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SOME CONTROL PROBLEMS FOR SIMPLEST DIFFERENTIAL MODELS OF PROLIFERATION CYCLE

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This paper presents probably the simplest models of chemotherapy considered as a control problem. The first-order tumour growth kinetic models both of Malthusian and Gompertzian type are discussed, and their "degenerated" control properties are indicated.

1. Introduction

The classical control design problem may be stated as follows. Let the dynamic properties of a system be described by its state and the external actions, i.e. control and disturbances be given by input variables. Moreover, assume that we are given a target set of required system states or outputs. Then, we are to find control actions which guarantee reachability of the desirable target region. If we are able to describe a disease by a finite number of dynamically changing parameters, we are also able to formulate a control problem in the sense mentioned above. Our control actions simply represent drug dosage or more generally therapeutic protocols and a region of the disease parameters considered as admissible defines a target set for the state. In the case of cancers the disease state should be represented by the size of the tumour defined for example by the number of transformed cells. Unfortunately, any control action, i.e. treatment by drugs, does not selectively disturb cancer tissues. Both chemotherapeutic agents and irradiation act on normal tissues. Thus, the control problem becomes much more intricate than in many industrial applications, because the unperturbed system (i.e. when therapy is not applied) leads always to an undesirable outcome.

Application of optimal control theory to cancer therapy was first discussed probably in (Bahrami and Kim, 1975), where the discrete maximum principle was 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 in (Kimmel and Świerniak, 1983) in the following form

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

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where $N(t)$ is a size of a cancer cell population, the term $1-u(t)$ represents the 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, whereas the coefficient 2 represents a mother cell symmetric division into two daugter cells.

A performance index in (Kimmel and Świerniak, 1983) is of the form

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

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

It has been shown, via direct optimization, that a solution to the problem can be non-unique.

In (Świerniak *et al.*, 1992; Świerniak and Duda, 1994) we have shown that the mathematical reason for nonuniqueness is total singularity of the optimal control. Moreover, in (Świerniak and Duda, 1994) we have pointed out that the same problem is present even if pharmacokinetics of the drug is modelled by the first-order inertia (see e.g. (Bellman, 1983)) or reactions of both cancer and normal tissues to the drug are encountered (as in (Zietz and Nicolini, 1979)). In (Świerniak and Duda, 1994) we suggest that singularity can be avoided by using Gompertz-type model. In this paper we briefly discuss the results presented in (Świerniak and Duda, 1994) but we indicate the complexity of the control problem based on the Gompertzian model. We show that singularity of the control problem may also appear in this case.

2. Optimal Chemotherapy Protocol for the Malthusian Growth 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 unable to divide further. The minimization of the performance index (2) takes into account a compromise between cancer cell population at the end of the chemotherapy and a negative cummulated cytostatic effect.

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

$$0 \leq u(t) \leq 1 \tag{3}$$

can be solved directly but we apply a 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

$$\frac{\mathrm{d}x}{\mathrm{d}t} = -a + 2a(1-u), \qquad x(0) = \ln N_0$$

Then

$$\frac{\mathrm{d}x}{\mathrm{d}t} = a - 2au \tag{5}$$

and the performance index (2) has the following form

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

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

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

Therefore, we have a static optimization problem with respect to

$$v = \int_0^T u\,\mathrm{d}t, \qquad 0 \le v \le T \tag{8}$$

Thus, we have

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

where $r_1 = re^{aT+x(0)}$. By differentiating (7) with respect to v and equating the result to zero

$$\frac{\mathrm{d}J}{\mathrm{d}v} = -2ar_1 e^{-2av} + 1 = 0$$

we obtain

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

which 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 fulfilled, then the control $u(t)$ is on the boundaries of the feasible control region. Solution (10) confirms the non-uniqness of the optimal control $u(t)$ because any $u(t)$ satisfying (8) and (10) is optimal. The order reduction (from a dynamic problem of the first order to a static problem) indicates the singularity of optimal control (Johnson, 1985).

A precise proof of the singularity based on the Pontryagin maximum principle (Pontryagin *et al.*, 1962) may be found in (Świerniak and Duda, 1994).

3. More Realistic Models of Chemotherapy

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

$$\frac{\mathrm{d}u}{\mathrm{d}t} = -bu + w, \qquad u(0) = 0, \qquad 0 \leq w \leq b \tag{12}$$

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

The second-order optimization problem (5), (12), (6) can be reduced to the first-order task. Similarly as in Section 2, introducing (8) leads to the performance index (9) and solution (10).

