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SOME CONTROL PROBLEMS RELATED TO OPTIMAL CHEMOTHERAPY–SINGULAR SOLUTIONS

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In the paper it has been proved that some optimal control problems resulting from the simplest models of cancer chemotherapy lead to singular control solutions. The singularity seems to be a characteristic feature of bilinear models even if dynamics of the drug activity or reaction of critical normal tissues is encountered. On the other hand, the singular control is absent when the Gompertz–type growth is applied.

1. Introduction

Cancer chemotherapy is based on suitable dosage (discrete or continuous) of pharmaceutical agents called cytostatics. The cytostatics do not only destroy cancer cells but also damage other tissues especially so–called critical normal tissues such as: endothelum medulla, hairs, mucous membrane of alimentary canal. Thus, it is necessary to work out control strategies (chemotherapy protocols) in order to maximize result of cancer cells destruction under constrains of normal tissues damage. It seems that some methods of optimal control can be applied to that problem.

Application of optimal control theory to cancer therapy was first discussed probably by Bahrami and Kim (1975), where the discrete maximum principle is proposed for elaboration of optimal protocols in *related* radiotherapy problem.

Application of control theory to optimize chemotherapy protocols appears first in (Swan and Vincent, 1977) for continuous models and in (Kim *et al.*, 1977) for discrete ones. In (Swan and Vincent, 1977) control strategy minimizes a toxic effect, while in (Kim *et al.*, 1977) it maximizes a destruction result on cancer population.

The simplest model of the proliferation cycle was proposed by Kimmel and Świerniak (1983) in the following form

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

where $N(t)$ is a size of a cancer cell population, $1-u(t)$ represents a probability of cell survival after a cytostatic dosage, $0 \leq u(t) \leq 1$, constant a is an inverse of average lenght of cell cycle time, 2 represents a mother cell symmetric division into two daugter cells.

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A performance index has a form (Kimmel and Świerniak, 1983)

$$\min \leftarrow J = rN(T) + \int_0^T u(t)dt \tag{2}$$

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

It has been shown, via direct optimization, that a solution to the problem can be nonunique. This property can be eliminated by taking into account a multicompartment model and effect of cytostatic phase sensitivity. The optimal control has a bang–bang form and it is determined by a solution to a two point value boundary problem.

In (Świerniak and Kimmel, 1984; Świerniak, 1989; 1990) a linear structure of system equations and partially analytical form of solutions are proposed. It seems to be more effective than the method STVM used to solve similar problems (Shin and Pado, 1982).

The objective of our paper is to show that nonuniqueness of the solution to the problem formulated by Kimmel and Świerniak (1983) results from a total singularity of the optimal control. In chapter 2 we present a solution to the problem in a simpler form than in (Kimmel and Świerniak, 1983) pointing out its singularity. Dynamics of the drug activity is introduced in chapter 3, while reactions of both cancer and normal tissues are discussed in chapter 4. It has been proved that optimal control is still singular. It seems that multicompartmental models discussed in (Świerniak and Kimmel, 1984; Świerniak, 1989; 1990; Shin and Pado, 1982) do not have this property. In chapter 5 we show that singular control is absent when non–linear models, e.g. Gompertz–type growth are applied.

2. Optimal Chemotherapy Protocol for the Simplest Model

Model (1) occurs under assumptions of linear outflow from the compartment i.e. a linear dependence of the number of cells leaving the proliferation cycle, a symmetric division of cells in mitosis and a monotonic (for feasible dosage) dependence between the dose of the drug and a fraction of cells incapable of further division.

The minimization of performance index (2) takes into account a compromise between cancer cell population at the end of the chemotherapy and a negative cumulated cytostatic effect.

