Long Term Optimal Control for HIV Treatment Using Spline Functions

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Abstract

This paper presents a long-term optimal control treatment of human immunodeficiency virus (HIV) infection. HIV destroys the body immune system, increases the risk of certain pathologies, damages body organs such as the brain, kidney, and heart, and causes death. Unfortunately, this infectious disease currently has no cure; however, there are effective retroviral drugs for improving the patients' health conditions. In this paper, two treatment drugs are considered to decrease the free HIV virus particles in the blood. Since excessive use of these drugs is not without harmful side effects, the prescription dosage should be minimum. Thus, we formulate an optimal control problem to reduce the HIV virus particles in the blood by using minimum drugs. To solve the obtained optimal control, direct method and spline functions are utilized. The main advantage of the direct method to the indirect method is the low computational cost of this solution. Spline functions are tools used in the direct solving approach to achieve the better solutions. Also, three different models are considered in this paper to evaluate the effectiveness of the proposed method in different conditions. In addition, in the end, we compare the results from the proposed approach with the results of the problem solving by indirect method. Furthermore, the sensitivity analysis is checked to demonstrate the performance of control system against parametric uncertainties.

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1. Introduction

HIV infection without control and treatment is very dangerous and deadly and according to the World Health Organization (WHO), this virus is the major cause of death from infections and disease. After years of discovering the disease, it is still very difficult to control the spread of the disease. These problems are due to the lack of appropriate medical facilities, as well as the unwillingness of people to take preventive measures. These problems are due to the lack of appropriate medical facilities, as well as the unwillingness of people to take preventive measures. Another major challenge is that in most parts of Africa, Europe and Asia, many infected people are not even aware of the disease due to illiteracy, lack of medical equipment and other factors. In addition, many people who are aware of their illness do not intentionally take precautions when they engage in sexual intercourse. Current measures to control the disease include prohibiting the reuse of used syringes, the use of condoms, treatment of infections and screening. It is noteworthy that in order to effectively control the spread of the disease, people susceptible to the disease should be protected from exposure, and sufferers should be adequately informed of the measures available to ensure that they do not transmit the disease to other people. Since there is currently no cure for this disease, it is important to examine different strategies to control the spread of the disease in order to minimize the spread of the disease. Hence, the need for better understanding and knowledge of the important parameters in the transmission of disease and the development of optimal and effective strategies for the prevention and control of the spread of this disease is very necessary.

Optimal control is a well-known approach that has been utilized to find optimal methods for

controlling a dynamic system. Today, the usefulness of the optimal control theory for studying different models in the treatment and control of the spread of various diseases, including HIV, is well known.

To investigate the dynamics of this disease, different dynamical models have been presented. Infection of the disease is modeled by considering certain aspects of its dynamics. In [1] the minimum duration of treatment periods and the optimal multidrug method for HIV type 1 infection presented. In [2], an optimal treatment approach considering age-structured model of HIV infection is presented. In [3], the evolution of the infection is modelled by an ordinary differential equation system which includes both immune response and multi-drug effects. A system of ordinary differential equation, which describes the HIV and T cells in the immune system is utilized in [4]. The model in ref [5] is given by the components of the basic three-component model which are the concentration of susceptible $CD4^{+}T$ cells, $CD4^{+}T$ cells infected by the HIV viruses and free HIV virus particles in the blood. A HIV model of on ordinary differential equation, which includes immune response, neutralizing antibodies and multi-drug effects is improved in [6]. There are also various formulations of optimal control problems in this field. Minimizing the population of viruses and the cost of medication [7], the maximization of T cells with minimization of therapeutic drug [8-9], and various other optimal control formulations mentioned below.

Initial efforts have been made to formulate simple mathematical models of AIDS in gay communities. Compared to the current epidemiological data on HIV infection and the incidence of AIDS, these models have been used to assess the impact of various processes on the early epidemic after the introduction of the virus [10].

