A Clinical Applicable Optimal Control of HIV Using Discretization Scheme

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ABSTRACT. Generally, to obtain a realistic optimal treatment strategy for Human Immunodeficiency Virus (HIV) infection, the amount of virus particles should be decreased and the amount of uninfected CD4+ T-cells must be increased. Since Nowak et al. have presented a mathematical model as an optimal control problem which involves five kinds of viruses and cells (state variables) that describe the dynamics of immune system, HIV and drug-resistant mutants, in this paper, a discretization method was used to convert the problem to a nonlinear programming one. Then, by solving this new problem, the optimal pair of control and states was obtained. Even the analytic solution of the nonlinear programming problem was perfectly acceptable but it was not suitable for physicians to apply. Therefore, by dividing the time interval to some subintervals and considering the control function as a piecewise constant function over these subintervals, a suboptimal control in therapy was obtained which was completely applicable for clinical purposes. Numerical simulations for both optimal and suboptimal strategies demonstrated that the obtained optimal treatments reduced the number of mutant virus particles and also increased the number of uninfected CD4+ T-cells count more than other optimal strategies.

Keywords: Discretization; Drug-resistant mutants; HIV dynamics; Nonlinear programming; Optimal control.

INTRODUCTION

HIV is a virus. Viruses such as HIV cannot grow or reproduce on their own; they need to infect the cells of a living organism in order to replicate (make new copies of themselves). The human immune system usually finds and kills viruses fairly quickly; but HIV attacks the immune system itself. AIDS is caused by HIV damaging the immune system cells until the immune system can no longer fight off other infections which would be usually killed. If left untreated, it takes around ten years on average for someone with HIV to develop AIDS. However, this average is based on the person with HIV having a reasonable diet and someone who is malnourished may well progress from HIV to AIDS more rapidly. Antiretroviral drugs keep the levels of HIV in the body at a low level so that the immune system is able to recover and work effectively. Antiretroviral drugs enable many HIV positive people to live long and healthy lives. Adhering to HIV treatment is important, particularly because not doing so increases the risk of drug resistance. Side effects to the HIV drugs can make the adherence difficult and sometimes very severe. There are ways for reducing the impact of these side effects, but sometimes it is necessary to change to an alternative HIV treatment regime.

Nowadays, to control and cure the HIV infection, a wide variety of mathematical models have been developed (Hadjijandreou et al., 2007). With regard to these mathematical models and using an optimal control approach, optimal treatment strategies can be obtained which can decrease the possibility of virus mutations, pharmaceutical side effects and complex and expensive medication burden. Among these mathematical models, the basic models typically include three variables of uninfected cells, infected cells and virus particles.

Researchers have used a control theoretic approach to derive an optimal treatment strategy for controlling HIV infection. Some of these approaches with different objective functions were addressed in (Hadjijandreou et al., 2009; Krakovska et al., 2007). The open loop control problems of HIV infection in different types of model and objective function were discussed in (Adams et al., 2005; Richman et al., 1994). Hee-dae-kown (Kown, 2007)
studied the model suggested by Nowak et al. in (Nowak et al., 1997) which incorporated mutant virus particles and cells infected by mutant virus; considering the prevention of the emergence of drug resistance is the most advantages of this model. Using Pontryagin Maximum Principle (PMP), Hee-dae-kwon (Kown, 2007) derived an optimal treatment strategy that was analytically acceptable but, since the applicable treatment for patients was a kind of on-off therapy, the presented method was not realistic. Analytic approaches such as using PMP are able to solve a few classes of nonlinear optimal control problems; furthermore, sometimes they are computationally expensive. So, numerical methods have been used to obtain an approximate solution for nonlinear optimal control problem. One of these methods aim to solve nonlinear optimal control problem based on optimization, which were presented in (Badakhshan et al., 2007; Farahi et al., 2008).

