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Optimal strategy in chemotherapy for Malthusian model of cancer growth

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Purpose: The problem of optimal strategy in cancer chemotherapy is reconsidered. Two incompatible goals should be completed: the number of cancer cells in the patient's body should be reduced and the toxic effect of the therapy should be minimized. Such problem may be formulated in optimal control. The control function is the amount of the drug administered in the time unit. *Methods*: The Malthusian model of cell population growth is employed where the rate of increase of the number of cancer cells is proportional to the number of cells in population and an intrinsic rate that usually is assumed to be constant. The performance index is the amount of the drug cumulated in the patient's body and it is minimized. A non-standard method of optimal control is used – method of Miele. *Results*: The optimal solutions are obtained for three cases: constant intrinsic rate, monotonically increasing/decreasing intrinsic rate and for periodic intrinsic rate. The optimal control is ununique for the first case – the result is irrespective of the strategy. Such result has been known earlier. The optimal control is unique for other cases and it is of bang-bang type. *Conclusions*: The ununique solution for constant intrinsic rate is surprising, therefore a mechanical analogy is given. The optimal strategy is in accordance with clinical experience for decreasing intrinsic rate. The optimal control is a periodic function of time for the intrinsic rate of sin/cos type – the drug should be administered, as its value is relatively high.

Key words: *optimal chemotherapy, Malthusian growth, periodic control*

Notation

A – initial point,
B – final point,
$\vec{F}$ – force,
J – performance index,
N – number of cancer cells,
r – weighting coefficient,
$\vec{r}$ – force position vector,
T – time of one period of the therapy,
t – time (independent variable),
u – control variable,
x^+, x^- – streams of cells,
α – intrinsic rate,
ω – fundamental function,
$(.)_A$ – initial value,
$(.)_B$ – final value.

1. Introduction

During cancer chemotherapy two incompatible goals should be completed: the number of cancer cells in the patient's body should be reduced and the toxic effect of the drug should be minimized. The control function is the amount of the drug administered in the time unit. We assume that it may be arbitrarily taken from the given range and that is achieved using an infusion pump. Such a problem may be formulated in calculus of variations or optimal control. The review of the models and the results obtained one can find, for example, in [2], [14]. One of the simplest models is Malthusian model of cell population growth, where the proliferation process of cancer cells is described

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by one ordinary differential equation and where the rate of increase of the number of cancer cells depends on the number of cells in population [1], [12]. The functional is the amount of the drug cumulated in the patient's body during the therapy and it is minimized. The optimal solution is surprising, however. For a constant intrinsic rate (a parameter of the model) the optimal result is irrespective of the strategy of the therapy [3], [15]–[17]. The aim of this paper is to show in a simple way that such a solution is valid only for constant intrinsic rate. The problem may be transformed to extremization of a linear integral. An analogy is also given. The work done by the force in the potential field of force also does not depend on the path, i.e., on the strategy. This fact is well known in theoretical mechanics. For strictly monotonically increasing/decreasing intrinsic rate the optimal control is unique and it is of bang-bang type with one switching point.

Formulation of the problem

We will employ the model of the process under consideration formulated by Kimmel and Świerniak [3]. The assumptions are as follows:

(1) The model considers the dynamics of cancer cell population growth. It does not consider the dynamics of health cell growth. The population is homogeneous.
(2) The increase of population is due to division of one mother-cell into two daughter-cells.
(3) The stream of cells (the number of cells increase in time unit) during division is proportional to the total number of cancer cells in population. This is the fundamental assumption of the Malthusian model.
(4) The drug kills daughter-cells just after division. It does not kill mother-cells. The maximum dosage of the drug when all daughter-cells are killed is known. When the drug is not administered the process of increase of cancer cell population is not disturbed.
(5) The number of cancer cells at the beginning of the therapy is known, and the number of cancer cells at the end (usually lower) is assumed. The model does not allow all cancer cells to be killed in the finite time of the therapy.
(6) The functional (performance index) proportional to the dose of the drug administered during the whole therapy is minimized.
(7) For the sake of brevity it is assumed that the time of the therapy is given.

