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The Control Parametrization Enhancing Technique for Multi-Objective Optimal Control of HIV Dynamic

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Abstract. In this paper, a computational approach is adopted for solving a multi-objective optimal control problem (MOOCP) formulation of optimal drug scheduling in human immunodeficiency (HIV) virus infected by individuals. The MOOCP, which uses a mathematical model of HIV infection, has some incompatible objectives. The objectives are maximizing the survival time of patients, the level of D4+ T-cells and the level of cytotoxic T-lymphocytes (CTLs), and minimizing the viral load and the drug costs. In this approach the fuzzy goals described by the linear membership functions, are incorporated for the objectives and the optimal solution is investigated by maximizing the degree of attainment of the aggregated fuzzy goals resulting a fuzzy goal optimal control problem (FGOCP). Using the minimum operator for aggregation of fuzzy goals, the FGOCP is converted into a constrained optimal control problem (OCP) in canonical form. The control parametrization enhancing technique (CPET) is used for approximating the OCP by an optimal parameter selection problem, with the final goal of implementing continuous and interrupted (structured treatment interruptions, STI) combinations of reverse transcriptase inhibitor (RTI) and protease inhibitor (PI) drug efficacies. Efficiency of the proposed method is confirmed by numerical simulations.

Keywords. Multi-objective problem, Optimal control, Fuzzy goal programming, Therapy optimization.
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1 Introduction

In the recent years, one of the most prevalent diseases which has caused a major global health problem is the acquired immunodeficiency syndrome (AIDS) caused by human immunodeficiency (HIV) virus. According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), there were approximately 36.9 million people living with HIV at the end of 2014 with 2.0 million more people becoming newly infected with HIV in 2014 throughout the world. Since the beginning of the HIV/AIDS epidemic in 1981, nearly 30 million people have died from AIDS-related causes [42].

HIV infection can be considered as a disease of the immune system which progressively depletes the defensive cells and results in immunosuppression and susceptibility to opportunistic infections. CD4+ T-cells, CTLs and the virus particles play important roles in HIV infection. CD4+ T-cells form a fundamental component of the human immune response system. These cells can be considered as the messengers or the command centers of the immune system and they signal to other immune cells that an invader is to be fought. The immune response cells, or cytotoxic lymphocytes (CTLs), are the cells that respond to this message and set out to eliminate the infection by killing infected cells. HIV can infect a number of different cells in the body, but its main target is the CD4+ T-cells. HIV enters these cells by a complex process and begins to replicate, then new virus particles are released by bursting the infected cells. CD4+ T-cells are generated from certain sources within the body and are lost either because of having finite life span or by bursting during the proliferation of HIV. This leads to a drop in the number of CD4+ T-cells. During the later stages this signals the onset of AIDS.

Some aspects of the host-pathogen interaction mechanisms during HIV infection and its progression to AIDS are still unknown. Mathematical modeling of HIV infection is of interest to the medical community as no adequate animal models exist to test efficacy of drug regimes. These models can test different assumptions and provide new insights into questions that are not easy to answer through clinical or experimental studies. A number of mathematical models have been formulated to describe various aspects of the interaction of HIV with healthy cells [18] HIV infection basically has three major phases: a peak in viral load following initial infection, a quasi-steady state or latent loss of CD4+ T-cells associated with the development of AIDS [32]. Some of proposed models predict the three stages of infection [18], whereas others can only predict the early phases of disease but do not predict any decrease in CD4+ T-cell counts and rise in peripheral virus seen in AIDS [30]. Up to now, drug treatments are still the only available control methods of HIV/AIDS. Highly active antiretroviral therapy (HAART) contains two major types of anti-HIV drugs that are reverse transcriptase inhibitors (RTI) and protease inhibitors (PI). RTIs prevent HIV from infecting cells by blocking the integration of the HIV viral code into the host cell genome while PIs prevent infected cells from replicating infectious virus particles. It also can reduce and maintain viral load below the limit of detection in many patients [1]. HAART inhibits the progression of HIV in the body and increases survival-time with a projected 11-19 years, depending on the type of drug regime and patient's response to treatment; however, it cannot stop its reproduction completely. This is mainly due to macrophages and latently infected CD4+ T-cells, which act as reservoirs of the virus as well as the side-effect of treatment with antiretroviral drugs where by a drug-resistant (mutated) virus emerges [12]. Each drug has a maximum efficacy which depends on many factors like virus strains present. By varying the dosage it is possible to change the efficacy of the medication from no effect to the maximum efficacy.

The mathematical models are used to design dynamical drug treatments. Already tens of papers have been written on using mathematical models in conjunction with Open-loop

control techniques [12, 14] or feedback control ones [9, 50] for planning HIV therapies. In [35] consider only RTI medication while in [17, 30] consider only PIs. In [44, 50] all effects of a HAART medication are combined in one control variable in the model. In [2, 12, 14, 18, 27, 29, 31] dynamical multidrug therapies based on RTIs and PIs are designed. In these therapies the dosages of both medications can change independently of each other. The present paper studies the dynamical multidrug therapies based on RTIs and PIs. In fact, the problem of designing drug administration in HIV-infected patients using mathematical models can be considered as a multi-objective optimal control problem (MOOCP). These objectives may include maximizing the level of healthy CD4+ T-cells and minimizing the cost of treatment [12, 14], minimizing the cost of treatment and viral load [1, 35], maximizing immune response and minimizing both the cost of treatment and viral load [2], maximizing both the level of healthy CD4+ T-cells and immune response and minimizing the cost of treatment [5, 50], maximizing the level of healthy CD4+ T-cells and minimizing both the cost of treatment and viral load [31], maximizing both the level of healthy CD4+ T-cells and immune response while minimizing both the viral load and drug cost [9] and maximizing survival time of patient subject to drug cost [28, 48]. Main objectives in this paper contain minimizing both the viral load and the cost of treatment and maximizing the survival time of patient, and the level of healthy CD4+ T-cells and CTLs.

In [28] the authors have proposed a concept for an optimal drug regime and formulated the problem as a time-optimal control problem which is solved by using the Control Parametrisation Enhancing Technique (CPET). The CPET has wide applications in the field of computational control [20]. In this paper, we use this technique to solve this problem.

The rest of this paper comprises the following sections. In Section 2, the mathematical models for HIV control are reviewed. Novel formulation of the MOOCP is described in Section 3. In Section 4, a fuzzy goal is assigned for each objective and a fuzzy goal optimal control problem is proposed to find a Pareto optimal solution with the best satisfaction performance. Two methods for defining optimal drug therapy protocols based on CPET are presented in Section 5. Section 6 contains the simulation results with discussion. The last section presents the conclusion of the paper.

2 Mathematical Models for HIV Infection

In the literature of the study, the basic model presented in [33] for mathematical modelling of HIV considers only three state variables (expressed as cell counts in blood per cubic millimeter) inside a whole body model. The model is mathematically presented as (1):

$$\begin{cases} \dot{x} = \sigma - dx - \beta xv \\ \dot{y} = \beta xv - ay \\ \dot{v} = ky - \tau v, \end{cases} \tag{1}$$

where x, y and v represent the number of uninfected CD4+ T-cells, infected CD4+ T-cells and virions, respectively, σ is the regeneration rate of CD4+ T-cells, d is the death rate of CD4+ T-cells, β is the rate at which CD4+ T-cells become infected, a is the death rate of infected CD4+ T-cells, k is the number of new virions produced by each infected cell during its life-time and τ is the clearance rate of free virions.

