Optimal Control for Anticancer Therapy

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Abstract In this report, the controlled Lotka–Volterra competition model is used to describe the interaction of the concentrations of healthy and cancer cells. For this controlled model, the minimization problem of the terminal functional is considered, which is a weighted difference of the concentrations of cancerous and healthy cells at the final moment of the treatment period. To analyze the optimal solution of this problem, which consists of the optimal control and the corresponding optimal solutions of the differential equations that determine the model, the Pontryagin maximum principle is applied. It allows to highlight the values of the model parameters under which the optimal control corresponding to them is a piecewise-constant function with at most one switching. Also, the values of the model parameters are found, under which the corresponding optimal control is either a bang–bang function with a finite number of switchings, or in addition to the bang–bang-type portions (nonsingular portions), it also contains a singular arc. Further, only numerical investigations of the optimal control are possible. Therefore, the report presents the results of numerical calculations performed using the software BOCOP-2.1.0 that lead us to the conclusions about the possible type of the optimal control and the corresponding optimal solutions.

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1 Introduction

In recent decades, a significant progress has been made in identifying and explaining the processes that arise in the development of cancer, as well as in developing methods and tools for its earlier diagnosis and treatment. A significant contribution to this progress was made by the use of mathematical modeling, which allowed to simulate a likely behavior of cells and organs before the actual disease develops. The most common are the mathematical models, describing the development of a cancerous tumor. The description of the tumor volume dynamics is possible in terms of the dynamics of competing populations of healthy and cancer cells. For this purpose, the classical Lotka–Volterra competing population model can be used [5, 6]. To find effective in some sense (that should be determined) treatment strategies, the optimal control theory can be applied.

2 Model

We consider the following nonlinear control system of differential equations:

$$\begin{cases} \dot{x}(t) = r(1-\kappa_1 w(t))(1-x(t)-a_{12}y(t))x(t) - m_1 u(t)x(t), \\ \dot{y}(t) = \quad (1-\kappa_2 w(t))(1-y(t)-a_{21}x(t))y(t) - m_2 u(t)y(t), \quad t \in [0,T], \\ x(0) = x_0, \ y(0) = y_0; \ x_0, y_0 > 0. \end{cases} \tag{1}$$

This model describes the interaction between the tumor cells, of population size or concentration $y(t)$, and normal cells, of population size or concentration $x(t)$. Functions $u(t)$ and $w(t)$ are bounded controls that represent the intensity of the therapies. These can be, for instance, drug concentration or intensity the radiotherapy. We assume that control $u(t)$ kills the cells (cytotoxic therapy), whereas control $w(t)$ inhibits their proliferation (cytostatic therapy), and that both controls are bounded:

$$0 \leqslant u(t) \leqslant u_{\max} \leqslant 1, \quad 0 \leqslant w(t) \leqslant w_{\max} < \min\{\kappa_1^{-1}, \kappa_2^{-1}\}.$$

In this model, r is the intrinsic growth rate of the normal cells; a_{12} and a_{21} represents the comparable compatibility of the tumor cells and healthy cells; m_1 and m_2 are the efficacy (killing rates) of the therapy with respect to the normal and tumor cells, respectively; κ_1 and κ_2 are the efficacies of the therapy in inhibiting the normal and tumor cells proliferation, respectively.

In the absence of the controls, model (1) is the classical Lotka–Volterra model of two competing populations. Qualitative behavior of such a system is completely determined by mutual location of lines $x + a_{12}y = 1$ and $y + a_{21}x = 1$. Figure 1 shows four possible robust scenarios of the system dynamics. (In this figure, we disregard the fifth case, where these two lines coincide, as this case occurs on a subset of the parameter space of measure zero.) It is easy to see that for these robust