Optimization problem (1), (2) with constrained control variable

$$0 \leq u \leq 1 \tag{3}$$

can be solved directly but we apply the control theoretic approach to show singularity of the solution. To solve the problem we transform equation (1) to a linear form substituting

$$x = \ln N \tag{4}$$

We obtain

$$\dot{x} = -a + 2a(1-u) \qquad x(0) = \ln N_0$$

Then

$$\dot{x} = a - 2au \tag{5}$$

and performance index (2) has the following form

$$J = re^{x(T)} + \int_0^T u(t)dt \tag{6}$$

Equation (5) describes an integral system. One can find that (6) can be written in the form

$$J = re^{aT+x(0)}e^{-2a\int_0^T u\,dt} + \int_0^T u\,dt \tag{7}$$

Therefore, we have a static optimization problem with respect to

$$v = \int_0^T u\,dt \quad 0 \le v \le T \tag{8}$$

Thus we have

$$J = r_1 e^{-2av} + v \tag{9}$$

where $r_1 = re^{aT+x(0)}$. By differentiating

$$dJ/dv = -2ar_1 e^{-2av} + 1 = 0$$

we obtain

$$v = \frac{1}{2a}\ln 2ar_1 = \frac{1}{2}T + \frac{1}{2a}\ln 2arN_0 \tag{10}$$

Formula (10) is the optimal solution under the condition

$$0 \le \ln 2ar_1 \le 2aT$$

or

$$-T \le \frac{1}{a}\ln 2arN_0 \le T \tag{11}$$

If condition (11) is not fulfiled, then control $u(t)$ is on the bounderies of the constraints. Solution (10) confirms the nonuniqness of the optimal control $u(t)$ because any $u(t)$ satisfying (8) and (10) is optimal. The order reduction (from a dynamical problem of the 1st order to a static problem) indicates a singularity of optimal control (Johnson, 1985). In order to prove precisely this property, we apply the maximum principle (Pontryagin *et al.*, 1965).

Hamiltonian for problem (5), (6) has the form

$$H = u + pa(1 - 2u)$$

where p is a costate variable described by an equation

$$\dot{p} = 0 \qquad p(T) = re^{x(T)} \tag{12}$$

Thus

$$p(t) = \text{ const } = re^{x(T)} \tag{13}$$

Necessary conditions of the optimality control have the form

$$u^{\circ} = \begin{cases} 0 & \text{if } p < 1/2a \\ 1 & \text{if } p > 1/2a \\ \text{singular} & \text{if } p = 1/2a \end{cases}$$

Since

$$x(T) = x(0) + aT - 2av$$

the substitution (10) implies

$$x(T) = -\ln 2ar \tag{14}$$

By (13) and (14) we have

$$p(t) = 1/2a \quad \text{for} \quad t \in [0,T] \tag{15}$$

Thus, control $u(t)$ is singular in the whole horizon.

3. Chemotherapy Model Including the Dynamics of Cytostatic Activity

In model (1) we assume immediate reaction of cancer cell population on cytostatic dosage. To include the inertia in the cytostatic activity we may introduce

$$\dot{u} = -bu + w, \quad u(0) = 0, \quad 0 \leq w \leq b \tag{16}$$

where u denotes once more cell destruction after the drug being applied, ($0 \leq u \leq 1$), and w is a control variable representing drug dosage.

The second order optimization problem (5), (16), (6) can be reduced to the first order task. Similarly as in chapter 2 substitution (8) leads to performance index (9) and solution (10).

After having integrating (16) we have

$$u(T) = -bv + \int_0^T w(\tau)d\tau \tag{17}$$

By substituting

$$u(T) = \int_0^T e^{b(\tau - T)} w(\tau) d\tau$$

and (10) to (17) we obtain

$$\frac{bT}{2} + \frac{b}{2a} \ln 2arN_0 = \frac{b}{2a} \ln 2ar_1 = \int_0^T [1 - e^{b(\tau - T)}] w(\tau) d\tau \tag{18}$$

