2^*}\\
T_2^* &= \frac{c}{\beta-c}
\end{aligned} \tag{2}$$

2) Local stability analysis

The Jacobian matrix of system (1) at $E_0 = (T_0,0,0,0)$ is given by:

$$J(E_0) = \begin{pmatrix}
e_{11} & -\frac{rT_0}{T_m} & -kT_0 & 0\\
0 & r_2 - d - \frac{r_2T_0}{T_m} & kT_0 & 0\\
0 & Nd & \frac{\alpha}{b}-\varepsilon & 0\\
0 & 0 & 0 & -c
\end{pmatrix},$$

with $e_{11} = r_1(1-\frac{2T_0}{T_m}) - a$.

All the roots of the characteristic equation at E_0 will be negative if

$$\begin{aligned}
&(\alpha - b\varepsilon)[r_2(1-T_0/T_m) - d] - kNbdT_0 < 0,\\
&\text{and} \quad r_1(1-2T_0/T_m) - a < 0.
\end{aligned} \tag{3}$$

Thus we have the following theorem:

Theorem 1 *The disease free system is stable if the conditions given in (3) are satisfied.*

Again, the system (1) is locally asymptotically stable around $E*$ if Routh-Hurwitz criterion is established. The Jacobian matrix at E^* is given by:

$$B=[b_{ij}]=\begin{pmatrix} b_{11} & -\frac{r_1T_2}{T_m} & -kT_2 & 0 \\ kV_2 & b_{22} & kT_2 & -\delta T_2^* \\ 0 & Nd & b_{33} & 0 \\ 0 & b_{42} & 0 & 0 \end{pmatrix},$$

with

$$b_{11}=r_1-a-2r_1T_2/T_m-r_1T_2^*/T_m-kV_2,$$

$$b_{22}=r_2-d-2r_2T_2^*/T_m-\frac{r_2}{T_m}T_2-\delta Z_2, \text{ and}$$

$$b_{42}=\frac{\beta Z_2}{1+T^*}-\frac{\beta T_2^*Z_2}{(1+T_2^*)^2}, b_{33}=\frac{\alpha b}{(b+V_2)^2}-\varepsilon.$$

The characteristic equation of system (1) corresponding to E^* is given by

$$\xi^4+A_1\xi^3+A_2\xi^2+A_3\xi+A_4=0, \quad (3)$$

where,

$$A_1=b_{11}+b_{22}+b_{33},$$

$$A_2=b_{11}b_{22}+b_{11}b_{33}+b_{22}b_{33}+b_{42}+kT_2(Nd-r_1V_2T_2/T_m),$$

$$A_3=b_{11}b_{22}b_{33}+b_{11}b_{42}+b_{33}b_{42}+kV_2T_2TT_2Nd(kV-b_{11})+kVT_2r_1b_{33}TT_2/T_m-\delta NdT^*T_2T_2b_{43},$$

$$A_4=b_{11}(b_{33}b_{42}-\delta T^*T_2Ndb_{43}).$$

According to Routh-Hurwitz criterion, E^* is stable if

$$A_1>0, A_4>0, \quad A_1A_2-A_3>0,$$

and $$A_1A_2A_3-A_3^2-A_4A_1^2>0. \quad (4)$$

The result can be summarised as below.

Theorem 2 *The endemic equilibrium E^* is stable if the conditions given in (4) are satisfied.*

Table 1: Variables and parameters used in the numerical simulations [14, 15].

Parameters	Definition	Values
λ	Constant rate of production rate of CD4+Tcells	12
r_1	Growth rate of healthy CD4+Tcells	0.05
r_1	Growth rate of infected $CD4^+T$ Cells	0.02
a	Death rate of Uninfected CD4+Tcells	0.01
k	Contact rate of Uninfected CD4+Tcells and virus	0.00024
d	Death rate of infected cells	0.1
δ	Killing rate of infected cells	0.01
N	Rate of simulation of virus	500
c	Death rate of CTL	0.05
α	Growth rate of virus from external source	0.2
b	Half saturation constant	15
T_m	Carrying capacity of $CD4^+$ T cells	1200