A detailed analysis of the dynamic model for describing the pathogen of HIV infection has been proposed which the immune deficiency syndrome (AIDS) can be explained by two phenomena: infection to HIV from the population of $CD4^{+}T$ cells and the production of HIV with Increased reproduction capacity [11].

The latest works in this field include the following:

In [12] a dynamical model for considering the impact of awareness programs on HIV/AIDS outbreak was presented. A control scheme is introduced to represent the effectiveness of an awareness program. The designed optimal strategy, is characterized in terms of the optimality system, based on Pontryagin's maximum principle. The simulations have been done using the Forward-Backward Sweep Method with a progressive-regressive Runge-Kutta fourth order.

In [13] a delayed model considering the relationship between HIV and the immune system during the natural course of infection has been proposed. An optimal control scheme considering time delays in both state and control variables was formulated that maximizes the number of uninfected $CD4^{+}T$ cells as well as CTL immune response cells, keeping the drug therapy as low as possible.

In [14] a state space model with two control signals as drug therapies to block the infection of new cell and prevent the production of new free virions was presented. The main concern was to apply optimal control signal using Pontryagin's principle to maximize the concentration of uninfected $CD4^{+}T$ cells in the body with minimum drug therapies.

In [22-26], some applications of direct approach for solving the optimal control problem in robotic trajectory planning in difference operating conditions have been investigated.

In most of the research on the treatment of HIV and AIDS with optimal control, indirect methods have been used to solve the problem. In this paper, direct method and Spline functions are used to solve the optimal control problem. Two main advantages of the direct approach to the indirect approach, are the less computational cost, and achievement to better solutions due to the higher free parameters in problem solving. Also, ability of adding different constraints in problem formulation is another advantage of this method. Furthermore, this approach have the appropriate robustness against the parametric uncertainties of model.

The paper is organized as follows. The dynamic model of HIV infection is presented in section II. In section III, the optimal control problem is formulated. In section IV, the optimal control problem is solved by using indirect and direct method. .Simulation results are given in section V .Sensitivity analysis is presented in section VI and finally, the conclusion of the paper is presented in section VI.

2. Dynamic Model

Mathematical model of HIV infection of $CD4^{+}T$ cells for the time interval $t_0 \le t \le t_f$ is as follows [15-19]:

$$\begin{aligned}
&\frac{dT}{dt} = q - \alpha T + rT\left(1 - \frac{T+I}{T_{\max}}\right) - kVT, T(\mathrm{t}_0) = \mathrm{T}_0 \\
&\frac{dI}{dt} = kVT - \beta I, I(\mathrm{t}_0) = I_0 \\
&\frac{dV}{dt} = \mu\beta I - \gamma V, V(\mathrm{t}_0) = \mathrm{V}_0
\end{aligned} \tag{1}$$

Which T(t) is the concentration of uninfected $CD4^{+}T$, I(t) is the infected $CD4^{+}T$, and V(t) is the free HIV virus particles in the blood.

It is considered that the healthy $CD4^{+}T$ cells are produced by body from precursors in the bone marrow and thymus with a constant rate q. Antigen or mitogen stimulate T cells and then multiply through mitosis at a rate r. The logistic growth of the healthy $CD4^{+}T$ cells is described by $\left(1-\frac{T+I}{T_{\max}}\right)$, while the proliferation of infected $CD4^{+}T$ cells is neglected. The maximum concentration of $CD4^{+}T$ cells in the body is denoted using $T_{\max}$.

The interaction between the viruses V with uninfected T cells causes the HIV infection. T cells are destroyed at rate $-kVT$ and I cells are generated at rate kVT due to the infection. α , β , γ are represented as natural turnover rates of uninfected T cells, infected I cells and virus particles V, respectively. Also, I is assumed that each infected cell produces μ virus particles over its lifetime. In addition, it is assumed that all of the parameters values in the above equations are positive.