Any $w(t)$ satisfying (18) is the optimal solution assuming that

$$-T \leq \frac{1}{a} \ln 2arN_0 \leq T - \frac{2}{b}(1 - e^{-bT}) \tag{19}$$

Singularity of control can be proved by the use of the maximum principle. Hamiltonian has the form

$$H = u + p_1(a - 2au) + p_2(w - bu)$$

where the costate variables $p_1(t)$ and $p_2(t)$ are described by equations

$$\dot{p}_1 = 0 \qquad p_1(T) = re^{x(T)} \tag{20}$$

$$\dot{p}_2 = -1 + 2ap_1 + bp_2 \qquad p_2(T) = 0 \tag{21}$$

Necessary optimality conditions have the form

$$w = \begin{cases} 0 & \text{if } p_2 > 0 \\ b & \text{if } p_2 < 0 \\ \text{singular} & \text{if } p_2 = 0 \end{cases}$$

Since $p_1(t) = \text{ const } = re^{x(T)} = 1/2a$ (see (14), (15)) thus

$$\dot{p}_2 = bp_2 \qquad p_2(T) = 0$$

Then

$$p_2(t) = 0 \quad \text{dla} \quad t \in [0, T] \tag{22}$$

We see that control $w(t)$ is singular in the whole horizon.

4. Chemotherapy Model Including the Efect of Cytostatic on Normal Tissues

So far, a negative impact of cytostatics on normal critical tissues has been taken into account by the second component in (2). Now, we introduce a model of the drug effect on normal tissues similarly as for cancer cells.

The system to be controlled is given by equation (1) for cancer cells and the following equation for normal ones

$$\dot{L} = -cL + 2(1-u)cL \qquad L(0) = L_0 \tag{23}$$

with the constraint $L(t) \geq L_{\min}$.

The performance index, which should be minimized has the form

$$J_0 = N(T) \tag{24}$$

Using (4) and the substition

$$y = \ln L \tag{25}$$

we obtain state equation (5) and

$$\dot{y} = c - 2cu \qquad y(0) = \ln L_0 > y_{\min} \tag{26}$$

the performance index

$$J_0 = e^{x(T)} \tag{27}$$

and the contraint $y(t) \geq y_{\min}$ where $y_{\min} = \ln L_{\min}$.

The solution to the minimization problem for performance index (27) could be found by minimizing

$$J_1 = x(T) \tag{28}$$

Hamiltonian to problem (5), (26), (28), (29) has the form

$$H = p_1(a - 2au) + p_2(c - 2cu) + \lambda(y - y_{\min}) \tag{29}$$

where costates $p_1(t)$ and $p_2(t)$ are described as follows

$$\dot{p}_1 = 0 \quad p_1(T) = 1 \quad \text{thus} \quad p_1(t) = 1 \tag{30}$$

$$\dot{p}_2 = -\lambda \tag{31}$$

The Lagrange multiplier $\lambda(t)$ has the form

$$\lambda(t) = \begin{cases} 0 & \text{if} \quad y > y_{\min} \\ < 0 & \text{if} \quad y = y_{\min} \end{cases} \tag{32}$$

Necessary optimality conditions have the form

$$u = \begin{cases} 1 & \text{if} \quad a + cp_2 > 0 \\ 0 & \text{if} \quad a + cp_2 < 0 \\ \text{singular} & \text{if} \quad a + cp_2 = 0 \end{cases}$$

For the switching line we have

$$p_2 = -a/c$$

$$\dot{p}_2 = 0$$

Thus, we have $\lambda = 0$ and $y > y_{\min}$.

For the initial moment we have $y(0) > y_{\min}$ and consequently $\lambda = 0$, $p_2 = \text{const}$ and the control cannot be switched. The control $u(0)$ is nonadmissible because x increases in this case. For $u(0) = 1$ we have

$$y(t) = y(0) - ct$$

Let $y(t_1) = y_{\min}$ for $t = t_1 < T$. Then $\dot{p}_2 > 0$, p_2 increases and the control should be 1, which is nonadmissible in the light of requirement $y(t) \geq y_{\min}$. If only

$$T \geq (y(0) - y_{\min})/c = (1/c)\ln(L_0/L_{\min})$$

then the control is singular. Its form can be found by the order reduction. Namely it follows

$$y(T) = y_{\min}$$

Hence

$$v = \int_0^T u dt = (y(0) - y_{\min})/2c + T/2 \tag{33}$$

$$x(T) = x(0) - a(y(0) - y_{\min})/c$$

Any control satisfying (33) is optimal.

