EVALUATION OF SOME OPTIMAL CHEMOTHERAPY PROTOCOLS BY USING A GRADIENT METHOD

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The paper presents some optimal problems resulting from cancer chemotherapy. Two bilinear models of a cell population cycle and a linear performance index are considered. A numerical gradient method is applied to solve the problems. Some properties and related simulation results of optimal control strategies are discussed.

1. Introduction

Cancer chemotherapy is based on suitable dosage of pharmacological agents called cytostatics. The cytostatics do not only destroy cancer cells but also damage other tissues such as the mucous membrane or alimentary canal. This influence is called the negative effect of the drug. In order to maximize the result of cancer cell destruction under constraint on the negative effect, it is necessary to work out control strategies (chemotherapy protocols). It seems that some methods of optimal control can be applied to the problem.

The cell cycle consists of phases passed by each cell from its birth to division. In general, these phases are called: the growth phase (G_1), the DNA synthesis phase (S), the preparation for division phase (G_2), and the division phase (M). After division two new cells usually re-enter the growth phase.

For the control purpose, different models of proliferation cycle are discussed in the literature. In the simplest model (Kimmel and Świerniak, 1983) all cell phases are clustered into a single compartment. Then, it has the following form:

$$\dot{N}(t) = -aN(t) + 2u(t)aN(t), \qquad N(0) = N_0 > 0 \tag{1}$$

where $N(t)$ is the size of cancer cell population; $u(t)$ represents a probability of cell survival after a cytostatic dosage, thus $0 \leq u(t) \leq 1$; constant a is an inverse of average length of cell cycle time; the coefficient 2 represents a cell symmetric division into two new cells. For $u = 0$ the maximum dose is used, whereas for $u = 1$ the drug is not administered and $0 < u < 1$ in all other cases.

A performance index has the form:

$$J = rN(T) + \int_0^T (1 - u(t))\, \mathrm{d}t \to \min \tag{2}$$

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where r is a weighting coefficient; the second component in (2) represents a negative cumulated cytostatic effect; T is the length of chemotherapy time.

In (Świerniak, 1989), there are discussed four modified one-compartmental models which lead to optimal control problems. It is shown that solutions are non-unique and singular. From the medical point of view this may suggest that the models under consideration are too simple.

The aim of the paper is to discuss more complicated models of the proliferation cycle and properties of corresponding solutions.

2. Problem Formulation for Two-Compartmental Model

Consider a two-compartmental model (Świerniak, 1989) in which two compartments are composed of the phases $G_1 + S$ and $G_2 M$. That model is the simplest one, which allows us to take into account phase sensitivity of the drugs. The equations of the model are bilinear:

$$\dot{N}_1 = -a_1 N_1 + 2u a_2 N_2, \qquad N_1(0) = N_{10} > 0$$
$$\dot{N}_2 = a_1 N_1 - a_2 N_2, \qquad N_2(0) = N_{20} > 0 \tag{3}$$

where N_1 and N_2 represent average numbers of cancer cells in $G_1 + S$ and $G_2 M$ phases, respectively; the constants a_1 and a_2 have the similar meaning as 'a' in (1); the control u represents the killing effect of a cytostatic which exists only for the cells in $G_2 M$.

The performance index which should be minimized has the form:

$$J = \int_0^T (1 - u)\, \mathrm{d}t + \sum_{i=1}^{2} r_i N_i(T) \tag{4}$$

and can be interpreted similarly to (2).

The necessary conditions of the optimality for the control of (3) with the performance index (4) given by the Maximum Principle (Pontryagin *et al.*, 1962) lead to the Two-Point Boundary-Value Problem (TPBVP). It can be solved by a semi-analytical method proposed in (Świerniak and Polański, 1993). In the sequel that problem will be solved by using a gradient method.

3. Problem Formulation for Three-Compartmental Model

Consider the cell cycle model which includes separate compartments for the G_1, S and $G_2 M$ phases. The objective is to keep cancer cells in the S phase by a cytostatic (v) and then release them just at the moment when another $G_2 M$ specific anticancer drug (u) has the maximum killing potential.

The equations of the model have the form:

$$\dot{N}_1 = -a_1 N_1 + 2u a_3 N_3, \qquad N_1(0) = N_{10} > 0, \qquad 0 \le u \le 1$$
$$\dot{N}_2 = a_1 N_1 - v a_2 N_2, \qquad N_2(0) = N_{20} > 0, \qquad v_m \le v \le 1 \tag{5}$$
$$\dot{N}_3 = -a_3 N_3 + v a_2 N_2, \qquad N_3(0) = N_{30} > 0$$

The performance index to be minimized is of the form:

$$J = \int_0^T (1 - u)\, dt + \sum_{i=1}^3 r_i N_i(T) \tag{6}$$

In the sequel, this problem will be solved by using the gradient method.