Let $N(t)$ denote the number of cancer cells in the instant of time t. Let $x^-(t)$ be the stream of cells disappearing from population (just after division). From assumption 3 the following equation is valid

$$x^-(t) = \alpha N(t), \tag{1}$$

where the intrinsic rate α may be regarded as an inverse of average cycle time – the average time between divisions. Assume that α is constant or it is a strictly monotonic function of time. It means that the cells divide slower or faster over time. If the drug is not administered the stream of daughter-cells is equal to

$$x^+(t) = 2x^-(t), \tag{2}$$

where the number 2 follows from assumption 2 (however the result of reasoning does not depend on this number).

If the therapy is applied, equation (2) takes the form

$$x^+ = 2u(t)x^-(t), \tag{3}$$

where $u(t)$ is a control variable representing probability of daughter-cell surviving. The value $u(t) = 0$ denotes that all daughter-cells are killed. It refers to maximum dose of the drug. The value $u(t) = 1$ denotes that all daughter-cells are alive – the drug is not administered. In fact, now equation (2) is satisfied. The control variable is any piecewise continuous function of time that belongs to the range

$$u(t) \in \langle 0, 1 \rangle \tag{4}$$

(One can find another definition of the control function that is proportional to the dose of the drug. For such a case the new control function is equal to $(1 - u(t))$). The rate of growth of the number of cancer cells follows from the balance equation

$$dN/dt = x^+(t) - x^-(t), \tag{5}$$

or after employing (1) and (3) from equation

$$dN/dt = \alpha N(2u - 1). \tag{6}$$

The goal of the therapy is reduction of the number of cancer cells from the given number at the beginning of the therapy N_A, to the assumed, usually lower, number of the cells at the end N_B

$$N(0) = N_A, \tag{7a}$$

$$N(T) = N_B, \tag{7b}$$

where T is the time of the therapy. The amount of the drug cumulated in the patient's body during the therapy is minimized

$$J = \int_0^T [1 - u(t)]\,dt \to \text{MIN}. \tag{8}$$

In fact, if the drug is not administered, $u(t) = 1$, the functional (performance index) (8) is equal to zero – no toxic effect. If the maximum dose is administered, $u(t) = 0$, the toxic effect attains its maximum value.

The problem under consideration is a problem of calculus of variations (optimal control). We should find a function of time $u(t)$ from the range (4) representing the probability of daughter-cell surviving to minimize the functional (8). Equation (6) representing the dynamics of the process with known initial state (7a) and assumed aim of the therapy (7b) should be satisfied.

The Pontryagin's maximum principle for the problem solution has been used earlier [3], [15]–[17]. In these papers, the final state of the process (7b) has been considered in the augmented functional (8)

$$J = \int_0^T [1-u(t)]dt + rN(T)\,, \tag{9}$$

where r is the weighting coefficient, and it should also be assumed. Such difficulty does not appear in Miele's method – the method of extermization of linear integrals via Green's theorem [10]. Such a method originally has been developed in dynamics of aircraft and rockets. (The same method has been used for performance optimization in downhill skiing, cycling, running and swimming [6]–[8]).

2. Materials and methods

The method of Miele may be applied to the functional linear to the derivative of unknown function (or the control variable),

$$J = \int_A^B [\varphi(x,y) + y'\psi(x,y)]dx = \int_A^B [\varphi(x,y)dx + \psi(x,y)]dy \tag{10}$$

and this functional is minimized. Symbols A and B stand for the points: initial and final ones (see Fig. 1). The functions φ and ψ are known and they result from formulation of the problem. The curve $y = y(x)$ that joins the points A and B in the (x, y)-plane is unknown.

Assume that all admissible paths are within or on the closed curve $\varepsilon(x, y) = 0$ bordering this domain in the (x, y)-plane. Initial and final points A and B are on this curve (Fig. 1).