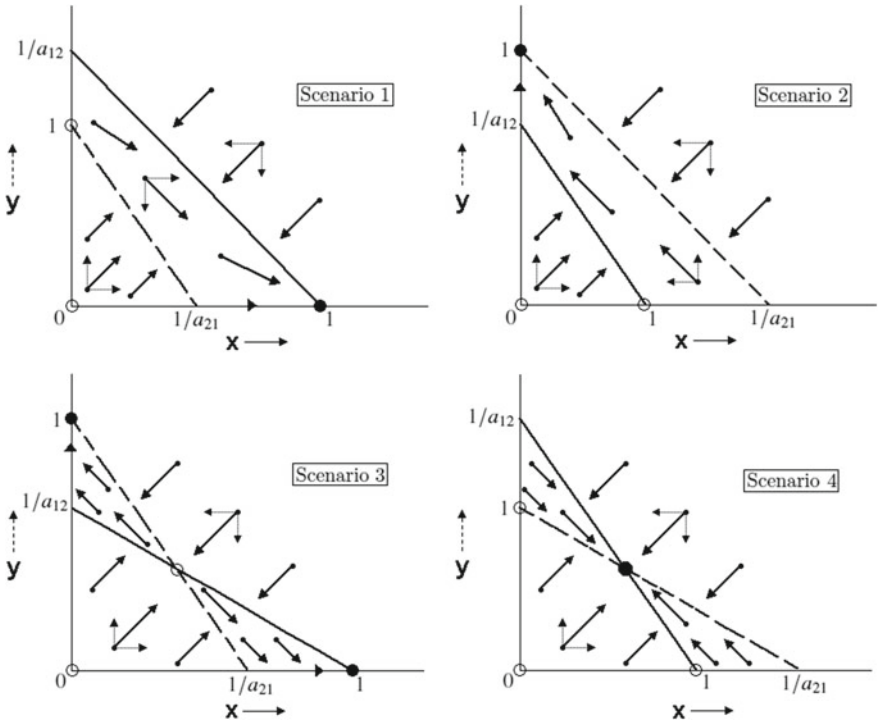

Fig. 1 Four robust scenarios possible for the Lotka–Volterra model of two competing populations. (Adopted from [7])

cases, the system has up to four nonnegative equilibrium states, namely (0, 0), (0, 1), (1, 0), and $\big((1-a_{12})/(1-a_{12}a_{21}),\ (1-a_{21})/(1-a_{12}a_{21})\big)$. The origin is always an unstable node, whereas types of the other points depend on the model parameters and can be either saddles (marked by circles in Fig. 1), or attracting nodes (marked by dots).

Figure 1 implies that cancer can appear and develop either in Scenario 2, or in Scenario 4, as in Scenarios 1 and 3, point (0, 1) is asymptotically stable, and, if a small number of malicious cells appear as a result of a mutation, these are to be eliminated by competition with the normal cells. This figure also suggests that the objective of a therapy is the transition of the system to Scenario 1 (ideally), or, at least, to Scenario 3, where cancer cells will be driven to extinction.

Let us assume that inequalities

$$a_{12} \cdot a_{21} \neq 1, \quad m_2 > m_1, \quad \kappa_2 > \kappa_1 \tag{2}$$

hold, and that control $w(t)$ is constant, $w(t) \equiv const$. Let us denote $q_1 = r(1-\kappa_1 w)$ and $q_2 = 1-\kappa_2 w$. Then we obtain the following system:

$$\begin{cases} \dot{x}(t) = q_1(1 - x(t) - a_{12}y(t))x(t) - m_1u(t)x(t), \\ \dot{y}(t) = q_2(1 - y(t) - a_{21}x(t))y(t) - m_2u(t)y(t), \quad t \in [0, T], \\ x(0) = x_0, \ y(0) = y_0; \ x_0, y_0 > 0. \end{cases} \tag{3}$$

Please note that under the above-made assumption, expressions $m_1q_2a_{21} - m_2q_1$ and $m_1q_2 - m_2q_1a_{12}$ cannot be equal zero at the same time:

$$m_1q_2a_{21} - m_2q_1 \neq 0, \ m_1q_2 - m_2q_1a_{12} \neq 0. \tag{4}$$

The set of admissible controls $\Omega(T)$ is formed by all Lebesgue measurable functions $u(t)$, which for almost $t \in [0, T]$ satisfy the constraints: $0 \leqslant u(t) \leqslant u_{\max} \leqslant 1$. The boundedness, positiveness, and continuation of solutions for system (3) are established by the following lemma.

Lemma 1 *For any admissible control $u(\cdot) \in \Omega(T)$, the corresponding solutions $x(t)$, $y(t)$ to system (3) are defined on the entire interval $[0, T]$ and satisfy inclusion*

$$(x(t), y(t)) \in \Theta = \left\{(x, y) : 0 < x < x_0e^{q_1T}, \ 0 < y < y_0e^{q_2T}\right\}, \quad t \in [0, T]. \tag{5}$$

For system (3), on the set of admissible controls $\Omega(T)$, we consider the problem of minimization of a terminal functional, which is a weighted difference of the concentrations of cancerous and normal cells at the final moment of the therapy:

$$J(u) = y(T) - \alpha x(T), \tag{6}$$

where $\alpha > 0$ is the given weighted coefficient. Lemma 1 guarantees the existence of the optimal solution for the minimization problem (6): for optimal control $u_*(t)$, $x_*(t)$, $y_*(t)$ are corresponding optimal solutions of system (3); see [2].