After integrating (12) we have

$$u(T) = -bv + \int_0^T w(\tau)\,\mathrm{d}\tau \tag{13}$$

By substituting

$$u(T) = \int_0^T e^{b(\tau - T)} w(\tau)\,\mathrm{d}\tau \tag{14}$$

and (10) into (13) we obtain

$$\frac{bT}{2} + \frac{b}{2a}\ln 2arN_0 = \frac{b}{2a}\ln 2ar_1 = \int_0^T [1 - e^{b(\tau - T)}]w(\tau)\,\mathrm{d}\tau \tag{15}$$

Any $w(t)$ satisfying (15) is the optimal solution assuming that

$$-T \leq \frac{1}{a}\ln 2arN_0 \leq T - \frac{2}{b}(1 - e^{-bT}) \tag{16}$$

Singularity of control can be proved by the use of the maximum principle (Świerniak and Duda, 1994).

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

$$\frac{\mathrm{d}L}{\mathrm{d}t} = -cL + 2(1 - u)cL, \qquad L(0) = L_0 \tag{17}$$

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

The performance index, to be minimized is of the form

$$J_0 = N(T) \tag{18}$$

Using equation (4) and the substitution

$$y = \ln L \tag{19}$$

we obtain state equation (5) and

$$\frac{dy}{dt} = c - 2cu, \qquad y(0) = \ln L_0 > y_{\min} \tag{20}$$

the performance index

$$J_0 = e^{x(T)} \tag{21}$$

and the constraint

$$y(t) \geq y_{\min} \tag{22}$$

where $y_{\min} = \ln L_{\min}$

The solution to the minimization problem for the performance index (21) could be found by minimizing

$$J_1 = x(T) \tag{23}$$

The Hamiltonian of the problem (5), (20), (22), (23) has the form

$$H = p_1(a - 2au) + p_2(c - 2cu) + \lambda(y - y_{\min}) \tag{24}$$

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

$$\frac{dp_1}{dt} = 0, \qquad p_1(T) = 1 \qquad \text{(hence} \quad p_1(t) \equiv 1) \tag{25}$$

$$\frac{dp_2}{dt} = -\lambda \tag{26}$$

The Lagrange multiplier λ(t) has the form

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

The necessary optimality conditions have the form

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

For the switching line we have

$$p_2 = -\frac{a}{c}, \qquad \frac{dp_2}{dt} = 0$$

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

At 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 $u(0) = 0$ is non-admissible 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, $dp_2/dt > 0$, p_2 increases and the control should be 1, which is non-admissible in the light of requirement $y(t) \geq y_{\min}$. If only

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

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

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

Hence

$$v = \int_0^T u \, dt = \frac{y(0) - y_{\min}}{2c} + \frac{T}{2} \tag{27}$$

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

Any control satisfying (27) is optimal.

4. Gompertz-Type Models of Perturbed Tumour 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 (Sullivan and Salmon, 1972).

The Gompertz-type equation of the uncontrolled growth is of the form

$$\dot{N} = gN \ln \left(\frac{N_{\max}}{N} \right) \tag{28}$$

where g and $N_{\max}$ are specific constants. Assuming the same cell-kill hypothesis as for exponential growth models, i.e. introducing the cell loss function depending linearly on the constant fraction of the population size, we are led to a model of perturbed growth of the form

$$\frac{dN}{dt} = gN \ln \left(\frac{N_{\max}}{N} \right) - 2auN, \qquad N(0) = N_0 \tag{29}$$

By applying (4) to (29) we have

$$\frac{dx}{dt} = -gx + gx_{\max} - 2au \tag{30}$$

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

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

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

$$\frac{\mathrm{d}p}{\mathrm{d}t} = pg, \qquad p(T) = re^{x(T)} \tag{31}$$

The necessary optimality conditions have the form

$$u^o = \begin{cases} 1 & \text{if} \quad p > 1/2a \\ 0 & \text{if} \quad p < 1/2a \\ \text{singular} & \text{if} \quad p = 1/2a = \text{const} \end{cases} \tag{32}$$