A five-state model was proposed by Wodarz and Nowak [45]. Although maintaining a simple structure, the model offers important theoretical insights into immune control of the virus based on treatment strategies and mathematically is shown as (2):

$$\begin{cases} \dot{x} = \sigma - dx - \beta xv \\ \dot{y} = \beta xv - ay \\ \dot{v} = ky - \tau v \\ \dot{w} = cxyw - cqyw - bw \\ \dot{z} = cqyw - hz. \end{cases} \tag{2}$$

Two differential equations are added to (1) to describe the dynamics of cytotoxic T-lymphocyte precursors CTLp(w), which are responsible for the development of immune memory and cytotoxic T-lymphocyte effectors CTLe(z), which are responsible for killing virus-infected cells. The last term in the second equation states that the infected cells are killed by CTL effectors at a rate pzy. According to experimental findings establishment of a lasting CTL response depends on CD4+ T-cells help and the function of HIV impairs CD4+ T-cells function. Thus, proliferation of the CTLp population is given by $cxyw$ and is proportional to both virus load (y) and the number of uninfected CD4+ T-cells (x). CTLp die at a rate bw and differentiate into effectors at a rate $cqyw$. CTL effectors die at a rate hz. This model can discriminate the trend of infection as the function of the rate of viral replication: if the rate is high a successful immune memory cannot be establish; conversely, if the replication rate is slow, the CTL-mediated immune memory helps the patient to successfully fight the infection [31, 45]. The variant to model (2) proposed by Nowak [30] and detailed below, is considered in [50] for investigating the model predictive control (MPC) based treatment scheduling (See (3)):

$$\begin{cases} \dot{x} = \sigma - dx - \beta xv \\ \dot{y} = \beta xv - ay - p_1 z_1 y - p_2 z_2 y \\ \dot{w} = c_2 xyw - c_2 qyw - bw \\ \dot{z}_1 = c_1 z_1 y - h_1 z_1 \\ \dot{z}_2 = c_2 qyw - h_2 z_2. \end{cases} \tag{3}$$

In such a model, a differentiation between helper-independent CTL z_1 and helper-dependent CTL z_2, is considered. The CTL expand at a rate $c_1 y z_1$ and decay at a rate $b_1 z_1$. They kill infected cells at a rate $p_1 z_1 y$. In this paper we use another modification to model (2) given in [18] where the constant β is substituted with the new state variable r, an index of the aggressiveness of the virus, in order to reach the first objective of mirroring the natural evolution of HIV infection as qualitatively described in several clinical studies. The modified model which is used in [31] reads as (4):

$$\begin{cases} \dot{x} = \sigma - dx - rxv \\ \dot{y} = rxv - ay - pzy \\ \dot{w} = cxyw - cqyw - bw \\ \dot{z} = cqyw - hz \\ \dot{v} = k(1 - m_P u_P)y - \tau v \\ \dot{r} = r_0(1 - m_R u_R). \end{cases} \tag{4}$$

According to the new equation which describes the r-state dynamics, r increases linearly with time in the case of an untreated HIV-infected individual, with a growth rate that depends on the constant r_0 (a higher r_0 value indicates a higher virulence growth

Table 1: Parameter values for the HIV model

Parameters	Value/unit	Description
σ	$7 cells \mu L^{-1} day^{-1}$	Production(source) rate of CD4+T-cells
d	$7 \times 10^{-3} day^{-1}$	Death rate of uninfected CD4+ T-cell population
a	$0.0999 day^{-1}$	Infected CD4+ T-cell death raten
p	$2 \mu L cells^{-1} day^{-1}$	Clearence rate of infected cells by CTL effectors
c	$5 \times 10^{-6} \mu L^2 cells^{-2} day^{-1}$	Proliferation rate of CTL precursors
q	$6 \times 10^{-4} \mu L cells^{-1} day^{-1}$	Production rate of CTL effectors from CTL precursors
b	$0.017 day^{-1}$	Death rate of CTL precursors
h	$0.06 day^{-1}$	Death rate of CTL effectors
k	300 copies $mL^{-1} cells^{-1} \mu L day^{-1}$	Production rate of virus from infected cells
τ	$0.2\ day^{-1}$	Virus natural death rate
r_0	$10^{-9} copies^{-1} mL day^2$	Aggressiveness growth rate of the Virus
m_P	0.7 dimensionless	PI drug effectiveness parameter
m_R	0.9 dimensionless	RTI drug effectiveness parameter

rate). In model (4) the coefficients m_R and m_P represent the drug effectiveness weights for specific external inputs u_R and u_P , which are the RTI and PI normalized drug uptakes. The effect of PI drugs is modeled by reducing the proliferation rate of viruses from infected cells, while the effect of RTI drugs is modeled by reducing the infection rate and in this way, blocking the infection of CD4+ T-cells by free virus. Hence, in this model the RTI drugs have an effect on virulence because their main role is halting cellular infection and preventing virus production by reducing the production rate from infected CD4+ T-cells. The model has several parameters that must be assigned for numerical simulations. The descriptions, numerical values and units of the parameters are summarized in Table (1). These descriptions and values are taken from [18]. We note that (4) with these parameters indicates the dynamics of fast progressive patients (FPP).

3 Multi-objective Optimal Control Formulation

In clinical practice, antiretroviral therapy is initiated at t_0, the time at which CD4+ T-cell counts reach $350 cells/\mu L$. Moreover transition from HIV to AIDS occurs at t_f , the time at which CD4+ T-cells count decreases below $x^* = 200 cells/\mu L$. Maximizing the level of CD4+ T-cells [12, 31], maximizing the immune response [2, 5, 50] and prolonging the onest of AIDS [28, 48] are goals of HIV antiretroviral therapies modeled as maximizing the following functionals (See (5))

$$\begin{aligned} J_1(t_f, u) = \int_{t_0}^{t_f} dt,\ J_2(t_f, u) = \frac{1}{(t_f - t_0)} \int_{t_0}^{t_f} x(t) dt, \\ J_3(t_f, u) = \frac{1}{(t_f - t_0)} \int_{t_0}^{t_f} z(t) dt, \end{aligned} \tag{5}$$

where $u = (u_P, u_R)$ and

$$x(t) \geqslant x^*, \quad t \in [t_0, t_f]. \tag{6}$$

Other functions of HIV antiretroviral therapy are reducing the viral load to the lowest level possible [1, 2] and reducing the systemic costs of treatments [1, 12, 35] which are modelled as the Maximize the following functional:

$$J_4(t_f,u)=-\frac{1}{(t_f-t_0)}\int_{t_0}^{t_f}v(t)dt,\ J_5(t_f,u)=-\frac{1}{(t_f-t_0)}\int_{t_0}^{t_f}u_P(t)dt,$$
$$J_6(t_f,u)=-\frac{1}{(t_f-t_0)}\int_{t_0}^{t_f}u_R(t)dt, \tag{7}$$

where x, v and z are the solutions of ODEs (4) corresponding to control function u. Note that the integrals in $J_j, j=2,...,6$ divided by the length of the integration interval indicate the mean values of immune cells, the viral load and drug costs in treatment period.