In this paper, the Nowak et al. model that includes both wild-type and mutant virus particles was considered. This model was chosen to reduce the amount of mutant virus particles which cause drug-resistant. The discretization method was used to derive an optimal treatment strategy for the HIV model. In this regard, using the work that was done in (Badakhshan et al., 2007; Farahi et al., 2008), the optimal control problem was transferred into a nonlinear programming problem and, then, this problem was solved to achieve optimal control and states. Based on this solution, to derive an applicable and realistic treatment protocol, the predefined time interval was divided to some subintervals and control function was considered as a piecewise constant function over these subintervals. Moreover, after consulting with a physician, the proposed suboptimal treatment strategy was revised and a suboptimal strategy of on-off type was found, which would fulfill the desired goals. Therefore, a suboptimal control was achieved which could reduce the viral load and also increase the number of uninfected CD4+ T-cells count. Moreover, in comparison with other strategies for the same model and parameters, both of the obtained optimal and suboptimals protocols were more acceptable.

**The Optimal Control Problem of the HIV Model**

The dynamics of HIV was described as a system of ordinary differential equations in (Kown, 2007; Nowak et al., 1997) as follows:

\[
\begin{align*}
\frac{dT}{dt} &= \lambda - dT - (1 - \varepsilon)k_{w}V_{w}T - k_{m}V_{m}, \\
\frac{dT_{w}}{dt} &= (1 - \varepsilon)k_{w}V_{w}T - \delta T_{w}, \\
\frac{dT_{m}}{dt} &= (1 - \varepsilon)k_{w}V_{w}T + k_{m}V_{m}, \\
\frac{dV_{w}}{dt} &= a_{w}T_{w} - c_{w}V_{w}, \\
\frac{dV_{m}}{dt} &= a_{m}T_{m} - c_{m}V_{m}.
\end{align*}
\]

(1)

In (1), state variables were \( T \), the uninfected CD4+ T-cells; \( T_{w} \), the wild-type virus-infected CD4+ T-cells; \( T_{m} \), the mutant virus-infected CD4+ T-cells; \( V_{w} \), the wild-type virus particles and \( V_{m} \), the mutant virus particles. The controller \( \varepsilon \) that represents drug efficacy was limited by 0 ≤ \( \varepsilon \) ≤ 1 so that “a” and “b” represent minimal and maximal drug efficacy, respectively. In addition, (1) had several parameters, the descriptions and numerical values of which were presented in (Nowak et al., 1997) and summarized in Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \lambda )</td>
<td>Production (source) rate of CD4+ T-cells</td>
<td>10</td>
</tr>
<tr>
<td>( d )</td>
<td>Death rate of CD4+ T-cells</td>
<td>0.01</td>
</tr>
<tr>
<td>( k_{w} )</td>
<td>Infection rate of wild-type virus</td>
<td>0.01</td>
</tr>
<tr>
<td>( k_{m} )</td>
<td>Infection rate of mutant virus</td>
<td>0.005</td>
</tr>
<tr>
<td>( \delta )</td>
<td>Infected cell death rate</td>
<td>0.5</td>
</tr>
<tr>
<td>( \mu )</td>
<td>The probability of mutation</td>
<td>0.0001</td>
</tr>
<tr>
<td>( a_{w} )</td>
<td>Rate at which wild-type virus is produced from infected cells</td>
<td>10</td>
</tr>
<tr>
<td>( a_{m} )</td>
<td>Rate at which mutant virus is produced from infected cells</td>
<td>10</td>
</tr>
<tr>
<td>( C )</td>
<td>Virus natural death rate</td>
<td>3</td>
</tr>
</tbody>
</table>

To minimize the population of wild-type and mutant virus particles and the systemic cost of drug treatment and also to maximize levels of healthy CD4+ T-cells, the following cost function was considered:

\[
J(\varepsilon) = \int_{0}^{t}(P_{1}V_{w}(t) + P_{2}V_{m}(t) + Q_{e}^{2}(t) + RT(t))
\]

(2)
Thus, the system (1) becomes:

\[ \mathbf{U} = \{ \mathbf{s}(t) \mid \mathbf{s}(t) \text{ is measurable, } 0 \leq \alpha \leq s \leq \beta \leq 1, t \in [t_0, t_1] \} \]

The existence of an optimal control for the above problem was proved in (Fleming et al., 1975).

As mentioned before, analytic methods for solving this nonlinear optimal control problem is computationally expensive and is also not applicable. Therefore, here, a discretization method was used to solve the optimal control problem of HIV infection.