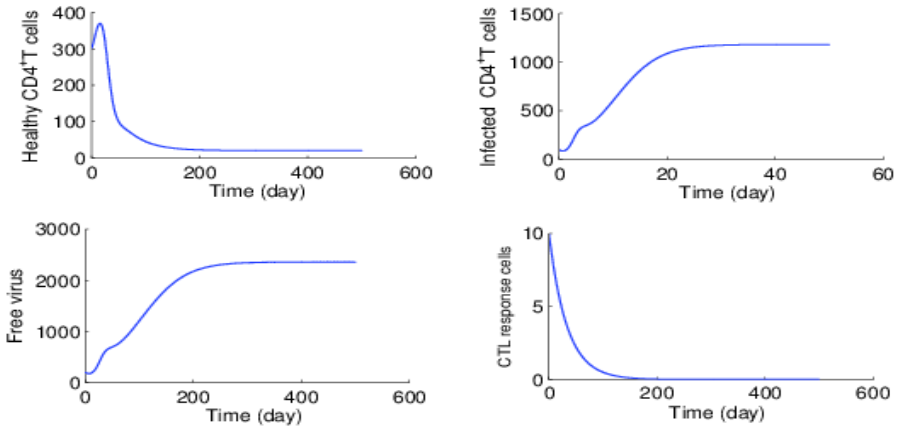

Figure 1: Time series solution of the system without drugs, taking the parameters values from Table 1.

III. Optimal control problem

Here we formulate the problem as an optimal control problem.considering u_1 and u_2 are the control parameter represent the drugs. The system with drug can be describe with the following equations:

$$\begin{aligned}
\frac{dT}{dt} &= \lambda + r_1 T(1-\frac{T+T^*}{T_m}) \\
&\quad - aT - (1-u_1)kVT, \\
\frac{dT^*}{dt} &= (1-u_1)kVT + r_2 T^*(1-\frac{T+T^*}{T_m}) \\
&\quad - dT^* - \delta T^* Z \\
\frac{dV}{dt} &= (1-u_2)NdT^* + \frac{\alpha V}{b+V} - \varepsilon V \\
\frac{dZ}{dt} &= \frac{\beta T^* Z}{1+T^*} - cZ.
\end{aligned} \tag{5}$$

We want to maximize uninfected $CD4^+T$ cells and minimize free virus. Thus together with the state system (5), we consider an optimal control problem with the objective function given by

$$J(u) = \int_{t_i}^{t_f} [T^{*2}(t) - T^2(t) + Pu_1^2(t) + Qu_2^2(t)]dt. \tag{6}$$

The systematic cost of the drug treatment is represented by the term $Pu_1^2(t) + Qu_2^2(t)$.

Here, the objective is to find the optimal control pair $u^*(t) = (u_1(t), u_2(t))$ such that

$$\begin{aligned}
&J(u_1^*, u_2^*) = \min\,(J(u_1, u_2) : (u_1, u_2) \in U) \\
&where\ \ U = U_1 \times U_2,
\end{aligned}$$

$$\begin{aligned}
&U_1 = (u_1(t) : u_1 \ is\ measurable\ and \\
&0 \le u_1 \le 1, t \in [t_i, t_f]) \ and \\
&U_2 = (u_2(t) : u_2 \ is\ measurable\ and \\
&0 \le u_2 \le 1, t \in [t_i, t_f]).
\end{aligned}$$

Here Pontryagin Minimum Principle [16] has been used to find the optimal control pair $(u_1^*(t), u_1^*(t))$.

Note that The two control functions u_1 and u_2 are bounded Lebesgue integrable functions. The control u_1 denotes the efficacy of drug therapy in blocking the infection of new cells, and the control u_2 denotes the efficacy of drug therapy in inhibiting the production of virus. If, for instance, $u_i = 1, i = 1,2$ the blockage is 100% effective and if $u_i = 0$, then there is no blockage.