4. Description of a Gradient Method

Consider a system described by the state equation:

$$\dot{N} = f(N, u) \tag{7}$$

where $f(\cdot)$ is a differentiable function and $N_0 \in \mathbb{R}^n$ is given. Without loss of generality assume that u is scalar and $-1 \leq u \leq 1$.

The performance index has the form:

$$J = \int_0^T l(N, u)\, dt + h[N(T)] \to \min \tag{8}$$

where $l(\cdot)$ and $h(\cdot)$ are given scalar functions; T – given horizon of optimization.

Let us denote by δu and δJ a variational form of u and J, respectively. Using the calculus of variations (Mohler, 1973) it follows that

$$\Delta J = J(u + \delta u) - J(u) \approx \int_0^T \frac{\partial H}{\partial u} \delta u\, dt \tag{9}$$

with the conditions

$$\dot{p} = -\left(\frac{\partial H}{\partial N}\right)^T, \qquad p(T) = \left(\frac{\partial h}{\partial N}\right)^T \tag{10}$$

where H is called the Hamiltonian and is defined as

$$H = l(N, u) + p^T f(N, u) \tag{11}$$

where p is a costate vector; T denotes transposition of a vector.

Now, assume that optimal control is a bang-bang process and for some N and given τ_j^N, $j = 1, 2, ..., N$ the control variable u is of the form:

$$u = \sum_{j=0}^N (-1)^j \left[\mathbb{1}(t - \tau_j^N) - \mathbb{1}(t - \tau_{j+1}^N) \right] \tag{12}$$

where $\mathbb{1}(\cdot)$ is the unit step function and τ_j^N, $j = 1, 2, ...N$ are called switching times; $\tau_0^N = 0$, $\tau_{N+1}^N = T$.

It can be shown that the variational form of u is given by

$$\delta u = 2 \sum_{j=1}^N (-1)^{j+1} \delta(t - \tau_j^N) \delta \tau_j^N \tag{13}$$

where $\delta(\cdot)$ is the Dirac delta function and $\delta\tau_j^N$ is the variation of the switching time τ_j^N.

If (13) is substituted into (9), it can be seen that

$$\Delta J \approx 2 \sum_{j=1}^{N} (-1)^{(j+1)} \left. \frac{\partial H}{\partial u} \right|_{\tau=\tau_j^N} \delta\tau_j^N \tag{14}$$

To minimize the performance index J, the variation $\delta\tau_j^N$ should fulfil the condition $\Delta J \leq 0$. It can be seen that:

$$\delta\tau_j^N = (-1)^j k_j \phi_j, \qquad j = 1, 2, ..., N \tag{15}$$

where $\phi_j = \left. \dfrac{\partial H}{\partial u} \right|_{\tau=\tau_j^N}$ and k_j is a positive coefficient.

The steps in the numerical algorithm are as follows:

1. Assume N and τ_i^N, $i = 1, 2, ..., N$.
2. Solve the state equation (7) for given (12).
3. Compute the vector $p(t)$ by integrating (10) backward in time.
4. Compute the variables ϕ_i, choose a suitable k_i and compute $\delta\tau_i^N$ from (15), $i = 1, 2, ..., N$.
5. Compute new switching times $(\tau_i^N + \delta\tau_i^N)$, $i = 1, 2, ..., N$.
6. Repeat Steps 2–5 until $\sum_{i=1}^{N}(\delta\tau_i^N)^2 < \epsilon$, where $\epsilon > 0$ is a given small number.
7. If an optimal $\tau_i^N \neq \tau_j^N$, then increase the number of switching times and repeat Steps 1–6 until some τ_i^N, τ_j^N tend to cluster.

For some form of bilinear state equations and a performance index, the gradient method is described in (Hestens, 1966).

5. Solution to the Two-Compartmental Model

Let us apply the gradient method to the model described by (3), (4) where u should satisfy $0 \leq u \leq 1$. After transformation $u = 0.5(1 + u^*)$, equations (3) and (4) can be written in the form:

$$\begin{aligned} \dot{N}_1 &= -a_1 N_1 + a_2 N_2 + a_2 N_2 u^*, \qquad -1 \leq u^* \leq 1 \\ \dot{N}_2 &= a_1 N_1 - a_2 N_2 \end{aligned} \tag{16}$$

$$J = 0.5 \int_0^T (1 - u^*)\,\mathrm{d}t + \sum_{i=1}^{2} r_i N_i(T) \tag{17}$$

From (7), (8), (10), (11) and (15) it results that

$$\begin{aligned} \dot{p}_1 &= a_1 p_1 - a_2 p_2, & p_1(T) &= r_1 \\ \dot{p}_2 &= -a_2 p_1 + a_2 p_2 + p_1 a_2 u^*, & p_2(T) &= r_2 \end{aligned} \tag{18}$$

$$\delta\tau_i^N = (-1)^i k_i(-1 + 2p_1 a_2 N_2)\big|_{\tau=\tau_i^N}, \qquad i = 1, 2, \ldots, N \tag{19}$$

For the assumed u^* given by (12) we can see that equations (16) and (18) are linear.