A pair (t_f,u) is called an admissible pair if $u:[t_0,t_f]\to R^2$ be a bourel measurable control function taking the values in the compact set $\mho\subseteq R^2$ and the solution of (4) corresponding to u satisfies the constraint (6). Let K denotes the class of all such admissible pairs. Therefore, the optimal drug regimen problem can be represented as:

$$\underset{(t_f,u)\in K}{Maximize}\{J_1(t_f,u),...,J_6(t_f,u)\}. \tag{8}$$

Remark 1. As stated in [18], the values $a_1=0, a_2=\frac{4}{7}$ and $a_3=1$ for u_P indicate the off, moderate and strong PI-therapy, respectively. Similarly, the corresponding values for RTI control are $b_1=0, b_2=\frac{5}{9}$ and $b_3=1$. In this case we set $\mho=\{a_1,a_2,a_3\}\times\{b_1,b_2,b_3\}$ which leads to the medication in piecewise constant levels. If drugs can assume any value from zero to maximum, we set $\mho=[a_1,a_3]\times[b_1,b_3]$ which leads to the continuous treatment. If $\mho=\{a_1,a_3\}\times\{b_1,b_3\}$, the amount of medications is on-off type. This treatment is also known as structured treatment interruption (STI) (See e.g. [1, 12, 29, 31, 50] and references therein).

Note that a decrease in drug costs leads to an increase in the viral load, a decrease in CD4+ T-cell counts and a fast progression to AIDS and exhaustion of immune response. Therefore, the objectives J_5 and J_6 conflict with other objectives. In general, there does not exist a pair $(t_f,u)\in K$ that maximizes the functional $J_i, i=1,...,6$, simultaneously and one uses the concept of Pareto optimality in the sense of following definition.

Definition 1. A pair $(t_f^*,u^*)\in K$ is said to be an Pareto optimal solution of the problem (8) if and only if, there exists no $(t_f,u)\in K$ such that $J_i(t_f^*,u^*)\leq J_i(t_f,u)$ for all $i\in\{1,...,6\}$ and $J_i(t_f^*,u^*)<J_i(t_f,u)$ for some $i\in\{1,...,6\}$.

As seen from Definition 1, in general there exist an infinite number of Pareto optimal solutions. There exists a wide variety of methods that can be used to compute Pareto optimal points. A widely used technique is reducing the multi-objective problem to a single objective one by means of "scalarization" procedure. The weighted sum (WS) method and normalization are commonly used scalarization techniques which consist of assigning each normalized objective function a weight coefficient, which represents the relative importance of each objective provided by decision-maker (DM) and then optimizing the function obtained by summing up all the objective functions scaled by their weight coefficients that only one solution can be rendered accordingly. By taking the weights as parameters, the method can generate several points in the Pareto set for various impersonal settings of the weights. Though computationally more expensive, this approach provides an idea of the shape of the Pareto front and provides the user with more information about the trade-off among the objectives. Even so, this method suffers an intrinsic drawback: non-convex parts of the Pareto set cannot be obtained by minimizing convex combinations of the objectives [6]. Recent scalar multiple objective optimization techniques such as Normal Boundary Intersection (NBI) [7] and Normalized Normal Constraint (NNC) [25] have

been found to mitigate the disadvantages of the WS method. Recently, these methods have been successfully combined with direct optimal control approaches for the efficient solution of multi-objective optimal control problems. For example, in [23], a successful application of NBI and NNC for the multiple objective optimal control of (bio) chemical processes has been reported and in [22] several scalarization techniques for multi-objective optimization, for example WS, NNC and NBI have been integrated with fast deterministic direct optimal control approaches. From a mathematical point of view, every Pareto optimal solution is equally acceptable as the solution to the multiobjective optimization problem. However, for practical reasons only one solution shall be chosen at the end and picking a desirable point out of the set of Pareto optimal solutions involves a DM. There are many techniques to find such solution [36]. The fuzzy goal programming technique [49] is one of the frequently used methods for obtaining a Pareto optimal solution with the best satisfaction performance. This approach along with measure theory has been used to multi-objective optimal control problems [46]. Moreover, this approach in conjunction with linear programming techniques has proved to be a very efficient tool for linear lumped-parameter systems [38, 39] and distributed-parameter systems [37, 47]. In the next section, we use this approach to formulate a fuzzy goal optimal control problem for finding a compromised Pareto optimal solution for formula (8).

4 The Fuzzy Goal Optimal Control Problem (FGOCP)

In this section we incorporate the fuzzy goals for our objectives and consider the equilibrium problem in terms of maximizing the degree of attainment for the aggregated fuzzy goals. The fuzzy goals are quantified by eliciting the corresponding membership functions, which usually are linear, through the interaction with the DM. Since we are interested in maximizing the objective functions, it is quite natural to define the linear membership function $\mu(J_i(t_f,u)), i=1,...,6$ for the fuzzy goal of the DM as (9):

$$\mu(J_i(t_f,u)) = \begin{cases} 0, & if J_i(t_f,u) < \underline{J}_i \\ \frac{J_i(t_f,u)-\underline{J}_i}{\bar{J}_i-\underline{J}_i}, & if \underline{J}_i \le J_i(t_f,u) \le \bar{J}_i \\ 1, & if J_i(t_f,u) > \bar{J}_i, \end{cases} \tag{9}$$

where $\underline{J}_i$ and $\bar{J}_i$ are, respectively a minimum value and a maximum value of totally desirable levels for J_i. Following the fuzzy decision of Bellman and Zadeh [3], the MOOCP (8) can be interpreted as (10):

$$\underset{(t_f,u)\in K}{Maximize} \ \min_{i=1,...,6} \mu(J_i(t_f,u)). \tag{10}$$

By introducing the auxiliary variable $\lambda = min_{i=1,...,6}\, \mu(J_i(t_f,u))$, the problem (10) can be equivalently transformed as:

$$\begin{aligned} &Maximize \qquad \lambda \\ &Subject\,to: \\ &J_i(t_f,u) - \lambda(\bar{J}_i - \underline{J}_i) \ge \underline{J}_i, \\ &(t_f,u) \in K, i=1,...,6. \end{aligned} \tag{11}$$

We note that the fuzzy goals of the DM can be described by the other forms of membership functions. Nerveless, for computational simplicity the linear form is of more

interest. Assume that $(t_i, u_i), i = 1, ..., 6$ maximizes the individual objective J_i over K. As stated in [36, 37, 47] the DM assesses suitable values for $\underline{J}_i$ and $\bar{J}_i$ within J_i^{max} and J_i^{min} , given by (12):

$$J_i^{max} = J_i(t_i, u_i) \; and \; J_i^m = \min_{j \in \{1,...,6\}} J_i(t_j, u_j). \tag{12}$$

If (t_f^*, u^*, λ^*) is a unique optimal solution of (11), then (t_f^*, u^*) is a Pareto optimal solution of (10) (See [36]). If this sufficient condition for Pareto optimality of (t_f^*, u^*) does not suffice, then we can test the Pareto optimality for (t_f^*, u^*) by solving the following problem:

$$\begin{aligned} &Maximize \qquad \epsilon_1 + ... + \epsilon_6 \\ &Subject\,to: \\ &J_i(t_f, u) + \epsilon_i = J_i(t_f^*, u^*), \\ &(t_f, u) \in K, i = 1, ..., 6. \end{aligned} \tag{13}$$

For the optimal solution of this problem, Theorem 1 holds (See [36]):

Theorem 1. Let $(\bar{t}_f, \bar{u}, \bar{\epsilon})$ be an optimal solution to problem (13). If all $\bar{\epsilon}_i = 0$, then (t_f^*, u^*) is a Pareto optimal solution. If at least one $\bar{\epsilon}_i > 0$, then instead of (t_f^*, u^*), $(\bar{t}_f, \bar{u})$ is a Pareto solution to the problem (10).