**The Discretization Approach**

Consider the time-dependent system (1) subject to \( \mathbf{X}(t) \in \mathbf{A}, \mathbf{s}(t) \in \mathbf{U}, t \in [t_0, t_1], \mathbf{X}(t_0) = \mathbf{X}_0 \) which is named problem (3); in which \( \mathbf{A} \) is a compact set that indicates the admissible region of states and \( \mathbf{X}(t_0) = \mathbf{X}_0 \) shows the initial condition of states.

The function \( \mathbf{F} : \mathbb{R}^{11} \to \mathbb{R}^+ \) can be defined as:

\[
\mathbf{F} \left( \mathbf{X}(t), \dot{\mathbf{X}}(t), \mathbf{s}(t) \right) = \left\| \dot{\mathbf{X}}(t) - \mathbf{g}(t, \mathbf{X}, \mathbf{s}) \right\|
\]

where \( \left\| \cdot \right\| \) shows the \( L_1 \)-norm on \( \mathbb{R}^8 \), \( \mathbf{X}(t) = (T, T, \ldots, T) \) and \( \mathbf{g}(t, \mathbf{X}, \mathbf{s}) \) is the matrix of the right hand side of the state system (1). So, by the above definition, the following calculus of variation problem can be presented:

\[
\text{Min} \quad J(\mathbf{X}(t), \dot{\mathbf{X}}(t), \mathbf{s}(t)) = \int_{t_0}^{t_1} \mathbf{F} \left( \mathbf{X}(t), \dot{\mathbf{X}}(t), \mathbf{s}(t) \right) \, dt
\]

\[
\text{S. to:} \quad \mathbf{X}(t) \in \mathbf{A}, \mathbf{s}(t) \in \mathbf{U}, t \in [t_0, t_1], \mathbf{X}(t_0) = \mathbf{X}_0.
\]

**Theorem 1.**

The necessary and sufficient condition for problem (3) to have a solution is that the optimal solution of problem (4) equals zero (Badakhshan et al., 2007).

Suppose \( N \) is a constant and sufficiently large natural number. Let \( \Delta = \frac{b-a}{N} \) be an ordered partition of \([a, b] \)

made as \( t_1 = a, t_j = t_{j-1} + \Delta, j = 2, 3, \ldots, N + 1 \).

Define \( \mathbf{X}_{ij} = \mathbf{X}_i(t_j), \mathbf{s}_j = \mathbf{g}(t_j) \) for \( i = 1, 2, \ldots, 5 \) and \( j = 1, 2, \ldots, N + 1 \). Define \( \mathbf{X}_{ij} \) and \( \mathbf{s}_j \) satisfy \( a \leq \mathbf{X}_{ij} \leq \mathbf{A}_j, i = 1, 2, \ldots, 5, j = 1, 2, \ldots, N + 1 \), and \( \alpha \leq \mathbf{X}_{ij} \leq \beta, j = 1, 2, \ldots, N \) can be presented.

According to the above definition, \( \dot{X}_{ij} = \lim_{h \to 0} \frac{X_i(t_{j+1}) - X_i(t_j)}{\Delta} \) is derived. Since it is supposed that \( N \) is a sufficiently large number, then \( \Delta = \frac{b-a}{N} \to 0 \) therefore, the following can be given:

\[
\dot{X}_{ij} = \frac{X_i(t_{j+1}) - X_i(t_j)}{\Delta}, i = 1, 2, \ldots, 5, j = 1, 2, \ldots, N.
\]

Thus, the system (1) becomes:

\[
\frac{X_{ij+1} - X_{ij}}{\Delta} = \mathbf{g}(t_j, \mathbf{X}_{ij}, \mathbf{s}_j), i = 1, 2, \ldots, 5, j = 1, 2, \ldots, N.
\]

Let \( f_{ij} = \frac{X_{ij+1} - X_{ij}}{\Delta} - \mathbf{g}(t_j, \mathbf{X}_{ij}, \mathbf{s}_j), i = 1, 2, \ldots, 5, j = 1, 2, \ldots, N \).