The dynamic of the healthy T cells without the HIV infection is as follows:

$$\frac{dT}{dt}=q-\alpha T+rT\left(1-\frac{T}{T_{\max}}\right),T(\mathrm{t}_0)=\mathrm{T}_0 \tag{2}$$

It can be shown that T cell concentration converges at T^{0} as follows [20]:

$$T^{0}=\frac{T_{\max}}{2r}\left[(r-\alpha)+\sqrt{(r-\alpha)^2+\frac{4qr}{T_{\max}}}\right] \tag{3}$$

In this representation, R_0 defined as the number of cases one infected case generates on average over the course of its infections period, in an otherwise uninfected population. For $R_0<1$, the infection will die out in the long run, but if $R_0>1$, the infection will be able to spread in a population. Therefore, the greater value of R_0, causes difficulty in control of epidemic.

In [17, 20], the basic reproduction number is defined by:

$$R_0=\frac{k\mu T^{0}}{\gamma} \tag{4}$$

This number represents the average number of secondary infection caused by a single infected cell in an entirely susceptible T cell population throughout its infectious period. In [17], have been proved that if $R_0\le 1$, the relevant equilibrium point $(T_0,0,0)$ is stable, i.e., the virus is removed and no HIV infection remains. But, if $R_0>1$, the relevant equilibrium point $(T_0,0,0)$ will be unstable and the HIV infection continues. In this situation, a unique chronic infection equilibrium $(\bar{T},\bar{I},\bar{V})$ exists and will be unstable for a range of r.

3. Optimal Control strategy for HIV Treatment

There is a highly active antiretroviral therapy (HAART) which decreases the rate of HIV progression. This therapy can increase the survival time about 11-19 years [8]. HAART is prescribing concurrently of at least two antiretroviral drugs: reverse transcriptase inhibitors (RTT) and protease inhibitor (PI). The HIV infection is decreased using RTIs which blocks the integration of the viral code into the $CD4^{+}T$ helper cell and PIs lessen the HIV replication [20]. RTIs, PIs, or a combination of the two can be prescribed to patients to reduce the amount of virus in their bodies.

The mathematical model with controls with time –dependent incorporated drugs is given as follows:

$$\begin{aligned}
&\frac{dT}{dt}=q-\alpha T+rT\left(1-\frac{T+I}{T_{\max}}\right)-(1-u_1)kVT,T(\mathrm{t}_0)=\mathrm{T}_0\\
&\frac{dI}{dt}=(1-u_1)kVT-\beta I,I(\mathrm{t}_0)=\mathrm{I}_0\\
&\frac{dV}{dt}=\mu(1-u_2)\beta I-\gamma V,\mathrm{V}(\mathrm{t}_0)=\mathrm{V}_0\\
&0\le u_1\le 1,0\le u_2\le 1
\end{aligned} \tag{5}$$

The control signals u_1 and u_2 are the effectiveness of RT inhibitor and the protease inhibitor, respectively.

This treatment methodology may cause the harmful effects for the patients, such as lactic acidosis and mitochondrial damage. But, discontinuity of drug treatment can lead to a fast come back of viral replication.

Thus, an optimal control strategy is formulated in order to minimize the virus population and the dosage of prescribing drugs:

$$J(u_1,u_2)=\int_0^{t_f}\left(C_1V(\mathrm{t})+\frac{C_2}{2}\left(u_1^2(\mathrm{t})+u_2^2(\mathrm{t})\right)\right)dt \tag{6}$$

The constant weights C_1 and C_2 used to balance the quantity of virus particles and the treatment drugs, respectively.

Therefore, the optimal control problem can be written as follows:

$$Min\quad J(u_1,u_2)=\int_0^{t_f}\left(C_1V(\mathrm{t})+\frac{C_2}{2}\left(u_1^2(\mathrm{t})+u_2^2(\mathrm{t})\right)\right)dt \tag{7}$$

$$\begin{aligned}
&\frac{dT}{dt} = q - \alpha T + rT\left(1-\frac{T+I}{T_{\max}}\right) - (1-u_1)kVT, T(t_0) = T_0\\
&\frac{dI}{dt} = (1-u_1)kVT - \beta I, I(t_0) = I_0\\
&\frac{dV}{dt} = \mu(1-u_2)\beta I - \gamma V, V(t_0) = V_0\\
&0 \le u_1 \le 1, 0 \le u_2 \le 1, t \in [t_0, t_f]
\end{aligned} \tag{8}$$

4. Solving of Optimal Control Problem

A) Indirect Method

Indirect method is based on Pontryagin's minimum principle. The optimal control solution is obtained by writing the Hamiltonian function and necessary conditions.