Numerical computational methods and efficient algorithms have been developed to solve the optimal control problems [26]. The control parameterization enhancing technique (CPET) has been adopted to compute solutions for generally constrained optimal control problems [41]. Using the CPET technique, optimal control problems can be approximated with an optimal parameter selection problems, which can be solved efficiently by the software package MISER3 [13]. The next section describes the solution of the problem (11) by using the CPET.

5 Control Parameterization Enhancing Technique

The CPET provides a computationally simple method for nonlinear optimal control problems which were introduced in [20]. This technique maps all the switching points of the original problem onto the set of integers, so that the time of the switching points can be accurately determined. In order to solve the problem (11), we use the $\epsilon - \tau$ method (See [41]) to approximate the state inequality constraint (6) as inequality constraints in canonical form:

$$\tau + \int_{t_0}^{t_f} \varphi_\epsilon(x - x^*) dt \geq 0, \tag{14}$$

where,

$$\varphi_\epsilon(\eta) = \begin{cases} \eta, & if \; \eta < -\epsilon \\ -\frac{(\eta - \epsilon)^2}{4\epsilon}, & if \; -\epsilon \leq \eta \leq \epsilon \\ 0, & if \; \eta > \epsilon. \end{cases} \tag{15}$$

It can be shown (See [41] and references therein) that for each $\epsilon > 0$, there exists a corresponding $\tau(\epsilon) > 0$ such that whenever $0 < \tau < \tau(\epsilon)$, constraint (14) implies

constraint (6). Therefore, setting $\xi = (x, y, w, z, v, r)$, we have an optimal control problem in the following form:

$$\begin{aligned} &Maximize \qquad \lambda \\ &Subject\,to: \\ &\int_{t_0}^{t_f} f_i(\xi, u)dt - (t_f - t_0)(\lambda(\bar{J}_i - \underline{J}_i) + \bar{J}_i) \geq 0, \\ &\tau + \int_{t_0}^{t_f} f_0(\xi, u)dt \geq 0, i = 1, ..., 6, \\ &\dot{\xi} = g(\xi, u), \xi(0) = \xi_0, u \in \mho, \end{aligned} \tag{16}$$

where $f_0(\xi, u) = \varphi_\epsilon(x - x^*)$, $f_1(\xi, u) = 1$, $f_2(\xi, u) = x$, $f_3(\xi, u) = z$, $f_4(\xi, u) = -v$, $f_5(\xi, u) = -u_P$, $f_6(\xi, u) = -u_R$ and $\dot{\xi} = g(\xi, u)$ is the HIV model (4) in the generic form with the initial condition ξ_0.

In this section, two CPET algorithms are presented to determine the optimal doses of RTI and PI drugs over a finite time interval and their simulated performance is evaluated and compared in the next section. Note that the Poteryagins minimum principle (PMP) [16], as a traditional optimal control technique for solving (16), gives the necessary optimality condition in the form of a highly nonlinear parametric boundary value problem which is not analytically solvable and the STI- type solutions are not achieved using the PMP. On the other hand, the spectral methods have been used to solve the optimal control problems in lumped [10] and the distributed [4] parameter systems are not suitable for (16) due to a box constraint on control functions and a free final time t_f. Moreover, although the MPC technique has been successfully implemented for designing continuous and STI therapy protocols for HIV infected patients [9, 31, 50]; it is useless for (16) because of the integral constraints in it.

5.1 CPET 1: A Continuous Dosage Approach

Here, we set $\mho = [0, 1] \times [0, 1]$ which means that drugs can assume any value from zero to its maximum value (See remark 1). To apply the CPET, we assume that the control function u has a piecewise constant form as (17):

$$u_M = \sum_{k=1}^{M} \alpha_k \chi_{[t_{k-1}, t_k)}(t), \tag{17}$$

where M is the number of control subintervals and $\chi_{[t_{k-1}, t_k)}$ is the characteristic function for the interval $[t_{k-1}, t_k)$. We note that $\alpha_k \in \mho$ and $t_k, k = 1, ..., M$ are the decision variables characterizing u where $t_0 \leq t_1 \leq ... \leq t_M = t_f$. Substituting (17) in (16) gives (18):

$$
\begin{aligned}
&Maximize \qquad \lambda \\
&Subject\,to: \\
&\sum_{k=1}^{M}\int_{t_{k-1}}^{t_k} f_i(\xi,\alpha_k)dt-(t_f-t_0)(\lambda(\bar{J}_i-\underline{J}_i)+\bar{J}_i)\geq 0, \\
&\tau+\sum_{k=1}^{M}\int_{t_{k-1}}^{t_k} f_0(\xi,\alpha_k)dt\geq 0, i=1,...,6, \\
&\dot{\xi}=g(\xi,\alpha_k),\xi(0)=\xi_0,t\in[t_{k-1},t_k),\alpha_k\in\mho,k=1,...,M.
\end{aligned}
\tag{18}
$$

Convergence is a key issue for any numerical method and control parametrization is no exception. In fact, one of the main virtues of the control parametrization method is its strong convergence property that is outlined in Theorem 2.

Theorem 2. Let u^* be the optimal control for the original optimal control problem (16) with the objective value $\lambda(u^*)$ and u_M^* be a solution of the approximate optimization problem (18), with the objective value $\lambda(u_M^*)$. We have $lim_{M\to\infty}\lambda(u_M^*)=\lambda(u^*)$.

Proof. See Chapter 6 of [40]. □

Now we relate the new time variable $s\in[0,M)$ to the original time variable $t\in[t_0,t_M)$ through the following ordinary differential equation:

$$
\begin{aligned}
&\frac{dt(s)}{ds}=\upsilon(s), \\
&t(0)=t_0,
\end{aligned}
\tag{19}
$$

where $\upsilon:[0,M)\to R$ is a new nonnegative piecewise-constant function called the time-scaling control. The time-scaling control is defined by (20):

$$
\upsilon(s)=\sum_{k=1}^{M}\beta_k\chi_{[k-1,k)}(s), \tag{20}
$$

where

$$
\beta_k=t_k-t_{k-1},k=1,...,M. \tag{21}
$$

Thus, the heights of the time-scaling control are the durations of the control subintervals in the original time horizon. Clearly from (19) we have $t(s)=t_0+\int_0^s\upsilon(\eta)d\eta$ which gives $t(j)=\sum_{k=0}^{j}\beta_k=t_j,j\in 0,...,M$ where $\beta_0=t_0$. Therefore,

$$
t_f=\sum_{k=0}^{M}\beta_k. \tag{22}
$$

Let $\hat{\xi}=\xi(t(s))$. Under the CPET transformation, problem (18) becomes:

$$
\begin{aligned}
&Maximize \qquad \lambda \\
&Subject\,to: \\
&\sum_{k=1}^{M} \beta_k \{ \int_{k-1}^{k} f_i(\hat{\xi}, \alpha_k) ds - \lambda(\bar{J}_i - \underline{J}_i) - \bar{J}_i \} \geq 0, \\
&\tau + \sum_{k=1}^{M} \beta_k \int_{k-1}^{k} f_0(\hat{\xi}, \alpha_k) ds \geq 0, i = 1, ..., 6, \\
&\frac{d\hat{\xi}}{ds} = \beta_k g(\hat{\xi}, \alpha_k), \hat{\xi}(0) = \xi_0, \\
&s \in [k-1, k), \alpha_k \in \mho, \beta_k \geq 0, k = 1, ..., M.
\end{aligned} \tag{23}
$$