Indeed, \( f_{ij} \)'s are the piecewise constant approximations of function \( F \) components in problem (4). Therefore, problem (2) can be approximated as follows:
Min \[ \sum_{i=1}^{N} \sum_{j=1}^{N+1} |f_{ij}| \]
S. to: \[ f_{ij} = \frac{x_{i+1} - x_i}{\Delta} - g(t_j, X_{ij}, \varepsilon_j); \quad i = 1, 2, ..., 5, \quad j = 1, 2, ..., N, \]
\[ a_i \leq X_{ij} \leq A_i; \quad i = 1, 2, ..., 5, \quad j = 1, 2, ..., N + 1, \]
\[ a \leq \varepsilon_j \leq b; \quad j = 1, 2, ..., N, \]
\[ X_{t1} - X_{a1}; \quad i = 1, 2, ..., 5. \] (5)

This is a nonlinear programming problem with a nonlinear objective function. For simplification, the objective function of problem (5) can be converted to the linear one by choosing appropriate variables.

Suppose that \( R_i = \max\{|f_{ij}|, 0\} \) and \( S_i = -\min\{|f_{ij}|, 0\} \); By these definitions, if \( f_{ij} \geq 0 \), then \( R_i = f_{ij} \) and \( S_i = 0 \); if \( f_{ij} \leq 0 \), then \( R_i = 0 \) and \( S_i = f_{ij} \). This implies \( R_i + S_i = |f_{ij}| \) and \( R_i - S_i = f_{ij} \). Therefore problem (5) becomes:

Min \[ \sum_{i=1}^{N} \sum_{j=1}^{N+1} (R_{ij} + S_{ij}) \]
S. to: \[ R_{ij} - S_{ij} = \frac{x_{ij+1} - x_{ij}}{\Delta} - g(t_j, X_{ij}, \varepsilon_j); \quad i = 1, 2, ..., 5, \quad j = 1, 2, ..., N, \]
\[ a_i \leq X_{ij} \leq A_i; \quad i = 1, 2, ..., 5, \quad j = 1, 2, ..., N + 1, \]
\[ a \leq \varepsilon_j \leq b; \quad j = 1, 2, ..., N, \]
\[ X_{t1} = X_{a1}; \quad i = 1, 2, ..., 5. \] (6)

**Theorem 2.**

If the optimal value of problem (6) is equal to zero and \((X^*, \varepsilon^*)\) are its piecewise constant solution almost everywhere, then \((X^*, \varepsilon^*)\) are the admissible solution of problem (3). (Farah et al., 2008)

3. The Discrete HIV Control Model

As mentioned before, the optimal control problem of HIV model is the cost function (2) subject to the system of ordinary differential Equation (1). By the above description, the system (1) could be transferred to a nonlinear programming problem by the method of discretization. Now, to add the cost function to the problem, with regard to the mean value theorem on a given partition, cost function can be transferred to the discrete one. In other words, the cost function can be approximated as \( J = \sum_{j=1}^{N+1} \left[ h(t_j, X_j, \varepsilon_j) \right] \frac{1}{N} \), where \( h(t_j, X_j, \varepsilon_j) \) is the integrand of the cost function (2) at the partition points.

Therefore, the new nonlinear programming problem is:

Min \[ J - \sum_{j=1}^{N+1} \left[ h(t_j, X_j, \varepsilon_j) \right] \frac{1}{N} \]
S. to: \[ R_{ij} - S_{ij} = \frac{x_{ij+1} - x_{ij}}{\Delta} - g(t_j, X_{ij}, \varepsilon_j); \quad i = 1, 2, ..., 5, \quad j = 1, 2, ..., N, \]
\[ a_i \leq X_{ij} \leq A_i; \quad a \leq \varepsilon_j \leq b; \quad i = 1, 2, ..., 5, \quad j = 1, 2, ..., N \quad \bigg| \quad 1, \]
\[ \sum_{i=1}^{N} \sum_{j=1}^{N+1} (R_{ij} + S_{ij}) < \varepsilon, \quad X_{t1} = X_{a1}; \quad i = 1, 2, ..., 5. \]

where \( \varepsilon > 0 \) shows the admissible error and the third constraint implies that approximation solution of real solution which is satisfied in (1) is achieved.

Thus, the optimal control problem of an HIV model can be transferred to the nonlinear programming problem. By solving this problem, the approximated solution of the optimal control problem is achieved.

