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Optimal switching control for drug therapy process in cancer chemotherapy

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ABSTRACT

In this paper, the drug therapy problem in cancer chemotherapy is formulated as an optimal control problem of switched systems. In this problem, the modes switch under state-dependent. This is different from the existing optimal control problem of switched systems, in which the modes switch under time-dependent. Thus, the existing optimal control approaches of switched systems with time-dependent switching can not directly used to solve this Problem, and a new numerical computation method is required to develop for solving such problem. Firstly, based on introducing a binary function, relaxing the binary functions and including a penalty term on the relaxation, we obtain an equivalent optimal control problem of constrained nonlinear system. By using the time-scaling transformation, the smoothing technique, and the idea of l_1 penalty function method, the equivalent optimal control problem is transformed into a nonlinear parameter optimization problem. Then, a gradient-based continuous filled function algorithm is developed for solving the nonlinear parameter optimization problem. Finally, a numerical example is used to illustrate our method is low time-consuming, has faster convergence speed, and yields a better objective function value than the existing algorithms.

1. Introduction

Chemotherapy is a type of cancer treatment that uses drugs to kill cancer cells [10]. The earliest differential equation model describing the growth in volume of a tumor appears to be in the paper by Mayneord [28]. Other, more detailed, differential equation models appear in [5,34]. Swan [38] seems to be the first one devoted entirely to mathematical models involving differential equations that deal with the dynamic, or time course, variation of cancer. These models are quite different from those in biostatistical analyses, which tend to deal with end-stage results. The basic idea in [38] is that a disease state, such as cancer, can be modeled via a differential equation system. The first paper to utilize optimal control theory for a chemotherapy problem involving a human tumor was by Swan and Vincent [39]. For more discussions on optimal control for cancer chemotherapy problems, the reader may refer to [20,33,36], and the references therein.

Switched systems are a particular class of hybrid systems, which are composed of several dynamical modes and a switching rule that orchestrates the switching among them to ensure stability and satisfied performance. Optimal control of switched systems involves finding both the continuous control input and the switching signal to jointly optimize certain system performance index. Optimal control of switched systems is in general challenging due to the discrete nature of the switching control input, which prevents us from directly applying the classical optimal control approaches to solve this problem. In order to address the challenge, the classical maximum principle or the dynamic programming approach was extended to switched systems [7,24,26,29,32]. However, it is still very difficult to numerically compute the optimal solutions based on these abstract necessary conditions [2,9,21]. In the past two decades, some numerical computation methods have been developed for solving switched system optimal control problems [12,16,18,25,31,37]. One well-known method is the so-called the bi-level optimization method [1,13,14,45,46,48]. The method divides the original optimal control problem into two optimization problems and solves them at different levels. At the lower level, the method fixes a switching subsystem sequence and optimizes the cost function over the space of switching time instants through

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the classical variational approach. At the upper level, the switching subsystem sequence is updated to optimize the cost function. Recently, an alternative method based on the so-called embedding method has been developed [2,40,41]. The method is closely related to the relaxed optimal control problems which optimize over the convex closure of the original control set. Some results concerning the existence property of the optimal solutions to the original problem have been discovered in the literature of relaxed optimal control problems [6,43]. The embedding based method adopts the idea of relaxing the control input and takes one step further by introducing a projection operator which maps the relaxed optimal control back to the original input space to generate the desired switching control. There are three major steps involved in the embedding-based approach. The first step is to embed the switched systems into a larger class of classical nonlinear systems with only continuous control inputs. Then, the optimal control of the relaxed system is obtained by using the classical optimal control algorithms. Once the relaxed optimal solution is obtained, the solution to the original problem can be computed by projecting the relaxed solution back to the original input space through certain carefully designed projection operators.

In this paper, the drug therapy problem in cancer chemotherapy is formulated as an optimal control problem of switched systems. In the problem, the modes switch under state-dependent. This is different from the existing optimal control problem of switched systems, in which the modes switch under time-dependent [19,44,47]. Thus, the existing optimal control approaches of switched systems with time-dependent switching can not directly used to solve this problem, and a new numerical computation method is required to develop for solving such problem. Firstly, based on introducing a binary function, relaxing the binary functions and including a penalty term on the relaxation, we obtain an equivalent optimal control problem of constrained nonlinear system. By using the time-scaling transformation, the smoothing technique, and the idea of l_1 penalty function method, the equivalent optimal control problem is transformed into a nonlinear parameter optimization problem. Then, a gradient-based continuous filled function algorithm is developed for solving the nonlinear parameter optimization problem. Finally, a numerical example is used to illustrate our method is low time-consuming, has faster convergence speed, and yields a better objective function value than the existing algorithms.

