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Optimal strategy in chemotherapy for a Gompertzian model of cancer growth

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The problem of optimal cancer chemotherapy is reconsidered. For the assumed result of the therapy the cumulative negative toxic effect of the drug is minimized. The unknown function to be optimized is the time-dependent dose of the drug. The Gompertzian model of cell population growth is employed. The formulated problem of the calculus of variations is solved using the method of Miele (the method of extremization of linear integrals via Green's theorem). The optimal solution is unique and of "bang-bang" type with one switching point.

Key words: *optimal chemotherapy, Gompertzian growth*

1. Introduction

The problem of cancer chemotherapy may be formulated in calculus of variations (optimal control). The cell population growth is represented by one state equation of Malthusian type for the simplest model (ŚWIERNIAK and DUDA [8], ŚWIERNIAK et al. [9], MAROŃSKI [3], [4], [5]. The physical interpretation of this model is clear (FORYŚ [1]). If the drug is not supplied the number of cancer cells increases exponentially, therefore the model is suitable only in the early stage of growing process because each population has a saturation tendency. This weakness does not appear for the Gompertzian model of cell population growth. The model fits well with measuring data (NORTON [7]), but its physical interpretation is not quite clear.

In the paper, the problem formulated by ŚWIERNIAK and DUDA [8] is reconsidered. A simple method of the problem solution is proposed – the method of MIELE [6]. It has been originally developed for aerospace systems and then successfully applied to many problems in the biomechanics of human movement in order to design optimal strategies for downhill skiing, running, swimming and cycling (MAROŃSKI [2]). This approach may be used to find some optimal solutions of the problems occurring in medicine. The problem considered here is exemplified by human breast cancer chemotherapy.

2. Formulation of the problem

The basic assumptions of the model:

- Only one kind of the cells is considered. The population is homogeneous.
- The maximum number $N_{\max}$ of cells in population is limited. It cannot increase to infinity even if the drug is not supplied. This is the basic difference between this model and the Malthusian (exponential) one.
- The numbers of cancer cells at the beginning (N_0) and at the end (N_T) of the therapy are given. The last number represents the goal of the therapy to be achieved.
- The time T of the therapy is also known.

The Gompertzian model of cell population growth under control is represented by (ŚWIERNIAK and DUDA [8], equation (34))

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$$\frac{dN}{dt} = g\,N \ln\frac{N_{\max}}{N} - 2\,a\,u\,N\,, \qquad (1)$$

where: N is the number of cancer cells at the instant of the time t, $N_{\max}$ is the limiting size (population capacity), $u(t)$ is the control function that should be computed, g and a are the constants given. If the cell growth is beyond control [$u(t) = 0$], this model is a version of the logistic model or the Verhulstian model that is well-known and often applied in biology (FORYŚ [1]).

The performance index to be minimized is in the form (ŚWIERNIAK and DUDA [8], equation (2))

$$J = \int_0^T u(t)\,dt \to \text{MIN}\,. \qquad (2)$$

The symbol $u(t)$ stands for the control function satisfying inequality constraints

$$0 \le u(t) \le 1\,, \qquad (3)$$

where $[1 - u(t)]$ represents the probability of cell survival after applying a cytostatic. For $u(t) = 0$, a medicine is not given, for $u(t) = 1$ the maximum medicine dose is given. The minimized performance index (2) represents the toxic effect of a medicine cumulated in patient's organism during the therapy. The differential equation (1) modelling the growth of cancer cell population should be completed with the boundary conditions representing the numbers of cancer cells at the beginning and at the end of the therapy

$$N(0) = N_0, \quad N(T) = N_T\,. \qquad (4)$$

The numbers N_0 and N_T are given.

The problem is formulated as follows: minimize the toxic effect of the therapy (2) whose aim is to stop cancer cell proliferative growth described by equation (1) with the initial condition (4a), the assumed goal of the therapy (4b), and the inequality constraints (3) imposed on the medicine dosage.