A suitable choice for M is important in the sense that a large value for M causes a computationally expensive problem and a small value for M decreases the precision of the solution. A reasonable heuristic approach for determining an approximation of the optimal number of switchings is the following [19]. Starting with a fixed M, we solve the Problem (23). We then increase the number of switchings (e.g. $M = M + 1$) and solve (23) again. If there is no decrease in the optimal cost, we take the previous value of M to be the optimal number of switchings. Otherwise we increase M. Note that while this approach yields satisfactory results in most practical problems, it cannot guarantee that the resulting M be indeed optimal.

5.2 CPET 2: A Discrete Dosage Approach

In this section we assume that the control variable can take values in $\mho = \{u_1, ..., u_m\}$. As stated in remark 1, $\mho = \{(0,0), (1,0), (0,1), (1,1)\}$ indicates the STI therapy. Here we use the CPET for optimal discrete-valued control problems introduced in [19] to obtain an optimal STI therapy. To this end, we construct a set $\{\alpha_i\}_{i=1}^{M}, M = (N+1)m$, where $\alpha_i = u_{((i-1) \bmod m)+1}, i = 1, ..., M$. A control function that takes values in $\mho$ and has N switching can be considered as (24):

$$
u_M(t) = \sum_{k=1}^{M} \alpha_k \chi_{[\tau_{k-1}, \tau_k)}(t), \tag{24}
$$

where $\tau_i \in [t_0, t_f]$ satisfies $t_0 = \tau_0 \leq \tau_1 \leq ... \leq \tau_{M-1} \leq \tau_M = t_f$. Note that u_M is now determined only by $\tau_i, i = 1, ..., M$. Now, we set

$$
\beta_k = \tau_k - \tau_{k-1}, k = 1, ..., M. \tag{25}
$$

We use the time scale control (20) to relate the new time variable $s \in [0, M)$ to the original time variable $t \in [t_0, t_M)$ through the equation (19). A similar procedure discussed in subsection 5.1 gives the following optimal parameter selection problem:

Table 2: Assessment values

	J_1	J_2	J_3	J_4	J_5	J_6
$\underline{J}_i$	450	281.4647	0.0727	-2.8638e+04	-1	-1
$\bar{J}_i$	16400	794.5960	0.1476	-2.4029e+03	0	0

Table 3: The optimal objective values and the satisfaction levels against M obtained by the CPET1

M	$J_1(t_f^*,u^*)$/ $\mu(J_1(t_f^*,u^*))$	$J_2(t_f^*,u^*)$/ $\mu(J_2(t_f^*,u^*))$	$J_3(t_f^*,u^*)$/ $\mu(J_3(t_f^*,u^*))$	$J_4(t_f^*,u^*)$/ $\mu(J_4(t_f^*,u^*))$	$J_5(t_f^*,u^*)$/ $\mu(J_5(t_f^*,u^*))$	$J_6(t_f^*,u^*)$/ $\mu(J_6(t_f^*,u^*))$	λ^*
5	5562.0636/ 0.3205	445.9261/ 0.3205	0.1324/ 0.7971	−8703.7121/ 0.7598	−0.6794/ 0.3205	−0.6795/ 0.3205	0.3205
10	5603.4551/ 0.3231	463.6019/ 0.3550	0.1281/ 0.7403	−9082.4276/ 0.7454	−0.6760/ 0.3240	−0.6769/ 0.3231	0.3231
20	5630.3852/ 0.3248	470.4465/ 0.3683	0.1289/ 0.7504	−9379.0233/ 0.7341	−0.6596/ 0.3403	−0.6752/ 0.3248	0.3248
40	5655.8313/ 0.3264	448.9426/ 0.3264	0.1276/ 0.7336	−9432.3975/ 0.7321	−0.6731/ 0.3269	−0.6736/ 0.3264	0.3264

$$
\begin{aligned}
&Maximize \quad \lambda \\
&Subject\,to: \\
&\sum_{k=1}^{M}\beta_k\{\int_{k-1}^{k} f_i(\hat{\xi},\alpha_k)ds - \lambda(\bar{J}_i-\underline{J}_i)-\bar{J}_i\}\geq 0, \\
&\tau+\sum_{k=1}^{M}\beta_k\int_{k-1}^{k} f_0(\hat{\xi},\alpha_k)ds\geq 0, i=1,...,6, \\
&\frac{d\hat{\xi}}{ds}=\beta_k g(\hat{\xi},\alpha_k),\hat{\xi}(0)=\xi_0, \\
&s\in[k-1,k),\beta_k\geq 0,k=1,...,M.
\end{aligned}
\tag{26}
$$

Table 4: The optimal objective values and the satisfaction levels against M obtained by the CPET2

M	$J_1(t_f^*,u^*)$/ $\mu(J_1(t_f^*,u^*))$	$J_2(t_f^*,u^*)$/ $\mu(J_2(t_f^*,u^*))$	$J_3(t_f^*,u^*)$/ $\mu(J_3(t_f^*,u^*))$	$J_4(t_f^*,u^*)$/ $\mu(J_4(t_f^*,u^*))$	$J_5(t_f^*,u^*)$/ $\mu(J_5(t_f^*,u^*))$	$J_6(t_f^*,u^*)$/ $\mu(J_6(t_f^*,u^*))$	λ^*
5	5541.2438/ 0.3192	445.2562/ 0.3192	0.1201/ 0.6328	−9617.6879/ 0.7250	−0.6808/ 0.3192	−0.6808/ 0.3192	0.3192
10	5555.5950/ 0.3201	448.9508/ 0.3264	0.1281/ 0.7391	−9045.6273/ 0.7468	−0.6786/ 0.3214	−0.6799/ 0.3201	0.3201
20	5617.8081/ 0.3240	450.8493/ 0.3301	0.1253/ 0.7018	−10286.548/ 0.6995	−0.6760/ 0.3240	−0.6760/ 0.3240	0.3240
40	5643.0043/ 0.3256	450.1933/ 0.3288	0.1227/ 0.6680	−9880.7484/ 0.7150	−0.6744/ 0.3256	−0.6744/ 0.3256	0.3256

The design of the STI therapies is studied by many scholars using the various methods which, for example, may be based on the dynamic programming technique [1, 12], the model predictive control (MPC) strategies [9, 31, 50] or the meta-heuristic search algorithms [29]. In these approaches it is assumed that the switching times of controls and the final time t_f are prefixed parameters which may be a restrictive assumption, while the CPET used in this section considers these parameters as the decision variables. In fact we have converted the OCP (16) into an optimal parameter selection problem, which can be solved by the optimal control software MISER 3 (See [13]).