3 Pontryagin Maximum Principle

To analyze the optimal control $u_*(t)$ and the corresponding optimal solutions $x_*(t)$, $y_*(t)$, we apply the Pontryagin maximum principle [3]. We define Hamiltonian

$$H(x, y, u, \psi_1, \psi_2) = (q_1(1 - x - a_{12}y)x - m_1ux)\psi_1 + (q_2(1 - y - a_{21}x)y - m_2uy)\psi_2,$$

where ψ_1, ψ_2 are the adjoint variables. By the Pontryagin maximum principle, for optimal control $u_*(t)$ and optimal solutions $x_*(t)$, $y_*(t)$, there exists vector function $\psi_*(t) = (\psi_1^*(t), \psi_2^*(t))$, such that

(i) $\psi_*(t)$ is a nontrivial solution of the adjoint system

$$\begin{cases} \dot{\psi}_1^*(t) = -(q_1(1 - x_*(t) - a_{12}y_*(t)) - q_1x_*(t) - m_1u_*(t))\psi_1^*(t) + \\ \qquad +q_2a_{21}y_*(t)\psi_2^*(t), \\ \dot{\psi}_2^*(t) = q_1a_{12}x_*(t)\psi_1^*(t) - (q_2(1 - y_*(t) - a_{21}x_*(t)) - q_2y_*(t) - \\ \qquad -m_2u_*(t))\psi_2^*(t), \\ \psi_1^*(T) = \alpha, \ \psi_2^*(T) = -1; \end{cases} \tag{7}$$

and

(ii) the control $u_*(t)$ maximizes the Hamiltonian $H(x_*(t), y_*(t), u, \psi_1^*(t), \psi_2^*(t))$ with respect to $u \in [0, u_{\max}]$ for almost all $t \in [0, T]$, and, therefore, the following relationship holds:

$$u_*(t) = \begin{cases} u_{\max} & \text{if} \quad L_u(t) > 0, \\ \text{any } u \in [0, u_{\max}] & \text{if} \quad L_u(t) = 0, \\ 0 & \text{if} \quad L_u(t) < 0. \end{cases} \tag{8}$$

Here, function $L_u(t) = -m_1x_*(t)\psi_1^*(t) - m_2y_*(t)\psi_2^*(t)$ is the switching function, which defines the optimal control $u_*(t)$ via formula (8). Introducing auxiliary adjoint variables $\phi_1(t) = -x_*(t)\psi_1^*(t)$ and $\phi_2(t) = -y_*(t)\psi_2^*(t)$, we can rewrite adjoint system (7) and the switching function as

$$\begin{cases} \dot{\phi}_1(t) = q_1x_*(t)\phi_1(t) + q_2a_{21}x_*(t)\phi_2(t), \\ \dot{\phi}_2(t) = q_1a_{12}y_*(t)\phi_1(t) + q_2y_*(t)\phi_2(t), \\ \phi_1(T) = -\alpha x_*(T) < 0, \ \phi_2(T) = y_*(T) > 0, \end{cases} \tag{9}$$

and

$$L_u(t) = m_1\phi_1(t) + m_2\phi_2(t).$$

Systems (3) and (9) allows to formulate the Cauchy problem

$$\begin{cases} \dot{L}_u(t) = m_1^{-1}q_1(m_1x_*(t) + m_2a_{12}y_*(t))L_u(t) + \\ \qquad +m_1^{-1}\Big(m_1(m_1q_2a_{21} - m_2q_1)x_*(t) + m_2(m_1q_2 - m_2q_1a_{12})y_*(t)\Big)\phi_2(t), \\ L_u(T) = -m_1\alpha x_*(T) + m_2y_*(T). \end{cases} \tag{10}$$

for function $L_u(t)$.

An important property of functions $\phi_1(t)$, $\phi_2(t)$ is established by the following lemma.

Lemma 2 *The auxiliary adjoint variables $\phi_1(t)$, $\phi_2(t)$ are sign definite on the entire interval $[0, T]$: $\phi_1(t) < 0, \ \phi_2(t) > 0, \ t \in [0, T]$.*

Our task is to estimate the number of zeros of the switching function $L_u(t)$ and investigate the existence of singular arcs; see [4]. Analysis of the Cauchy problem (10) together with inequalities (4) leads us to the following conclusions:

(i) Let $m_1q_2a_{21} - m_2q_1 \geqslant 0, m_1q_2 - m_2q_1a_{12} \geqslant 0$ hold. If there is $t_0 \in [0, T]$ such that $L_u(t_0) = 0$, then $\dot{L}_u(t_0) > 0$. Then, by (8), the optimal control $u_*(t)$ is a piecewise constant function with one switching of the type

$$u_*(t) = \begin{cases} 0 & t \in [0, \theta_*], \\ u_{\max} & t \in (\theta_*, T], \end{cases}$$

where $\theta_* \in (0, T)$ is the moment of switching.