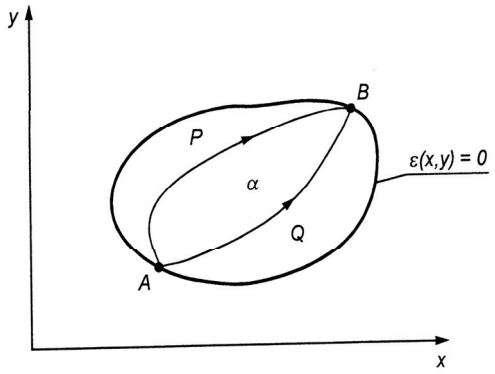

Fig. 1. The admissible domain

We should find the curve $y(x)$ that minimizes the functional (10). Consider two arbitrarily taken curves AQB and APB. The increment of the functional on them is as follows

$$\Delta J = J_{AQB} - J_{APB} = \int_{AQB} (\varphi dx + \psi dy) - \int_{APB} (\varphi dx + \psi dy) = \oint_{AQBPA} (\varphi dx + \psi dy) \tag{11}$$

and it is equal to a cyclic integral over a path $AQBPA$. Applying Green's theorem this integral may be transformed to the surface integral over a surface α limited by the curve $AQBPA$

$$\Delta J = \iint_\alpha \omega(x,y)dx\,dy. \tag{12}$$

The function ω is called the fundamental function and it is in the form

$$\omega(x,y) = \frac{\partial \psi}{\partial x} - \frac{\partial \varphi}{\partial y}. \tag{13}$$

Only two cases are important for the problem under consideration.

(a) The fundamental function ω is identically equal to zero. It means that the increment ΔJ is equal to zero as well, $\Delta J = 0$. The curves (strategies) are taken arbitrarily, therefore the value of the functional does not depend on the path $y(x)$ that joins the points A and B.

(b) The fundamental function ω has the same sign, say $\omega > 0$. It means that $\Delta J > 0$, then $J_{AQB} > J_{APB}$. Every curve on the left hand-side gives the lower value of the functional. In the limit the minimizing curve is on the border of admissible domain on its left hand-side. By analogy, for $\omega < 0$, the minimizing curve is on the right hand-side.

The case when the sign of the fundamental function changes within the admissible domain does not

appear for Malthusian model of cell population growth. It means that so-called singular arc does not appear [10].

3. Results

The optimal strategy problem in cancer chemotherapy is considered in (t, N)-plane for the given cell population growth model. The borders of the admissible domain are obtained after integration of the state equation (6) forward (from $t = 0$ to $t = T$) and backward (from $t = T$ to $t = 0$) for the control variable $u = 0$ and $u = 1$, respectively (cf. [10]). The functional (8) may be transformed into a line integral (10) employing (6) for elimination of the control variable u. Then,

$$J = \int_A^B \varphi(t,N)dt + \psi(t,N)dN \tag{14}$$

where

$$\varphi(t,N) = 0.5, \quad \psi(t,N) = -\frac{1}{2\alpha(t)N}. \tag{15}$$

The fundamental function (13) takes the form

$$\omega(t,N) = \frac{\partial\psi}{\partial t} - \frac{\partial\varphi}{\partial N} = \frac{1}{2\alpha^2(t)N}\frac{d\alpha}{dt}. \tag{16}$$

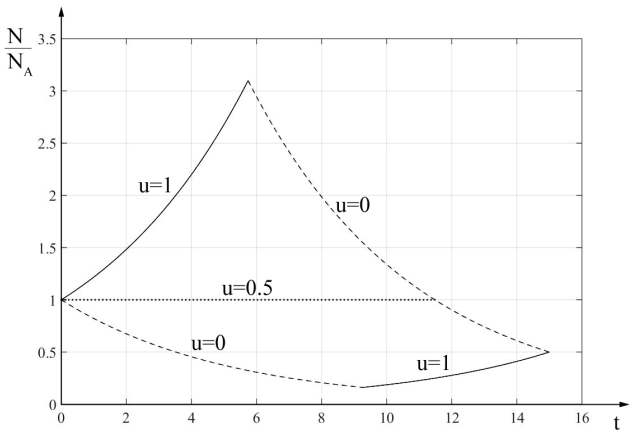

Fig. 2. The admissible domain in optimal cancer chemotherapy problem for $N_B = 0.5\ N_A$ and $\alpha = \text{const}$

The following three cases are considered:

(a) The intrinsic rate α is constant, $\alpha = \text{const}$, then $d\alpha/dt = 0$. The fundamental function ω is identically equal to zero within the admissible domain. The functional (14) does not depend on the strategy and such a case has been considered in [3], [15]–[17].