6 Numerical Results

We implement two therapy protocols based on the CPET described in Section 5. Therapy is initiated at $t_0 = 147$, the time at which the number of CD4+ T-cells reaches 350 $cells/\mu L$ and the assessment values of $\underline{J}_i$ and $\bar{J}_i, i = 1, ..., 6$, for Both CPETs are outlined in Table (2). The CPETs have been solved with different values for M. The values of objective function corresponding to the continuous and STI therapies as well as their satisfaction levels are outlined in Tables 2 and 3, respectively. Some small variation in the optimal value with respect to the number of knots in the discretization is noted. Preliminary investigation suggests that this is due in part to the inaccuracies in the numerical solution of the differential equations and the optimization problem. The results in Tables (3) and (4) corresponding to $M = 40$ show that the minimum of satisfaction levels λ^* is lower in the case of the CPET2. The comparison between the CPET1 and the CPET2 shows that, although the value of λ^* for the CPET1 is more, this solution does not dominate the one given by the CPET2. In fact, the solution given by the CPET2 offers slightly better performance in terms of the quantity of medications and the level of healthy cells (J_2, J_5 and J_6) but worse performance than the CPET1 with respect to the viral load, the immune effectors and the survival time (J_1, J_3 and J_4). Actually, as discussed in [12], the STI has received considerable attentions as a way for reducing the risk of HIV mutating to strains which are resistant to current medication regimens. STI approach might also reduce any possible long-term toxicity of the drugs. Nevertheless, no well-controlled clinical study has demonstrated a clear advantage of STIs over continuous therapy. In fact, it has been suggested that STIs are associated with a decline in CD4+ T-cell counts, an increase in viral population, no virologic or immunologic benefit and as a result greater progression of diseases despite continuous treatment. The continuous and the STI therapies obtained by the CPET methods are depicted in Figures 1 and 4, respectively. Since the conflicting objectives J_1, J_2, J_5 and J_6 have equal satisfaction levels; it is concluded that the optimal control functions obtained by the CPET methods are globally optimal solutions. Figures 2, 3, 5 and 6 indicate the CD4+ T-cells counts and the number of HIV particles under the continuous and the STI drug schedule. From Figures 2 and 5, we see a drop in the number of CD4+ T-cells and a rise in viral load following the initial infection until about the third month. After this time, CD4+ T-cells start recovering and virus starts decreasing due to the immune response, but it can never be eradicated completely. Then CD4+ T-cells level decreases and viral load increases due to destruction of immune system. Moreover, the decreasing rate of CD4+ T-cells is reduced such that the progression to AIDS is postponed for more than 15 years and the virus is controlled to very low levels. Furthermore, these figures indicate an inverse coloration between viral load and CD4+ T-cells level.

For the therapy designed by the CPET2 the behaviour of the CD4+ T-cells and that of the viruses is much more oscillatory due to short breaks in the medications. In the rest of this section the capability of the CPET for solving multi-objective optimal control problems is investigated through studying more examples.

Car Example [22]. Let $x_1(t)$ and $x_2(t)$ denote the position, the velocity and the acceleration of a car at time t, respectively. The acceleration of the car is controlled by pushing the accelerator, or applying the brakes. A simple dynamic model for the car is $\dot{x}_1 = x_2$ and $\dot{x}_2 = u$. The aim is to drive $400m$, starting and ending at rest, while minimizing on the one hand, the control effort for accelerating and on the other hand travelling time. Assume that the control effort is proportional to $u^2(t)$ at time t. Therefore, we have a MOOCP which involves minimizing the functional $J_1(t_f, u) =$

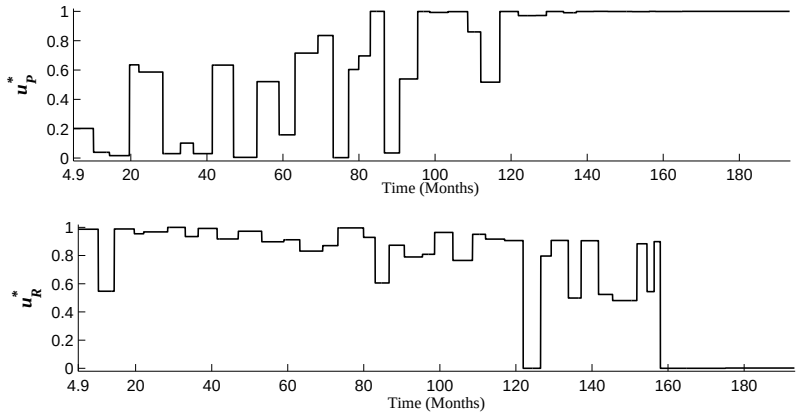

Figure 1: The optimal controls obtained by the CPET1

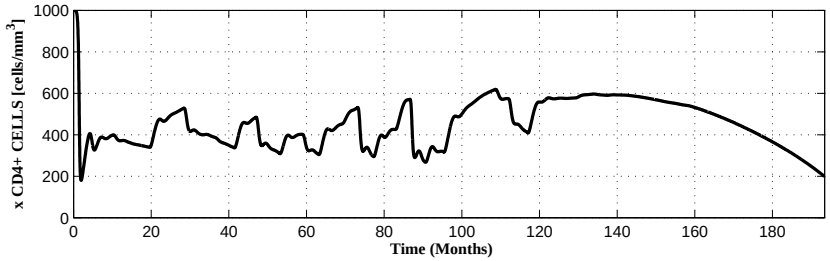

Figure 2: The response of the state variable x to the control functions obtained by the CPET1

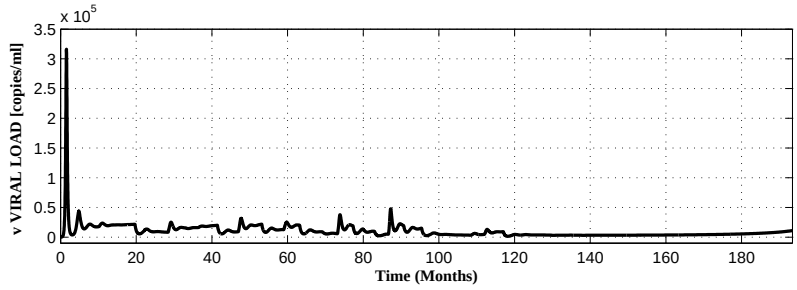

Figure 3: The response of the state variable v to the control functions obtained by the CPET1

$\int_0^{t_f} u^2(t)dt$ and $J_2(t_f, u) = \int_0^{t_f} dt$ over the constraints given by $\dot{x}_1 = x_2$, $\dot{x}_2 = u$ with the boundary conditions $x_1(0) = x_2(0) = x_2(t_f) = 0$ and $x_1(t_f) = 400$. Objectives J_1 and J_2 are obviously conflicting objectives since a small travelling time requires a high speed and hence, also a large control effort for reaching this speed. The simple structure of the problem makes it possible to represent the exact analytical solution of this example using the PMP and nonlinear programming techniques. Let $\underline{J}_i$ and $\bar{J}_i$ be, respectively, a minimum value and a maximum value of totally desirable levels for $J_i, i = 1, 2$. Corresponding to this example, we have a problem similar to (16) which has an exact analytical solution given by $u^*(t) = at + b$ and $t_f^* = \frac{20\sqrt{6}}{\sqrt{b}}$ with $\lambda^* = \frac{1-\bar{J}_2}{\bar{J}_2-\underline{J}_2}$ where