First, the Hamiltonian function is obtained as follows:

$$\begin{aligned}
&H(X(t), u(t), \lambda(t), \omega(t)) = C_1 V + \frac{C_2}{2}\left(u_1^2 + u_2^2\right)\\
&+\lambda_1\left(q - \alpha T + rT\left(1-\frac{T+I}{T_{\max}}\right) - (1-u_1)kVT\right)\\
&+\lambda_2\left((1-u_1)kVT - \beta I\right) + \lambda_3\left(\mu(1-u_2)\beta I - \gamma V\right)\\
&+\omega_{11}(1-u_1) + \omega_{12}(u_1 - 0) + \omega_{21}(1-u_2) + \omega_{22}(u_2 - 0)
\end{aligned} \tag{9}$$

Where λ_1, λ_2 and λ_3 are the co-state variables and $\omega_{11}(t), \omega_{12}(t), \omega_{21}(t), \omega_{22}(t) \ge 0$ are penalty multipliers satisfying:

$$\begin{aligned}
&\omega_{11}(1-u_1) = 0, \omega_{11}(u_1 - 0) = 0, \quad at \quad u_1 = u_1^*\\
&\omega_{21}(1-u_2) = 0, \omega_{22}(u_2 - 0) = 0, \quad at \quad u_2 = u_2^*
\end{aligned} \tag{10}$$

Then, the necessary conditions are written as follows:

$$\begin{cases}
\dfrac{d\lambda_1}{dt} = -\dfrac{\partial H}{\partial T}\\
\rightarrow \dfrac{d\lambda_1}{dt} = -(r-\alpha)\lambda_1 + \dfrac{2r}{T_{\max}}T^*\lambda_1\\
+\dfrac{r}{T_{\max}}I^*\lambda_1 + (1-u_1)kV^*(\lambda_1 - \lambda_2)\\
\dfrac{d\lambda_2}{dt} = -\dfrac{\partial H}{\partial I}\\
\rightarrow \dfrac{d\lambda_2}{dt} = \dfrac{r}{T_{\max}}T^*\lambda_1 + \beta\lambda_2 - \mu(1-u_2)\beta\lambda_3\\
\dfrac{d\lambda_3}{dt} = -\dfrac{\partial H}{\partial V}\\
\rightarrow \dfrac{d\lambda_3}{dt} = -C_1 + (1-u_1)kT^*(\lambda_1 - \lambda_2) + \gamma\lambda_3
\end{cases} \tag{11}$$

$$\begin{cases}
\dfrac{\partial H}{\partial u_1} = 0 \rightarrow C_2 u_1 + kV^*T^*\lambda_1 - kV^*T^*\lambda_2 - \omega_{11} + \omega_{12} = 0\\
\dfrac{\partial H}{\partial u_2} = 0 \rightarrow C_2 u_2 - \mu\beta I^*\lambda_3 - \omega_{21} + \omega_{22} = 0
\end{cases} \tag{12}$$

where u_1^* and u_2^* can be found as follows:

$$\begin{cases}
u_1^* = \dfrac{(\lambda_2 - \lambda_1)kV^*T^* + \omega_{11} - \omega_{12}}{C_2}\\
u_2^* = \dfrac{\mu\beta I^*\lambda_3 + \omega_{21} - \omega_{22}}{C_2}
\end{cases} \tag{13}$$