We try to find out an optimal control pair $u^* = (u_1^*, u_2^*)$, such that

$$J(u^*) = \min\{J(u)/u \in U\}$$

We apply Pontryagin's Minimum Principle [16] to determine the specific optimal control u^* of our problem. To do this, we start by defining a Hamiltonian. The Hamiltonian for our problem consists of the integrand of the cost functional and the right hand side of the state equations through the adjoint variables $\xi_1, \xi_2, \xi_3, \xi_4$, penalty multipliers P, Q.

The Hamiltonian is defined as follows:

$$\begin{aligned}
H(T, T^*, V, Z, \xi) &= [T^{*2}(t) + Pu_1^2(t) + Qu_2^2(t)] \\
&\quad + \sum \xi_i f_i
\end{aligned} \tag{5}$$

Using minimum principle, we have the following theorem.

Theorem 3 *Corresponding to the state system (5) and the optimal control pair* $u^* = (u_1^*, u_2^*)$, *there exist adjoint variables* $\xi_1, \xi_2, \xi_3, \xi_4$ *satisfying*

$$\begin{aligned}
\frac{d\xi_1}{dt} &= -[\xi_1\{-a + r_1[1-(2T+T^*)/T_m] - kV\} \\
&\quad + \xi_2(\alpha kV - r_2 T^*/T_m] \\
\frac{d\xi_2}{dt} &= -[2T^* - \xi_1 r_1 T/T_m + \xi_2(-d + \\
&\quad r_2(1-2T/T_m) - \delta Z) + \xi_3 Nd], \\
\frac{d\xi_3}{dt} &= -[-\xi_1 kT + \xi_2 k\alpha T + \xi_3(-\varepsilon, \\
&\quad - \alpha V/(b+V)^2 + \alpha/(b+V)] \\
\frac{d\xi_4}{dt} &= -[-\xi_3 \delta T^* + \xi_4(-c + \beta T^*/(1+Z)^2)].
\end{aligned} \tag{7}$$

with the transversality condition $\omega_i(t_f) = 0$ for $i = 1,2,3$. Further $u^*(t)$ is represented by:

$$\begin{aligned}
u_1^* &= \max\{0, \min\{1, (\frac{\xi_1 kVT - \xi_2 \alpha kVT}{2P})\}\}, \\
u_2^* &= \max\{0, \min\{1, (\frac{\xi_3 NdT^*}{2Q})\}\}.
\end{aligned} \tag{8}$$

Proof. We differentiate the Hamiltonian H, with respect to T, T^*, V and Z respectively and then the adjoint system can be written as

$$\xi_1' = -\frac{\partial H}{\partial x}, \xi_2' = -\frac{\partial H}{\partial y}, \ \xi_3' = -\frac{\partial H}{\partial z}, \xi_4' = -\frac{\partial H}{\partial z}.$$

To find the optimal control we differentiate the Hamiltonian H, with respect to u, which gives

$$\frac{\partial H}{\partial u} = 0 \ at \ u = u^*$$

Solving (12), we get

$$u_1^* = \max\{0, \min\{1, (\frac{\xi_1 kVT - \xi_2 \alpha kVT}{2P})\}\},$$

$$u_2^* = \max\{0, \min\{1, (\frac{\xi_3 NdT^*}{2Q})\}\}.$$

Thus equation (5) together with (7) and (8) (13) represent the optimally controlled system considering the drugs as control agents with the boundary conditions $\xi_i(t_f) = 0$. Moreover, its a two point boundary value problem.