As an example let us consider (16) and (17) for $a_1 = 0.197$, $a_2 = 0.356$, $r_1 = 6.94$, $r_2 = 3.94$, $N_{10} = 0.83$, $N_{20} = 0.57$ $T = 10$. From numerical investigations it results that there exist two local minima for one switching time. The optimal solutions are as follows:

- the first solution: $u = 1$ for $0 \le \tau \le 5.32$ and $u = 0$ for $5.32 < \tau \le 10$;
- the second solution: $u = 0$ for $0 \le \tau \le 4.67$ and $u = 1$ for $4.67 < \tau \le 10$.

The optimal value of the performance index for these solutions is $J^{\text{opt}} = 8.3587$. It is interesting that for other data there exists only one optimal switching time.

6. Solution to the Three-Compartmental Model

Consider model (5). After transformations $u = 0.5(1+u^*)$, $v = 0.5[v^*(1-v_m)+(1+v_m)]$ we can transform (5) and (6) into the form

$$\dot{N}_1 = -a_1 N_1 + a_3 N_3 + a_3 N_3 u^*, \qquad\qquad\qquad -1 \le u^* \le 1$$

$$\dot{N}_2 = a_1 N_1 - 0.5(1+v_m)a_2 N_2 + 0.5(v_m - 1)a_2 N_2 v^*, -1 \le v^* \le 1 \tag{20}$$

$$\dot{N}_3 = 0.5(1+v_m)a_2 N_2 - a_3 N_3 + 0.5(1-v_m)a_2 N_2 v^*$$

The performance index which should be minimized has the form

$$J = 0.5 \int_0^T (1 - u^*)\cdot \mathrm{d}t + \sum_{i=1}^3 r_i N_i(T) \tag{21}$$

It is easy to notice that from (7), (8), (10) and (11) it results that:

$$\dot{p}_1 = a_1 p_1 - a_1 p_2$$

$$\dot{p}_2 = 0.5\big[(1+v_m)a_2 + (1-v_m)a_2 v^*\big]p_2$$
$$\qquad -0.5[(1+v_m)a_2 + (1-v_m)a_2 v^*]p_3 \tag{22}$$

$$\dot{p}_3 = -a_3(1-u^*)\dot{p}_1 + a_3 p_3$$

with $p_1(T) = r_1$, $p_2(T) = r_2$, $p_3(T) = r_3$.

The variations of switching times for u^* and v^* are as follows:

$$\delta_{iu^*}^N = (-1)^i k_{iu^*}(-1 + 2p_1 a_3 N_3)\big|_{\tau=\tau_{iu^*}}$$
$$\delta_{iv^*}^N = (-1)^i k_{iv^*}\big[(v_m - 1)a_2 p_2 N_2 + (1-v_m)a_2 N_2 p_3\big]\big|_{\tau=\tau_{iv^*}} \tag{23}$$

To solve this problem the gradient method can be used.

As an example consider (5) and (6) for $a_1 = 0.197$, $a_2 = 0.356$, $a_3 = 0.5$, $r_1 = 6.94$, $r_2 = 3.54$, $r_3 = 2.1$, $v_m = 0.9$, $N_{10} = 0.83$, $N_{20} = 0.57$, $N_{30} = 0.2$, $T=10$. The optimal solution is as follows:

$$u = 1 \quad \text{for} \quad 0 \le \tau \le 3.15, \quad u = 0 \quad \text{for} \quad 3.15 < \tau \le 10,$$

$$v = v_m \quad \text{for} \quad 0 \le \tau \le 2.95, \quad v = 1 \quad \text{for} \quad 2.95 < \tau \le 10.$$

The optimal value of the performance index is $J^{\text{opt}} = 10.57$.

For changed $v_m = 0.1$ the optimal results are:

$$u = 1 \quad \text{for} \quad 0 \le \tau \le 6.8, \quad u = 0 \quad \text{for} \quad 6.8 < \tau \le 10,$$

$$v = v_m \quad \text{for} \quad 0 \le \tau \le 6.5, \quad v = 1 \quad \text{for} \quad 6.5 < \tau \le 10.$$

The corresponding optimal value of the performance index is $J^{\text{opt}} = 8.42$.

For other data there exists only one switching time for the control u and v.

Acknowledgment

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