By considering the bounds of the controls, optimal control pair of the optimal control problem (7), is obtained as follows:

$$u_1^* = \begin{cases}
\dfrac{(\lambda_2 - \lambda_1)kV^*T^*}{C_2} & if \quad \dfrac{(\lambda_2 - \lambda_1)kV^*T^*}{C_2} < 1\\
0 & if \quad \dfrac{(\lambda_2 - \lambda_1)kV^*T^*}{C_2} \le 0\\
1 & if \quad \dfrac{(\lambda_2 - \lambda_1)kV^*T^*}{C_2} \ge 1
\end{cases} \tag{14}$$

$$u_2^* = \begin{cases}
\dfrac{\mu\beta I^*\lambda_3}{C_2} & if \quad \dfrac{\mu\beta I^*\lambda_3}{C_2} < 1\\
0 & if \quad \dfrac{\mu\beta I^*\lambda_3}{C_2} \le 0\\
1 & if \quad \dfrac{\mu\beta I^*\lambda_3}{C_2} \ge 1
\end{cases} \tag{15}$$

And in a compact notation:

$$u_1^* = \min\left\{\max\left\{0, \frac{(\lambda_2 - \lambda_1)kV^*T^*}{C_2}\right\}, 1\right\} \tag{16}$$

$$u_2^* = \min\left\{\max\left\{0, \frac{\mu\beta I^*\lambda_3}{C_2}\right\}, 1\right\} \tag{17}$$

B) Direct Method

In direct method, the variables of optimal control problem are approximated with various functions. There are three approaches based on kind of approximation: approximation of state variables, approximation of control variables and approximation both of them.

Also, there are different functions that can be used to approximate problem variables.

In this paper, both of state and control variables are approximated with spline functions as follows:

$$\begin{aligned}
&\hat{T}(t) = \sum_{k=1}^{N_{cx}} \alpha_k B_{k,r}(t),\\
&\hat{I}(t) = \sum_{k=1}^{N_{cy}} \beta_k B_{k,r}(t)\\
&\hat{V}(t) = \sum_{k=1}^{N_{cy}} \delta_k B_{k,r}(t)\\
&\hat{u}_1(t) = \sum_{k=1}^{N_{cy}} \gamma_k B_{k,r}(t)
\end{aligned} \tag{18}$$

$$\hat{u}_2(t)=\sum_{k=1}^{N_{cv}}\lambda_k B_{k,r}(t)$$

Where $\hat{T}(t)$, $\hat{I}(t)$, $\hat{V}(t)$, $\hat{u}_1(t)$ and $\hat{u}_2(t)$ are the approximation of state and control variables $T(t)$, $I(t)$, $V(t)$, $u_1(t)$ and $u_2(t)$. Also, α_k, β_k, δ_k, γ_k and λ_k are unknown coefficients and $B_{k,r}(t)$ is the Spline basis function that is defined as follows:

$$B_{i,0}(t)=\begin{cases}1 & t_i\le t\le t_{i+1}\\ 0 & otherwise\end{cases}$$
$$B_{i,k}(t)=\frac{t-t_i}{t_{i+k+1}-t_i}B_{i,k-1}(t)+\frac{t_{i+k}-t}{t_{i+k}-t_{i+1}}B_{i+1,k-1}(t) \quad (19)$$

By approximating of state and control variables with spline functions, optimal control problem is transformed to a nonlinear programming problem as follows:

$$Min\quad \hat{J}(\alpha_k,\gamma_k,\lambda_k)=\int_0^{t_f}\left(\begin{array}{l}C_1\hat{V}(\delta_k,t)\\ +\frac{C_2}{2}\left(\hat{u}_1^2(\gamma_k,t)+\hat{u}_2^2(\lambda_k,t)\right)\end{array}\right)dt \quad (20)$$