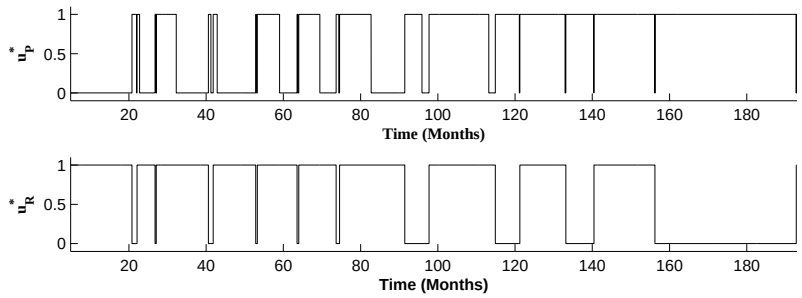

Figure 4: The optimal controls obtained by the CPET2

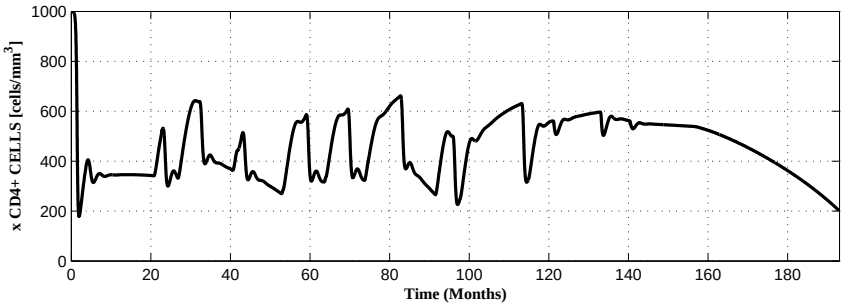

Figure 5: The response of the state variable x to the control functions obtained by the CPET2

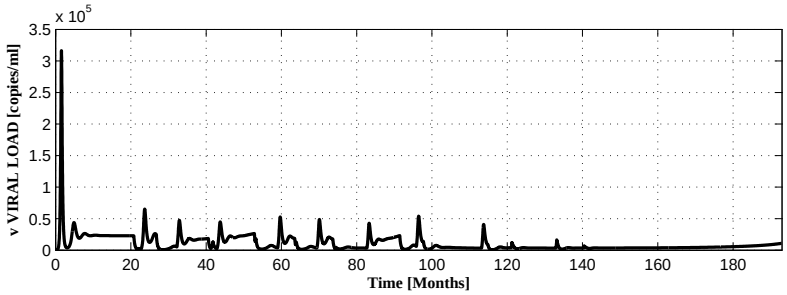

Figure 6: The response of the state variable v to the control functions obtained by the CPET2

$b = \sqrt{3\lambda^*(\bar{J}_1 - \underline{J}_1) + 3\bar{J}_1}$ and $a = \frac{-2b}{t_f^*}$. The CPET is implemented with $M = 10, \bar{J}_1 = -288.687, \underline{J}_1 = -1223.828, \bar{J}_2 = -4.330$ and $\underline{J}_2 = -18.357$. With these parameters the exact solution is $t_f^* = 13.0271$ and $u^*(t) = -2.1712t + 14.1421$ with $\lambda^* = 0.38$. The CPET gives $t_f^* = 13.0764$ with $\lambda^* = 0.3765$ which is near to optimal. The exact and approximate optimal controls and state trajectories are shown in Figures 7-9.

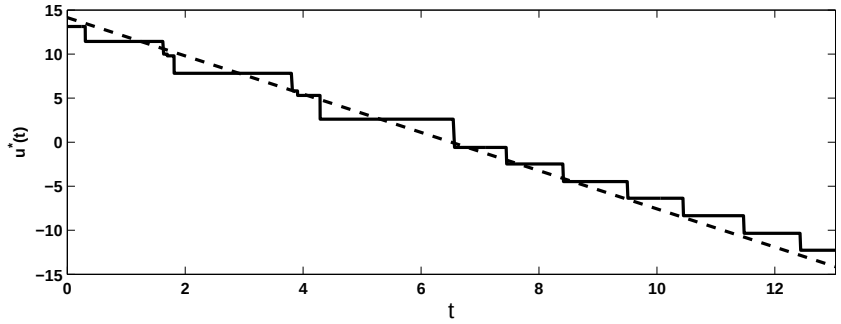

Figure 7: The exact (the dashed line) and the approximate (the solid line) optimal control

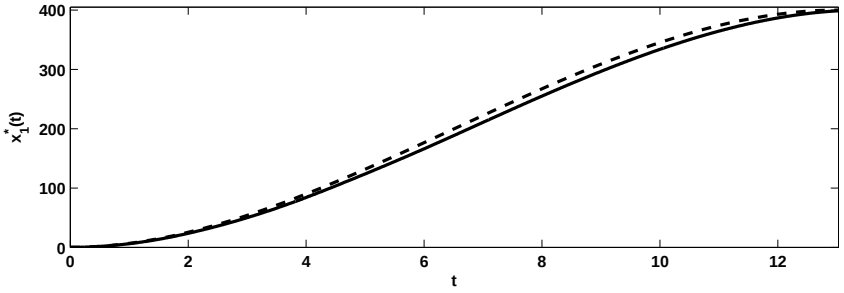

Figure 8: The exact (the dashed line) and the approximate (the solid line) optimal state x_1^*

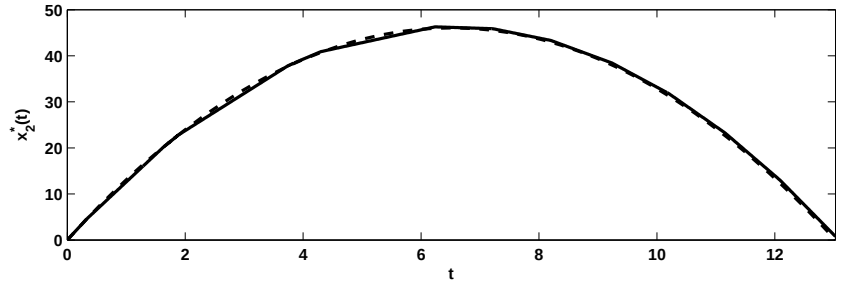

Figure 9: The exact (the dashed line) and the approximate (the solid line) optimal state x_2^*

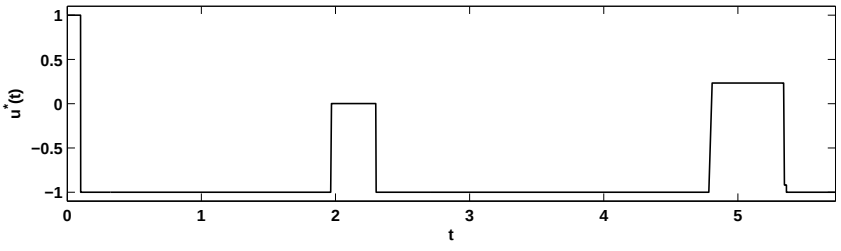

Figure 10: The optimal control obtained by the CPET1

Aircraft Example [15]. State space representation of a non-linear dynamical model of the F-8 fighter aircraft is given as (27)