The formulation of this problem differs slightly from that given by ŚWIERNIAK and DUDA [8], where the performance index

$$J = r\,N(T) + \int_0^T u(t)\,dt \to \text{MIN} \qquad (5)$$

is minimized and the final condition in the form of (4b) is not considered. In the formulation presented in this paper, the difficulty connected with a proper selection of the weighting coefficient r in equation (5) disappears.

3. Solution of the problem

The problem may be solved using the method of Miele in (t, N)-plane (MIELE [6]). It is necessary to depict the so-called admissible domain integrating forward and backward equation (1) for $u(t) = 0$ and $u(t) = 1$, respectively. For one set of the model parameters four curves border this domain. Next, the performance index (2) should be transformed into a line integral using (1) in order to eliminate the control $u(t)$:

$$J = \int_{(0,N_0)}^{(T,N_T)} \varphi(t,N)\,dt + \psi(t,N)\,dN\,, \qquad (6)$$

where

$$\varphi(t,N) = \frac{g}{2\,a}\ln\frac{N_{\max}}{N}, \quad \psi(t,N) = -\frac{1}{2\,a\,N}\,. \qquad (7)$$

The character of the optimum solution depends on the behaviour of the so-called fundamental function (MIELE [6])

$$\omega(t,N) = \frac{\partial\psi}{\partial t} - \frac{\partial\varphi}{\partial N} = \frac{g}{2\,a\,N} > 0\,. \qquad (8)$$

The fundamental function ω is greater than zero within the admissible domain. From the method it follows that the optimum path is on the border of this domain on the left-hand side as one moves from the point $(0, N_0)$ to the point (T, N_T). This means that we deal with a two-stage therapy: in the first stage, the drug is not given [$u(t) = 0$], and in the second one, the maximum dose is given [$u(t) = 1$]. The singular solution does not appear because $\omega \neq 0$ everywhere within the admissible domain.

4. Example

A human breast cancer growth is considered as an example. We assume that at the end of the therapy the number of cancer cells is the same as at the beginning:

$$N_0 = N_T = 7.2\cdot 10^{10}.$$

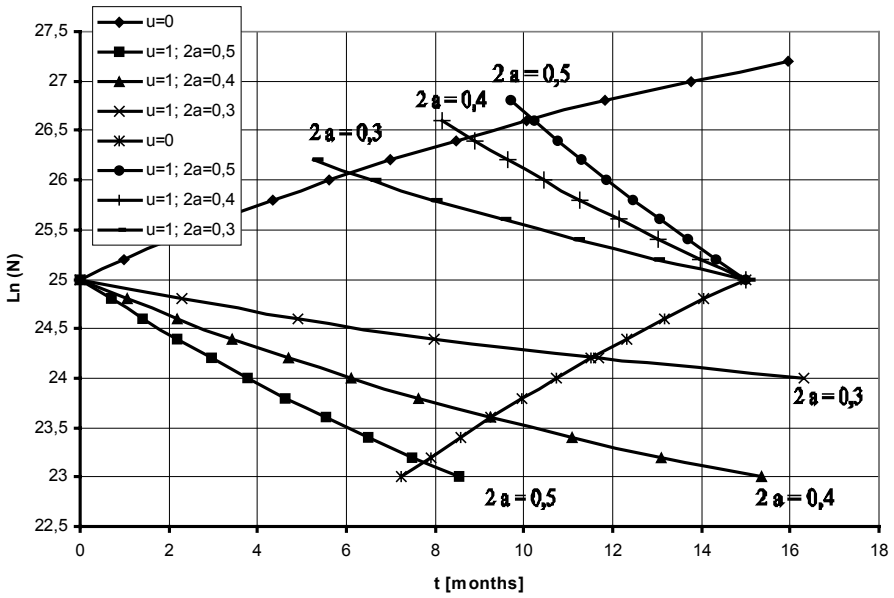
This is equivalent to 72 cm^3 of densely packed tumour cells (NORTON [7]) and above the clinical diagnosis ranging from $1\cdot 10^9$ to $5\cdot 10^9$ cells. The tumour is assumed to be lethal at $1\cdot 10^{12}$ cells (1 dm^3). Other data according to NORTON [7] are as follows:

$N_{max} = 3.1 \cdot 10^{12}$ (3.1 dm^3);

$g = 0.055$; $T = 15$ months.