$$\begin{aligned}&\frac{d\hat{T}(\alpha_k,t)}{dt}=q-\alpha\hat{T}(\alpha_k,t)\\ &+r\hat{T}(\alpha_k,t)\left(1-\frac{\hat{T}(\alpha_k,t)+\hat{I}(\beta_k,t)}{T_{\max}}\right)\\ &-\left(1-\hat{u}_1(\gamma_k,t)\right)k\hat{V}(\delta_k,t)\hat{T}(\alpha_k,t)\\ &\frac{d\hat{I}(\beta_k,t)}{dt}=\left(1-\hat{u}_1(\gamma_k,t)\right)k\hat{V}(\delta_k,t)\hat{T}(\alpha_k,t)-\beta\hat{I}(\beta_k,t)\\ &\frac{d\hat{V}(\delta_k,t)}{dt}=\mu\left(1-\hat{u}_2(\lambda_k,t)\right)\beta\hat{I}(\beta_k,t)-\gamma\hat{V}(\delta_k,t)\\ &0\le\hat{u}_1(\gamma_k,t)\le 1,0\le\hat{u}_2(\lambda_k,t)\le 1,t\in[t_0,t_f]\end{aligned} \quad (21)$$

To demonstrate the computational efficiency of the proposed method, simulations are performed. The numerical values of model parameters are given based on three references in Table 1 (model 1 [21], model 2 [3, 6, 8, 16], model 3 [15, 17, 18]).
Long term horizons considered as $t_0=0days$, $t_f=500days$ and the constant weights of cost function are considered as $C_1=0.1$, $C_2=10$ .The basic reproduction number $R_0=\frac{k\mu T_0}{\gamma}>1$ for all three models.

Fig. 1 to 3 show the state variables without control for three models. It can be seen that, there is a sharp decrease in the concentration of uninfected $CD4^+T$ cells over 500 days. Also, the concentration of infected $CD4^+T$ cells has increased over the period. In addition, there are HIV virus particles in the blood after this time. Overall, model 3 has the worst conditions between the three models.

Table.1.
Model Parameters

Parameter	*Model 1*	*Model 2*	*Model 3*	*Unit*
q	10	10	0.1	$(mm^{-3}day^{-1})$
α	0.02	0.02	0.02	(day^{-1})
r	0.03	0.03	3	(day^{-1})
k	6.5×10^{-5}	2.4×10^{-5}	2.7×10^{-3}	$(mm^{-3}day^{-1})$
β	0.35	0.24	0.3	(day^{-1})
μ	1500	1000	10	-
γ	31.2	2.4	2.4	(day^{-1})
$T_{\max}$	1500	1500	1500	(mm^{-3})
$T(t_0)$	1000	1000	1000	(mm^{-3})
$I(t_0)$	0	0	0	(mm^{-3})
$V(t_0)$	0.001	0.001	0.001	(mm^{-3})
T^0	1000	1000	1490	-
R_0	3.12	10	16.76	-

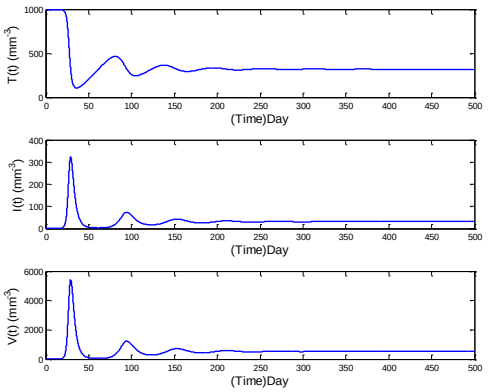

Fig. 1. Model 1: state variables without control

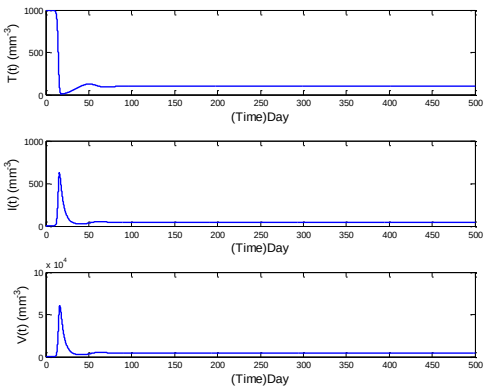

Fig. 2. Model 2: state variables without control

The state variables with control for three models are illustrated in Fig 4 to 6. It is clear that the concentration of uninfected $CD4^{+}T$ cells is converged to T^{0} at the end of treatment period in all their models.