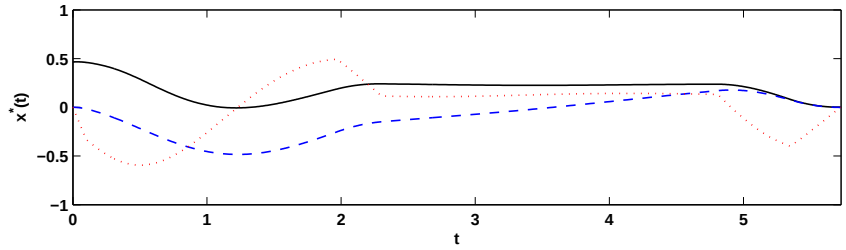

Figure 11: The optimal states x_1^* (the solid line), x_2^* (the dashed line) and x_3^* (the dotted line) obtained by the CPET1

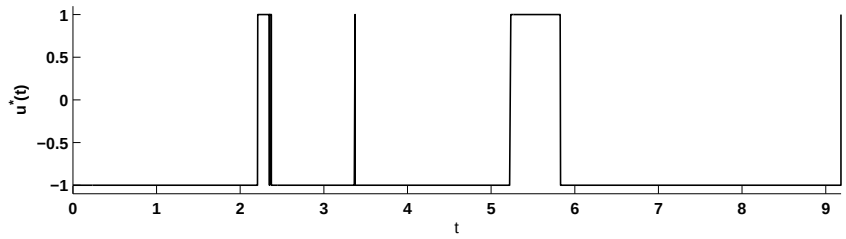

Figure 12: The optimal control obtained by the CPET2

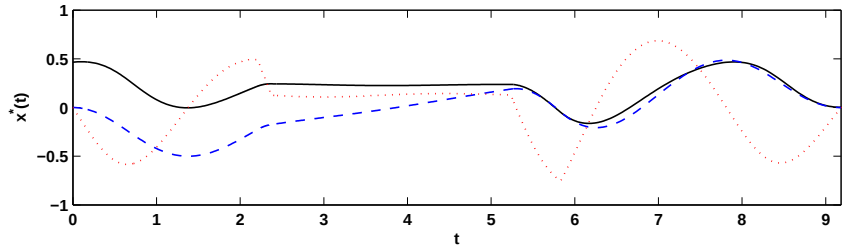

Figure 13: The optimal states x_1^* (the solid line), x_2^* (the dashed line) and x_3^* (the dotted line) obtained by the CPET2

$$\begin{aligned}
\dot{x}_1 &= -0.877x_1 + x_3 - 0.088x_1x_3 + 0.47x_1^2 - 0.019x_2^2 - x_1^2x_3 \\
&\quad + 3.84x_1^3 - 2.215u + 2.28x_1^2u + 0.47x_1u^2 + 0.63u^3, \\
\dot{x}_2 &= x_3, \\
\dot{x}_3 &= -4.208x_1 - 0.396x_3 - 0.47x_1^2 - 3.564x_1^3 - 20.967u \\
&\quad + 6.265x_1^2u + 46x_1u^2 + 61.4u^3,
\end{aligned} \tag{27}$$

where x_1 is the angle of attack in radians, x_2 is the pitch angle, x_3 is the pitch rate and the control input u is the tail deflection angle. Stabilization of the F-8 aircraft was studied in various works [15, 24]. Here we use the CPET to find the control inputs that steer the aircraft dynamic model from the initial state $x(0) = (0.4655, 0, 0)$ to the origin at minimum time. In fact this is a single-objective optimization as a special case of multi-objective optimization. The control input is bounded by 3^o; i.e.$|u| \leq 0.05235$ *rad* and by replacing the control variable u with $0.05235u$, we normalize the control set to be $U = [-1, 1]$. The CPET1 with $M = 10$ gives the optimal time $t_f^* = 5.7369$. We note that the optimal time obtained by using the measure theoretical approach in [24] is $t_f^* = 6.7069$

and the optimal time obtained by using the switching time computation method in [15] is $t_f^* = 6.3867$. Therefore, the CPET1 gives the better results. The optimal control obtained by the CPET1 and the corresponding optimal state trajectories are shown in Figures 10 and 11. Moreover, Figures 12 and 13 show the bang-bang optimal controls and the corresponding trajectories obtained by the CPET2 with $M = 10$. Note that the CPET2 gives $t_f^* = 9.1829$.

7 Conclusions

In this paper, we have studied a multi-objective optimal control problem (MOOCP) for designing the optimal anti-HIV treatment strategies in continuous and STI form which prolongs the onset of AIDS while enhancing the immune response and controlling the CD4+ T-cells concentration and the viral load. To this end, we converted the MOOCP into an optimal control problem in canonical form by using the Zimmermann's fuzzy approach. The resulting problem whose solution is a compromise Pareto optimal is solved using the CPET. Numerical results demonstrate that the problem is solved successfully using MISER3, despite the fact that nonlinear differential equations are introduced. The solution to the optimal problem indicates the therapies with minimal cost that yield a substantial improvement in the survival time of patient and the immune response and controls the CD4+ T-cells concentration and the viral load. As illustrated in this paper, CPET can accurately determine any switching time of the control, which has not been considered in previous researches. Moreover, the successful implementation of CPET in controlling the car and the aircraft dynamic model demonstrates the effectiveness and accuracy of this technique in handling multi-objective optimal control problems.

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کنترل بهینه چندهدفه دینامیک HIV به کمک تکنیک پارامتری کردن کنترل

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چکیده
دراین مقاله یک ایده محاسباتی برای حل یک مسئله فرمول‌بندی کنترل بهینه چندهدفه زمان‌بندی درمان بهینه در افراد آلوده به ویروس نقص ایمنی انسانی (HIV) مطرح می‌شود. مسئله کنترل بهینه چندهدفه که از یک مدل ریاضی عفونت HIV استفاده می‌کند، دارای چند هدف غیرهمسو است. مانند طول عمر بیمار، سطح سلول‌های CD۴+ و سطح CTL که باید بیشینه گردند، سطح ویروس و هزینه‌های دارو که باید کمینه گردند. دراین ایده آرمان‌های فازی توصیف شده توسط توابع عضویت خطی، به اهداف اضافه شده و جواب بهینه با بیشینه‌سازی درجه حصول آرمان‌های فازی انباشته شده، مورد جستجو قرار گرفته و یک مسئله کنترل بهینه آرمانی فازی نتیجه می‌شود. با استفاده از عملگر کمینه برای انبوهش آرمان‌های فازی، مسئله کنترل بهینه آرمانی فازی تبدیل به یک مسئله کنترل بهینه محدود در فرم کانونی می‌شود. روش پارامتری کردن کنترل برای تقریب مسئله کنترل بهینه با یک مسئله انتخاب پارامتر بهینه با هدف نهایی پیاده‌سازی ترکیبات پیوسته و منقطع (STI) کارایی داروهای دسته PI و RTI به کارمی‌رود. کارایی ایده بیان شده توسط شبیه‌سازی‌های عددی مورد تایید قرار می‌گیرد.

کلمات کلیدی
مسئله چندهدفه، کنترل بهینه، برنامه‌ریزی آرمانی فازی، بهینه‌سازی درمان.