5. Nonlinear Model of Cancer Cells Population Growth

An assumption of the exponential growth of the uncontrolled cell population is a great simplification. Each population has a saturation tendency. In the literature a Gompertz–type growth (Wheldon, 1988) is considered very often although its biological interpretation is not quite clear. We present the simplest model of this type including the effect of chemotherapy and we show that the singular control is absent in this case. The model presented here can be well–fitted to measuring data (Speer *et al.*, 1984).

The Gompertz model of the cell population growth under control has the following form

$$\dot{N} = gN\ln(N_{\max}/N) - 2auN \tag{34}$$

By applying (4) to (34) we have

$$\dot{x} = -gx + gx_{\max} - 2au \tag{35}$$

Taking into account performance index (2) or (6) we have the Hamiltonian

$$H = u + p(-gx + gx_{\max} - 2au) \tag{36}$$

where the costate variable $p(t)$ is described by equation

$$\dot{p} = pg \qquad p(T) = re^{x(T)} \tag{37}$$

Necessary optimality conditions have the form

$$u = \begin{cases} 1 & \text{if} \quad p > 1/2a \\ 0 & \text{if} \quad p < 1/2a \\ \text{singular} & \text{if} \quad p = 1/2a = \text{ const} \end{cases} \tag{38}$$

Since $p(t) = re^{x(T)-g(T-t)}$ a singular control does not exist in the problem.

Let us assume that $u(0) = 1$. It is the case when $p(0) = re^{x(T)-gT} > 1/2a$. Since p increases, u cannot be switched. We have

$$x(T) = x(0)e^{-gT} + (x_{\max} - 2a/g)(1 - e^{-gT})$$

The following condition has to be satisfied

$$2are^{-gT+x_{\max}}e^{(x(0)-x_{\max})e^{-gT}}e^{-(2a/g)(1-e^{-gT})} > 1$$

or

$$2arN_{\max}e^{-gT}\left((N_0/N_{\max})e^{2a/g}\right)^{e^{-gT}}e^{-2a/g} > 1$$

Alternatively

$$(1 - e^{-gT})(\ln(N_{\max}/N_0) - 2a/g) + \ln 2arN_0 - gT > 0 \tag{39}$$

If model parameters do not satisfy (39), the optimal control has the sequence $\{0, 1\}$ with switching at the time t_1 described as follows

$$x(T) = x(0)e^{-gT} + x_{\max}(1 - e^{-gT}) - (2a/g)(1 - e^{-g(T-t_1)})$$

$$\frac{1}{2a} = p(t_1) = re^{-g(T-t_1)+x(0)e^{-gT}+x_{\max}(1-e^{-gT})-(2a/g)(1-e^{-g(T-t_1)})}$$

Then

$$\frac{1}{2a} = re^{-g(T-t_1)}(N_0/N_{\max})^{e^{-gT}}N_{\max}e^{-(2a/g)(1-e^{-g(T-t_1)})}$$

or

$$(2a/g)e^{-g(T-t_1)} - g(T-t_1) - 2a/g + ln2arN_0 + (1-e^{-gT})\ln(N_{\max}/N_0) = 0 \quad (40)$$

Equation (40) should be solved numerically.

6. Final Remarks

In this paper four simple models of optimal chemotherapy protocols which lead to optimal control problems are presented. Three of them are based on the assumption of expontential cell population growth and lead to bilinear state equations. The negative cytostatic effect on critical tissues is taken into account in the performance index or in the state equation for normal tissues. The optimal control is singular in the problems mentioned above. The result is interesting, because control singularity has not been discussed in the literature (Swan, 1990). The singular control does not exist when Gompertz–type model is applied. It seems that also other models of nonlinear growth e.g. Pearl–Verhulst do not lead to singular controls.

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