4. Simulation

To show the power of the method of discretization numerically, a patient who has not undergone any medical treatment after HIV infection was considered. Thus, in this case, the initial conditions were taken from (Kown, 2007) as:
\[ T(0) = \frac{3r}{\kappa \bar{w} \bar{t}_w (1 - \mu)}, \quad T_w(0) = \frac{c(1 - dT(0))}{T(0) (\kappa \bar{w} \bar{t}_w + \kappa \bar{m} \bar{t}_m \bar{d}_m)}, \quad T_m(0) = T_w(0) \lambda, \quad V_w(0) = \frac{T_w(0)}{\bar{w}}, \quad V_m(0) = \frac{T_m(0)}{\bar{m}}. \]

where \( A = \frac{\kappa \bar{w} \bar{t}_w}{1 - \kappa \bar{m} \bar{t}_m \bar{d}_m} \). The parameters of the model were selected from Table 1 and the treatment was simulated for 100 days.

As mentioned in (Kwon, 2007), the drug efficacy bound was given as \( a = 0 \) and \( b = 0.7 \), the weight constant values were chosen as \( P_1 = 1, P_2 = 5, Q = 1 \) and \( R = 1 \). Then, the developed algorithm in the previous section was used to derive a nearly optimal control law for a specified region.

The algorithm was run over the region \( 13 \leq T \leq 52, \ 8 \leq T_w \leq 48, \ 0.0002 \leq T_m \leq 1.9998, \ 25 \leq V_w \leq 120 \) and \( 0.00069 \leq V_m \leq 6.99991 \), in which the lower and upper bounds of states were taken from (Kwon, 2007). \( N = 200 \) and \( \varepsilon = 10^{-8} \) were selected and the LINGO and the MATLAB software were used to solve and obtain the diagrams.

The dynamics of the optimal treatment strategy proposed by this approach is shown in Figure 1. In comparison with the optimal strategies presented in (Kwon, 2007) for the same model and parameters, the new strategy can maintain the mutant virus-infected T-cells and the mutate virus load at the low level, which are beneficial for the patient because they prevent from the emergence of drug-resistant.

![Figure 3. Dynamics of the optimal treatment strategy by the mentioned discretization method.](image)

**Suboptimal Treatment Strategy**

The optimal strategy that obtained using the discretization method was analytically acceptable; but, since the control function was continuous, it was not realistic and applicable for clinical purposes. Therefore, to derive the suboptimal control which is acceptable and realistic in terms of medicine, the predefined time interval was divided to some subintervals and control function was considered as a piecewise constant function over the subintervals. So, a piecewise continuous optimal control over the treatment time interval was achieved. By assuming the relationship between the drug efficacy and doses' rate in each time interval, the achieved strategy was executable. Otherwise, after consulting with a physician, the suboptimal strategy was adjusted to a kind of on-off treatment protocol which was executable and clearly defined the time intervals in which the drug treatment was on. In this regard, for each interval that the drug efficacy was larger than or equal to 0.5, it was considered 0.7; otherwise, it was considered 0.

Therefore, in this new strategy, if in a time interval, the control was 0, it meant drug treatment was off on a particular interval and, if the control was 0.7 in a time interval, it indicated drug treatment as on for that time interval. The simulation results for the previous example showed that the obtained suboptimal protocols can control the mutant virus particles and the mutant virus-infected T-cells at the low level among the simulation time interval. (See Figure 2 and Figure 3).
The method of discretization was used for designing optimal treatment protocol in order to treat the HIV infection. In this regard, the optimal control problem was transferred to a nonlinear programming problem which was solved by LINGO and MATLAB software. The results of the obtained optimal protocol were acceptable but it was not applicable for physicians. Therefore, a suboptimal treatment strategy that was realistic and applicable was also derived by considering the optimal control as a piecewise continuous function over the predefine time interval. The simulation results showed the effectiveness of the proposed method in comparison with other presented methods in (Kown, 2007) for the same model. Because of medical point of view, it is important to note that the mutant viruses are divided into two subgroups; the first group is the viruses that had been already mutant virus type when they have transmitted into patient's body; this type of viruses are resistant to drug treatment and rarely are controlled. The second group is the viruses that had been not mutant types at first, but during the drug treatment, by emerging the resistant, they are converted to mutant viruses. The latter was our goal in this article. Indeed, we wanted to prevent the emergence of resistant and also the increase of mutant virus by introducing an optimal treatment strategy of on-off type.

An important advantage of the resulting strategy was that the mutant virus load was controlled at low level and the pharmaceutical side effects were also reduced. Moreover, the new treatment could reduce the costs of treatments as well.

REFERENCES