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 if $p(0) = re^{x(T)-gT} > 1/2a$. Since p increases, u cannot be switched. We have

$$x(T) = x(0)e^{-gT} + \left(x_{\max} - \frac{2a}{gT}\right)(1 - e^{-gT}) \tag{33}$$

The following condition has to be satisfied

$$2are^{-gT+x_{\max}}e^{(x(0)-x_{\max})e^{-gT}}e^{-\frac{2a}{g}(1-e^{-gT})} > 1 \tag{34}$$

or

$$2arN_{\max}e^{-gT}\left(\left(\frac{N_0}{N_{\max}}\right)e^{\frac{2a}{g}}\right)^{e^{-gT}}e^{-\frac{2a}{g}} > 1 \tag{35}$$

Alternatively

$$(1 - e^{-gT})\left(\ln\left(\frac{N_{\max}}{N}\right) - \frac{2a}{g}\right) + \ln 2arN_0 - gT > 0 \tag{36}$$

If model parameters do not satisfy (36), the optimal control is the sequence $\{0, 1\}$ with switching at the time t_1 described as follows

$$x(T) = x(0)e^{-gT} + x_{\max}(1 - e^{-gT}) - \left(\frac{2a}{g}\right)(1 - e^{-g(T-t_1)}) \tag{37}$$

$$\frac{1}{2a} = p(t_1) = re^{-g(T-t_1)+x(0)e^{-gT}+x_{\max}(1-e^{-gT})-(2a/g)(1-e^{-g(T-t_1)})} \tag{38}$$

Then

$$\frac{1}{2a} = re^{-g(T-t_1)}\left(\frac{N_0}{N_{\max}}\right)^{e^{-gT}}N_{\max}e^{-(2a/g)(1-e^{-g(T-t_1)})} \tag{39}$$

or

$$\frac{2a}{g}e^{-g(T-t_1)} - g(T - t_1) - \frac{2a}{g} + \ln 2arN_0 + (1 - e^{-gT})\ln\frac{N_{\max}}{N_0} = 0 \tag{40}$$

Equation (40) should be solved numerically.

The control problem seems to be regular and this result suggests that the reason for singularity of the optimal control lies in the assumption about the exponential growth. But the Gompertz-type equation of the uncontrolled tumour growth may be rewritten in a variety of ways. One interpretation has a form of a linear time-varying equation whose growth rate parameter itself declines exponentially with time

$$\dot{N} = \gamma(t)N, \qquad N(0) = N_0 \tag{41}$$

where

$$\gamma(t) = \gamma_0 \exp(-gt) \tag{42}$$

or equivalently

$$\dot{\gamma} = -g\gamma, \qquad \gamma(0) = \gamma_0 \tag{43}$$

where $N_0 \exp(\gamma_0/g) = N_{\max}$.

If the control action representing the effect of the drug is introduced similarly as in all previously considered models, i.e. by the additive term $2auN$ the perturbed growth model is given by

$$\dot{N} = \gamma(t)N - 2auN \tag{44}$$

The same change of variable as in (4) leads to the equation:

$$\dot{x} = \gamma(t) - 2au \tag{45}$$

Since

$$x(T) = x(0) + \int_0^T \gamma(t)\,\mathrm{d}t - 2a\int_0^T u(t)\,\mathrm{d}t \tag{46}$$

the performance index depends only on the integral v (cf. equation (8)) of the control action and once more the optimal control is non-unique and totally singular because the same analysis as in Section 2 follows.

Since the Gompertzian model has no biological sense and may be treated as a behavioural well-fitted model only in the uncontrolled case, it is difficult to define which description of the growth (28) or (41), (43) is correct and which model of the perturbed growth (29) or (44), (43) should be applied.

5. Conclusions

In the paper four simple models of optimal chemotherapy protocols which lead to optimal control problems are presented. Three of them are based on the assumption about exponential 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 the Gompertz-type nonlinear model is applied.

However, it appears once more when the Gompertz-type time-varying equivalence for uncontrolled growth is considered. The models discussed in the paper are poor in that they do not allow for consideration of cell-cycle-phase-specificity of the drugs.This effect may be encountered in the multicompartmental models of cell cycle kinetics (see e.g. (Świerniak, 1989)). Although in this case singularity is an exception rather than a rule, we have found that the optimal control problem is still endowed with some irregularities (see Świerniak *et al.*, 1992; Świerniak and Polański, 1993; 1994).

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