The rest of the paper is organized as follows. Section 2 presents the optimal control problem of drug therapy in cancer chemotherapy. By introducing a binary function, Section 3 obtains an equivalent constrained nonlinear system optimal control problem with pure continuous variables. In Section 4, by using the time-scaling transformation, the smoothing technique, and the idea of l_1 penalty function method, the constrained nonlinear system optimal control problem is transformed into a nonlinear parameter optimization problem, which can be solved by any gradient–based optimization method. Then, a gradient-based continuous filled function algorithm is developed for solving such problem. In Section 6, a numerical example is provided to show the effectiveness our method.

2. Problem formulation

The drug concentration at the cancer site is described by the following ordinary differential equation derived by Bellman [3]:

$$\frac{dA(t)}{dt} = u(t) - \alpha A(t), \tag{1}$$

$$A(0) = A_0, \tag{2}$$

where $A(t)$ is the concentration of anti-cancer drug at the tumour site at time t; $u(t)$ is the drug delivery rate at time t; A_0 is the drug concentration at the instant before chemotherapy begins; and α is a given constant.

The tumour growth rate is the net change due to cell proliferation and cell death from the anti-cancer drug. Note that the cell proliferation can be described by using the Gompertz equation [8], and the cell death only occurs when the drug concentration is above a certain threshold [11]. Thus, the tumour growth rate can be described by using the following mathematical model:

$$\frac{dB(t)}{dt} = aB(t)\ln\left(\frac{b}{B(t)}\right), \quad if\ A(t) \leqslant A_{th}, \tag{3}$$

$$\frac{dB(t)}{dt} = aB(t)\ln\left(\frac{b}{B(t)}\right) - c(A(t) - A_{th})B(t), \quad if\ A(t) \geqslant A_{th}, \tag{4}$$

$$B(0) = B_0, \tag{5}$$

where $B(t)$ is the number of tumour cells at time t; B_0 is the number of tumour cells at time t; A_{th} is the threshold of the drug concentration; $a > 0$, $b > 0$ are given constants; and $c > 0$ is the proportion of tumour cells killed per unit time per unit drug concentration.

In the paper, two restrictions will be imposed on the drug concentration to ensure that the patient can tolerate its toxic side effects. Firstly, the drug concentration at the cancer site is bounded above by a given parameter $A_{max} > 0$:

$$0 \leqslant A(t) \leqslant A_{\max}, \quad t \in [0, t_f], \tag{6}$$

where t_f is a given terminal time. A measure of drug toxicity is the drug concentration multiplied by the time of exposure [11]. This can be quantified mathematically as the integral of the drug concentration over a specified period of time. When the period is the entire therapy, the constraint is upon the total cumulative toxicity:

$$\int_0^{t_f} A(t)dt \leqslant A_{cum},$$

where $A_{cum} > 0$ is a given constant. Applying the mean value theorem for integrals to (7), we have

$$A(\xi)t_f - A_{cum} \leqslant 0, \tag{7}$$

where $0 \leq \xi \leq t_f$.

Drug resistance is considered to be a significant factor in chemotherapeutic failure [35] and it has been shown that drug resistant cells are more likely to emerge as the tumour burden increases [15]. One way of achieving a low intermediate tumour burden is to force the tumour size to decrease at, or faster than, a given rate. The following restriction is imposed on the tumour size to ensure that it decreases at, or faster than, a specified rate:

$$B(t_k) \leqslant \eta B(t_{k-1}), \quad k = 1, \ldots, M, \tag{8}$$

where $0 < \eta < 1$ is a given fraction; t_i, $i = 1, \ldots, M$ are fixed; and $0 = t_0 < t_1 < \cdots < t_M < t_f$.

In addition, an upper bound also is required to be imposed on the drug delivery rate:

$$0 \leqslant u(t) \leqslant u_{\max}, \quad t \in [0, t_f], \tag{9}$$

where $u_{\max}$ is a given constant. Then, an optimization problem can be defined as follows:

Problem 1. Given the ordinary differential equations (1), (3), and (4) with the initial condition (2) and (5), choose a drug delivery rate $u(t)$ such that the final tumour population $B(t_f)$ is minimized subject to the constraints (6)–(9).

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