(b) The intrinsic rate α strictly monotonically increases over time, $d\alpha/dt > 0$, then $\omega(t, N) > 0$. The optimal solution is on the border of admissible domain (the upper curve in Fig. 2). The drug is not delivered at the beginning (the number of cancer cells N rapidly increases). The maximum dosage should be delivered at the end of the therapy.

(c) The intrinsic rate α strictly monotonically decreases, $d\alpha/dt < 0$, then $\omega(t, N) < 0$. The optimal solution is on the border of the admissible domain (the bottom curve in Fig. 2). The maximum dosage is delivered at the beginning. Only such strategy is in accordance with clinical experience.

Example 1

An example is considered illustrating the case when the intrinsic rate α is constant, therefore $d\alpha/dt = 0$. It is assumed that the number of cancer cells at the end of the therapy should be reduced to 50% of the number at the beginning, $N_B = 0.5\ N_A$. The solutions of equation (6) may be obtained in an analytical form for $u = 0$ or $u = 1$, respectively. The data for computations are: $\alpha = 0.197$, $T = 15$ (cf. [16]).

The admissible domain is depicted in Fig. 2. Consider three strategies:

- maximal drug dosage at the beginning ($u = 0$) and a medicine is not given at the end of therapy ($u = 1$) – the bottom border of admissible domain,
- a medicine is not given at the beginning ($u = 1$) and the maximal drug dosage at the end is delivered ($u = 0$) – the upper border of admissible domain,
- the number of cancer cells is kept at the same level over time, $N(t) = N_A$, $u = 0.5$, and that is in accordance with equation (6). Then, the maximum dosage of the drug is administered, $u(t) = 0$, to reach the assumed result of the therapy, $N_B = 0.5\ N_A$.

The performance index (8) attains the same value $J = 9.259$ for all these strategies. The result of therapy does not depend on strategy.

Example 2

An example is considered illustrating the cases (b) and (c), when the intrinsic rate α varies with time. Let α be of sin/cos type (see the bottom of Fig. 3). It means that the cells divide periodically faster or slower over time. The goal of the therapy is to keep the number of cancer cells at approximately the same level, therefore $N_A = N_B = N_0$. We assume that the therapy consists of equidistant periods where α is

strictly monotonic function of time – the period is T. The long-term strategy is a combination of solutions considered earlier. The number of cancer cells during the optimal therapy varies according to the bold line (see Fig. 3 in the middle). The optimal control variable $u(t)$ is given in Fig. 3 at the top and it is of bang-bang type. The function $u(t) = 0$ refers to the maximum dosage of the drug (all daughter-cells are killed). Comparing the functions $\alpha(t)$ and $u(t)$ one can find that the maximum dosage of the drug should be administered when $\alpha(t)$ is greater than its average value – when the cells divide relatively fast. If the cells divide relatively slow, the drug is not administered. Such an optimal strategy is in accordance with intuition. The values of the performance index computed over time interval $4T = 60$ are: $J_{\mathrm{MIN}} = 21.402$ (bold curves in Fig 3 in the middle), $J(u = 0.5) = 30$ and $J_{\mathrm{MAX}} = 38.598$ (thin curves in Fig. 3 in the middle).