The author of this paper has not found the data referring to the parameter $2a$ that represents the efficiency of killing agent, therefore its three different values are considered, $2a = 0.3$, 0.4 and 0.5. The admissible domains for these parameters are depicted in figure. The optimum paths are on the left-hand side as one moves from the initial point to the final point – upper curves. This means that the drug should not be given at the beginning of the therapy [$u(t) = 0$], and then the maximum dose should be administered [$u(t) = 1$]. Based on the reasoning employed it can be inferred that this property does not depend on the parameters of the Gompertzian model.

toxic effect of the therapy can be minimized. The method of Miele shows that the optimal solution for that model is unique and on the border of the admissible domain. The optimal control function is of "bang-bang" type with one switching point. The singular controllers in the sense of classical calculus of variations, when the Euler–Lagrange equation degenerates into an algebraic equation, do not appear. The results suggest that the maximum dose of the killing agent should be administered for a relatively large number of cancer cells at the end of the therapy which is not in accordance with clinical experience, but is compatible with the results of the Gompertzian model obtained by ŚWIERNIAK and DUDA [8] using the Pontryagin maximum principle. However, the reasoning based on the method of Miele seems to be much simpler.



Strategies minimizing the performance index at assumed boundary values of the cancer cell number and different values of the parameter $2a$ representing the effectiveness of the killing agent (upper curves). Bottom curves maximize the performance index

Performance indices at different values of the parameter $2a$ representing the effectiveness of the killing agent

$2a$	J_{min}	J_{max}
0.3	8.9	11.5
0.4	6.2	9.25
0.5	4.8	7.75

5. Summary

In the paper, the problem of optimal cancer chemotherapy is reconsidered based on the Gompertzian model of cancer proliferative growth. The negative

References

[1] FORYŚ U., *Matematyka w biologii*, WN-T, Warszawa, 2005.

[2] MAROŃSKI R., *Metody rachunku wariacyjnego w biomechanice*, Oficyna Wydawnicza Politechniki Warszawskiej, Warszawa, 1999.

[3] MAROŃSKI R., *"Strange" solutions of optimal control problem in cancer chemotherapy*, Acta of Bioengineering and Biomechanics, 2004, Vol. 6, Suppl. 1, 105–109.

[4] MAROŃSKI R., *Optimal strategy in cancer chemotherapy for exponential model of cell population growth*, Zeszyty Naukowe Katedry Mechaniki Stosowanej Politechniki Śląskiej, 2006, 26, 231–234.

[5] MAROŃSKI R., *Co ma wspólnego chemioterapia raka z mechaniką?* Pierwszy Kongres Mechaniki Polskiej, Warszawa, 28–31 sierpnia 2007 (na płycie CD).

[6] MIELE A., *Extremization of linear integrals by Green's theorem*, [in:] Leitmann G. (ed.), *Optimization techniques with application to aerospace systems*, Academic Press, New York, London, 1962, 69–98.

[7] NORTON L., *A Gompertzian model of human breast cancer growth*, Cancer Research, 1988, 48, 7067–7071.

[8] ŚWIERNIAK A., DUDA Z., *Some control problems related to optimal chemotherapy – singular solutions*, Applied Mathematics and Computer Sciences, 1992, Vol. 2, No. 2, 293–302.

[9] ŚWIERNIAK A., POLAŃSKI A., KIMMEL M., *Optimal control problems arising in cell-cycle-specific cancer chemotherapy*, Cell Prolif., 1996, 29, 117–139.