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OPTIMAL DRUG SCHEDULING OF CANCER CHEMOTHERAPY

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Abstract

An optimal piecewise constant control policy for cancer chemotherapy is given, such that the size of a tumor is minimized at the end of a given time interval, and so that all the state constraints are satisfied. Due to the large number of state constraints, direct search optimization was used. A sequence of computer runs was necessary to establish the optimal control policy. The results from a previous run were used to establish the parameters for the next run. The results were thus improved from one run to the next until the global optimal control policy was established. The results obtained are significantly better than have been previously reported for this problem.

Keywords: optimal control, iterative dynamic programming, cancer chemotherapy.

Introduction

An important problem in cancer chemotherapy is to determine the rate at which the drug should be administered, so that after a fixed period of treatment, the size of the cancerous tumor is minimized. Recently MARTIN (1992) showed the difficulty of trying to solve this optimal control problem by using nonlinear programming. The results were improved quite considerably by BOJKOV et al (1993) by using the direct search optimization procedure proposed by LUUS and JAAKOLA (1973), which was recently used for optimization of heat exchanger networks (1993). One advantage of the direct search optimization method is that there is no need for introduction of auxiliary variables and therefore the procedure is easy to implement.

The purpose of this paper is to show how the direct search optimization can be used successfully on complex optimal control problems, and to illustrate in detail how the optimum can be established in a highly constrained problem. We would also like to present the global optimum solution which somehow has eluded numerous researchers studying the drug scheduling problem of cancer chemotherapy.

Problem Formulation

The effects of chemotherapy, as outlined by MARTIN (1992), are given by the differential equations

$$\frac{dx_1}{dt} = -\lambda x_1 + k(x_2 - \beta)H(x_2 - \beta), \tag{1}$$

$$\frac{dx_2}{dt} = u - \mathbf{y}x_2, \tag{2}$$

$$\frac{dx_3}{dt} = x_3, \tag{3}$$

with the initial state $\mathbf{x}^T(0) = [\ln(100) \quad 0 \quad 0]$, where

$$H(x_2 - \beta) = \begin{cases} 1 & \text{if} \quad x_2 \geq \beta \\ 0 & \text{if} \quad x_2 < \beta \end{cases}. \tag{4}$$

The tumor mass is given by $N = 10^{12}\exp(-x_1)$ cells, x_2 is the drug concentration in the body in drug units [D], and x_3 is the cumulative effect of the drug. The parameters are: $\lambda = 9.9 \cdot 10^{-4}$ days^{-1}, $k = 8.4 \cdot 10^{-3}$ days^{-1} [D]$^{-1}$, $\beta = 10$ [D], and $\mathbf{y} = 0.27$ days^{-1}. The performance index to be maximized is

$$I = x_1(t_f), \tag{5}$$

where the final time $t_f = 84$ days.

The optimization is to be done subject to the constraints on the drug delivery

$$u \geq 0, \tag{6}$$

and on the state variables

$$x_2 \leq 50, \tag{7}$$

$$x_3 \leq 2.1 \cdot 10^3. \tag{8}$$

Furthermore, there should be at least 50 per cent reduction in the size of the tumor mass every three weeks as calculated from the initial tumor size, so that

$$x_1(21) \geq \ln(200), \tag{9}$$

$$x_1(42) \geq \ln(400), \tag{10}$$

$$x_1(63) \geq \ln(800). \tag{11}$$

The maximum value of the performance index reported by MARTIN (1992) is 16.836 which corresponds to the final tumor size $N = 4.878 \cdot 10^4$ cells. BOJKOV et al (1993) improved the value of the performance index to 17.223 which corresponds to $N = 3.31 \cdot 10^4$ cells. Direct search optimization along with intuitive approach was used, so it was not quite clear whether the global optimum was obtained. In the present work we shall use direct search optimization directly without any attempt to narrow the search by any intuitive feel for the problem. We consider the problem of determining the daily drug delivery rate, by considering this optimal control problem as an 84-dimensional optimization problem, where the drug administration is done at a constant rate on each day. For optimization we use the direct search method of LUUS and JAAKOLA (1973).

Numerical Results

Since the number of variables is very large, and the equations are highly nonlinear, we approached this problem by attempting to reduce the number of variables in a sequence of runs. For the first run, we chose $u^{(0)}(k) = 6.75$, and $r^{(0)} = 30$, $k = 0, 1, 2, \ldots, 83$, a region contraction factor of 0.95 which is frequently a good factor to use for complex problems as was shown by SPAANS and LUUS (1992), and a contraction factor of 0.70 to reduce the starting region size at the beginning of each pass. In each iteration 5000 sets of random points were used. After 5 passes of 20 iterations each, we reached a performance index $I = 16.077$. We observed that $u(0), u(1), \ldots, u(9)$ were nearly zero and that the use of a very large number of randomly chosen points was not really necessary. Therefore, for the second run, we put the first ten control variables to zero, and carried out optimization on the remaining 74 variables, using 1000 randomly chosen sets of values at each iteration. The resulting value of the performance index was $I = 16.108$ with $u(10)$ and $u(11)$ both zero. Proceeding in this fashion of reducing the dimensionality of the optimization problem, after 21 runs, we were left with a 2-dimensional search on $u(20)$ and $u(48)$. The resulting performance index was $I = 17.476$ with the optimal control policy given in *Fig. 1.*

The optimal control policy shows two humps where the drug concentration is brought to its maximum allowable value very rapidly. The corresponding final tumor size is $2.57 \cdot 10^4$ cells. This is an improvement of 22% over the results of BOJKOV et al (1993) and an improvement of 47% over the results of MARTIN (1992).

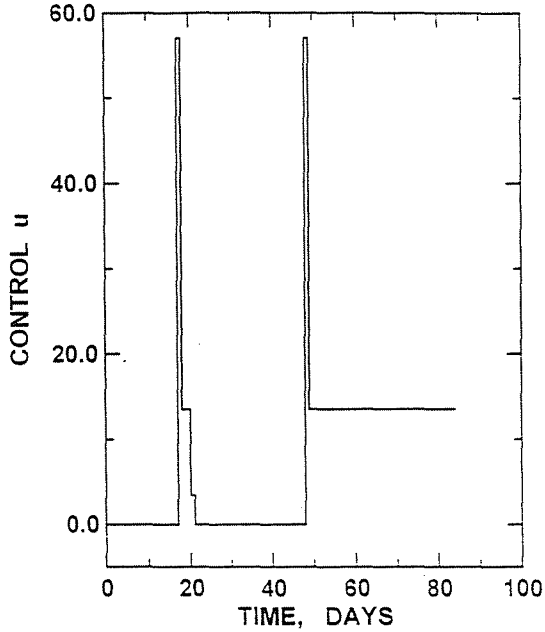

Fig. 1. Optimal drug delivery schedule for cancer chemotherapy

Conclusions

This very interesting optimal control problem shows why further research is necessary before very complicated optimal control problems can be solved with absolute confidence. It is always important to cross-check the resulting control policy with methods that do not rely on the gradient. The availability of very fast digital computers now enables one to consider less efficient methods that have a higher probability of obtaining the global optimum. This example also illustrates the importance of thoroughly examining the results after every run.

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