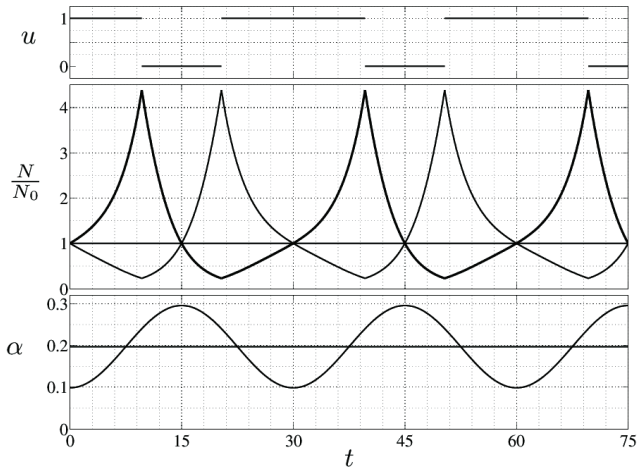

Fig. 3. The optimal strategy for periodic intrinsic rate

4. Discussion

The result obtained for constant intrinsic rate, α = const, is confusing – the strategy is ununique. This result is valid for Malthusian model of proliferation growth and for linear performance index. The applied Miele's method gives necessary and sufficient conditions of optimality. Verification of the result by an experiment is impossible but one can find a mechanical analogy.

Consider a mechanical work done in two-dimensional field of force. The work is defined as a line integral of a scalar product

$$L = \int_A^B \vec{F} \cdot d\,\vec{r} = \int_A^B F_x(x,y)dx + F_y(x,y)dy, \qquad (17)$$

where $\vec{F} = [F_x, F_y]$ is the force and $\vec{r} = [x, y]$ is the force position vector.

This work does not depend on the path that joins the points A and B if the curl operator is equal to zero (the field is vortexless) [13]

$$\frac{\partial F_y}{\partial x} - \frac{\partial F_x}{\partial y} = 0\,. \qquad (18)$$

Comparison of equations (18) and (16) for the case a (α = const, then $d\alpha/dt = 0$) shows that it is the same property of the linear integral.

One can find also an analogy in the foundations of electricity [11]. The voltage induced in a conductor is proportional to the rate of change of lines of magnetic field that pass through the conductor (Faraday's low of induction). On the contrary, the lack of change over time does not cause any effect.

The optimal control problem investigated in the paper is based on the simplest model of cancer cells population growth – the Malthusian model. This is a very popular model in demography but not specially in cancer chemotherapy. The model has been adopted to the problem under consideration by Kimmel and Świerniak [3]. The approach presented in this paper contains two new elements comparing with earlier investigations: the new method that gives necessary and sufficient conditions of optimality is employed – the method of Miele, and considerations are extended to the case when the intrinsic rate $\alpha(t)$ varies with time. Up to now this parameter has been regarded as a constant one. For constant intrinsic rate the results presented in the paper are convergent with the results of other authors [3], [15]–[17]. The result of the therapy does not depend on the strategy. This property of the model is illustrated in Example 1. The problem with variable intrinsic rate $\alpha(t)$ has not been considered earlier. Here the solution is unique for strictly monotonically increasing/decreasing $\alpha(t)$, but only when $\alpha(t)$ is decreasing the obtained result is in accordance with clinical experience. When the intrinsic rate $\alpha(t)$ periodically varies the solution is unique and it is compatible with intuition and practice (Example 2). It seems to be an achievement of the present approach.

The method shows that so-called singular arc is not optimal. The optimal control is of bang-bang type. This eliminates treatments when only a portion of the full drug dose is administered. The result is conver-

gent with the results for more sophisticated models [4], [5].

5. Conclusions

The problem of optimal strategy in cancer chemotherapy for Malthusian model of proliferation growth is reconsidered. For constant intrinsic rate α = const the solution is ununique – the goal of the therapy may be achieved regardless of the strategy. This conclusion is out of accordance with intuition, therefore the mechanical analogy is given. In the potential field of force the mechanical work also does not depend on the path (strategy) but on the positions of initial and final points. It has been shown in the paper that it is the same property of the linear integral.

For strictly monotonically increasing/decreasing intrinsic rate α the optimal solution is unique and it is on the border of the admissible domain. The optimal therapy has two stages with minimum or maximum dosage of the drug with one switching point. The intermediate control functions do not appear. The optimal chemotherapy strategy is in accordance with clinical experience only for increasing the average cycle time (for α decreasing). If the intrinsic rate is of sin/cos type and the number of cells is to be kept at approximately the same level, the control function is also periodic one. The drug should be administered when the intrinsic rate is relatively high.

The same approach as the one used in the paper employing Miele's method may be used for Gompertzian model of cancer cell proliferation growth [9].

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