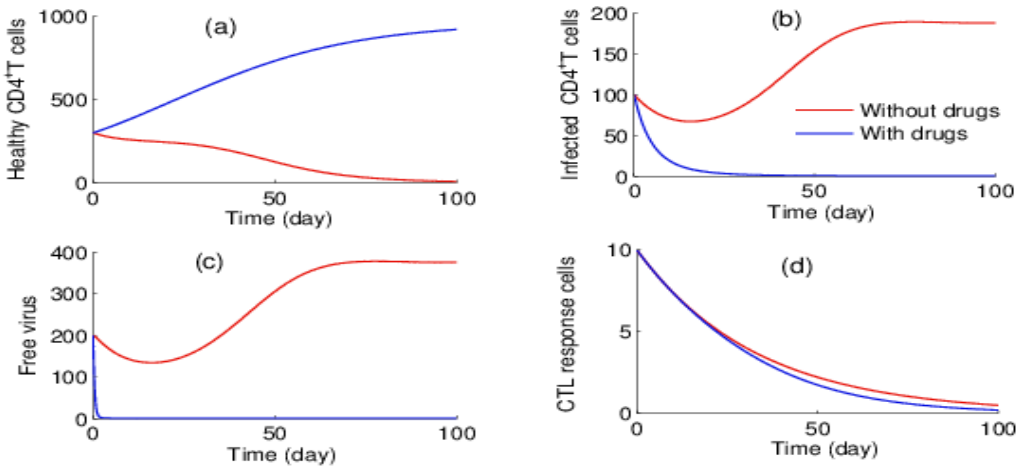

Figure 2: Solution of the system with drugs (blue lines) and without drugs (red lines), taking the parameters values from Table 1.

III. NUMERICAL SIMULATION

In this section, we solve the model system (1) and the optimal control system, numerically in Matlab, in order to gain a better understanding of the previous analytical results. We have chosen the default values of the parameters from their reported range in various articles. The model parameters together with their default values are given in the Table 1.

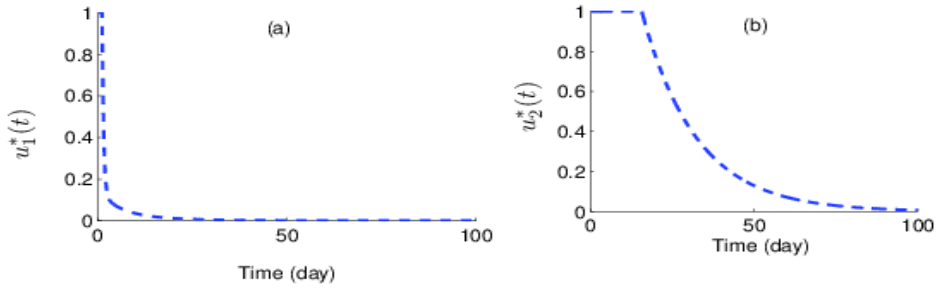

Figure 3: Optimal drugs profiles are plotted with time, taking the parameters values from Table 1.

In Figure 1, is the time series solution of system (1) is presented as function of time without drugs. We have seen that the uninfected $CD4^+$ T cell count decreases. It has also been observed that the level of infected $CD4^+$ T cell increases. We have also seen that the viral load increases drastically without treatments whereas with treatments there is no increase in the concentration of free virus.

From Figure 2, it is clearly observed that as the drug efficacy increases, the uninfected cell population increases towards its maximum population density and the virus and infected cells move towards extinction. However, increasing

the efficacy of RTIs and PIs, do not produce any remarkable change in any of the cell populations being studied. Thus, selecting a highly efficacious drug during the condition.

Figure 3, represents the control pair u^* for RTI and PI drugs for the parameter set as given in Table 1. Both the drugs are administered at nearly full level for 100 days approximately and after that it is reduced to zero at 100 days. In the Figure we see that during the treatment period, the infected T cells decreases, and the CTL responses also increases almost linearly. Thus, optimal drug doses are required with the change in time to block new infection of cells and prevent viral production with minimum side effects.

IV. Discussion and Conclusions

In this paper, we have proposed and analyzed a mathematical model, with two control variables each for Reverse transcriptase inhibitors and Protease inhibitors, describing HIV infection of CD4+T cells. Stability analysis of the proposed model is studied. Also, Pontryagin minimum principle is adopted to solve the formulated optimal control problem. The numerical simulation results shows that the effectiveness of the model in maximizing the concentration of uninfected CD4+T cells, minimizing the free virions in the body with a minimum dose of combination of drug therapies. The aim was to advert the adverse effects associated with excessive use of drug, and also indirectly minimizing the cost of treatment.

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