Also, the infected cells and the virus population are reduced closed zero over the treatment window.

The control signals for three models are shown in Fig. 7 to 9. It can be seen that the protease inhibitor u_2 is prescribed more often than the reverse transcriptase inhibitor u_1, for the most part of the treatment because it is the less toxic drug.

A numerical index called the integral of the square of control signal for the result of proposed method and indirect method is calculated and given in Table 2. As seen in Table 2, the numerical index obtained from the direct method is lower than the numerical index obtained from the indirect method which suggests that the amount of treatment drug in direct method is less than the amount of treatment drug in the indirect method.

Also, the simulation run times of two methods are given in Table 3. It is clear that the computational cost of direct method is less than indirect method.

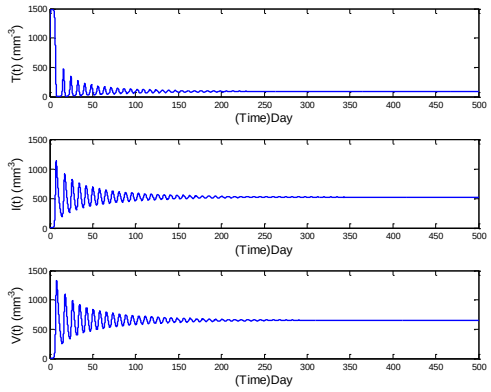

Fig. 3. Model 3: state variables without control

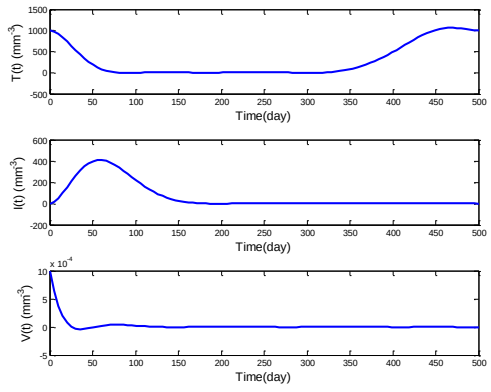

Fig. 4. Model 1: state variables with control

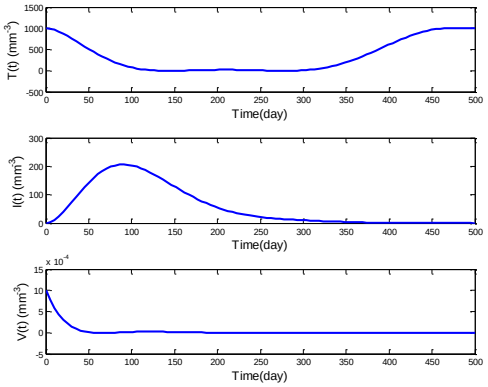

Fig. 5. Model 2: state variables with control

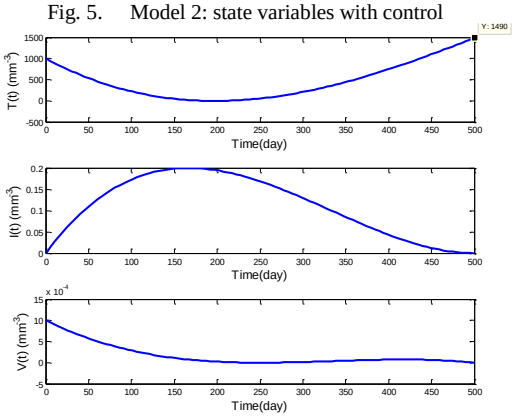

Fig. 6. Model 3: state variables with control

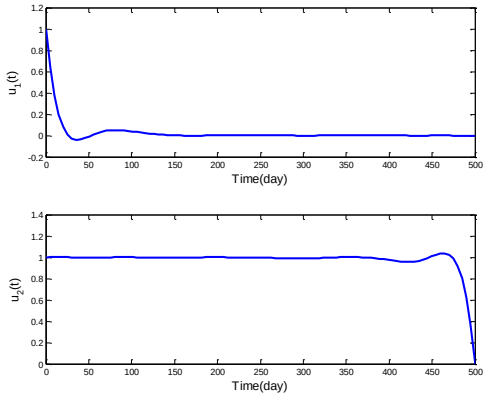

Fig. 7. Model 1: control signals

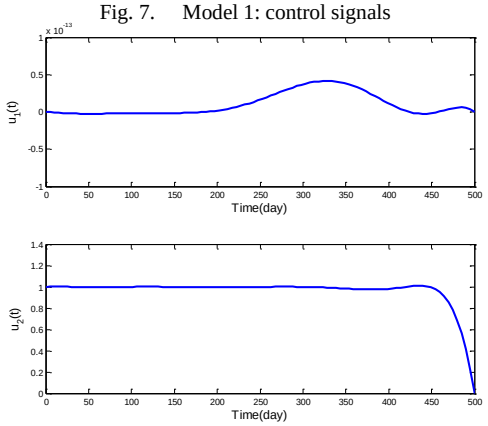

Fig. 8. Model 2: control signals

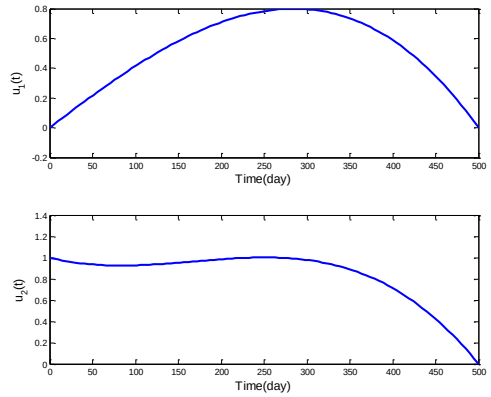

Fig. 9. Model 3: control signals

Table.2.
The Integral of the Square of Control Signal

Method	*Model 1*	*Model 2*	*Model 3*
Indirect method	1.03	0.97	1.12
Direct method	0.98	0.94	1.08

Table.3.
Simulation Run Times

Method	*Model 1*	*Model 2*	*Model 3*
Indirect method	0.015 (s)	0.011 (w)	0.018 (s)
Direct method	0.0034 (s)	0.0031 (s)	0.0038 (s)

5. Sensitivity Analysis

In this section sensitivity analysis is presented to study the impact of model parameters uncertainties on the results. To simulate this condition, 20% are added to nominal model parameters in model 2. The simulation results are shown in Fig. 10.

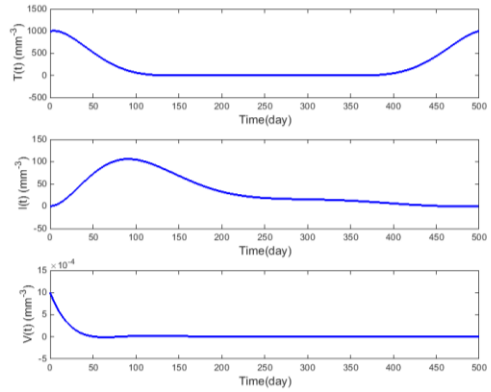

Fig. 10. State variables with control and parametric uncertainties

As seen in Fig. 10, the performance of system is preserved in presence of parametric uncertainties in model.

6. Conclusions

In his paper, long term optimal control for HIV treatment was presented. The HAART strategy with two drugs was considered for HIV-infected patient. Due to side effects of drugs, an optimal control problem was formulated to reduce the free HIV virus particles in the blood and the prescribing drugs. To solve optimal control problem direct method and spline functions was utilized. Finally, the proposed method was simulated and he simulation results demonstrated the effectiveness of proposed method in treatment of HIV infection. Also, the obtained results was compared to indirect method which the direct method had the better performance in minimization of drug dosages and simulation run times.

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