(ii) Let $m_1q_2a_{21} - m_2q_1 \leqslant 0, m_1q_2 - m_2q_1a_{12} \leqslant 0$ hold. If there is $t_0 \in [0, T]$ such that $L_u(t_0) = 0$, then $\dot{L}_u(t_0) < 0$. Hence, by (8), the optimal control $u_*(t)$ is a piecewise constant function with one switching of the type

$$u_*(t) = \begin{cases} u_{\max} & t \in [0, \theta_*], \\ 0 & t \in (\theta_*, T], \end{cases}$$

where $\theta_* \in (0, T)$ is the moment of switching.

(iii) Let either $m_1q_2a_{21} - m_2q_1 \geqslant 0$ and $m_1q_2 - m_2q_1a_{12} \leqslant 0$, or $m_1q_2a_{21} - m_2q_1 \leqslant 0$ and $m_1q_2 - m_2q_1a_{12} \geqslant 0$ hold. Then switching function $L_u(t)$ can become zero on some interval $\Delta \subset [0, T]$. This means that the optimal control $u_*(t)$ can have a singular arc on this interval. Then, on the interval Δ equalities $L_u(t) = 0$ and $\dot{L}_u(t) = 0$ hold. Therefore,

$$m_2(m_1q_2 - m_2q_1a_{12})y + m_1(m_1q_2a_{21} - m_2q_1)x = 0. \tag{11}$$

By equalities $L_u(t) = 0$ and $\dot{L}_u(t) = 0$, and assumption (2), the necessary condition of the optimality of a singular arc (the Kelly condition, see [8]) in a strengthened form

$$\frac{\partial}{\partial u}\ddot{L}_u(t) = -m_1^{-1}m_2(m_2 - m_1)(m_1q_2 - m_2q_1a_{12})y_*(t)\phi_2(t) > 0. \tag{12}$$

By Lemmas 1 and 2 and formula (11), one can immediately conclude that the Kelly condition (12) holds if $m_1q_2a_{21} - m_2q_1 > 0$ and $m_1q_2 - m_2q_1a_{12} < 0$ hold. This implies that the necessary condition of the optimality of a singular arc is valid in the strengthened form. Hence, on interval Δ, the optimal control $u_*(t)$ is

$$u^*_{\text{sing}}(t) = \frac{q_2 - q_1}{m_2 - m_1} + \frac{(m_1 + m_2)q_1q_2a_{12}a_{21} - (m_1q_2^2a_{21} + m_2q_1^2a_{12})}{m_2(m_1q_2 - m_2q_1a_{12})}\, x_*(t).$$

That is, the optimal control has the form of a feedback that depends only on the optimal solution $x_*(t)$.

If the inclusion $u^*_{\text{sing}}(t) \in (0, u_{\max})$ holds for all $t \in \Delta$ (we are only interested in such controls), then it is possible to concatenate the singular arc $u^*_{\text{sing}}(t)$ with bang–bang control portions $u_*(t)$.

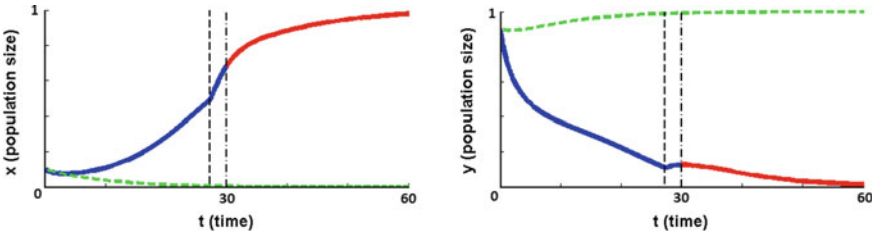

Fig. 2 Optimal solutions $x^*(t)$ and $y^*(t)$. Here, $x_0 = 0.1$, $y_0 = 0.9$, $\alpha = 1$, $u_{max} = 0.6$, $r = 0.6$, $a_{12} = 1.25$, $a_{21} = 1.25$, $\kappa_1 = 0.2$, $\kappa_2 = 0.6$, $m_1 = 0.2$, $m_2 = 0.4$, $T = 30$, and $w = 1$

If $m_1 q_2 a_{21} - m_2 q_1 < 0$ and $m_1 q_2 - m_2 q_1 a_{12} > 0$, then the Kelly condition (12) is not hold and, hence, the necessary condition of the optimality of a singular arc is not valid. Therefore, in this case the optimal control $u_*(t)$ does not have a singular arc on the interval Δ, and the optimal control on entire interval $[0, T]$ is a bang–bang control taking the values 0 or $u_{\max}$ with a finite number of switchings.

4 Numerical Results

To illustrate possible outcomes of the optimal controls, we run calculations using software package BOCOP 2.1.0; see [1]. Some results of these are given in Figs. 2, 3, and 4.

The optimal solutions in Figs. 2 and 3 correspond to the optimal control of the type

$$u_*(t) = \begin{cases} u_{\max} & t \in [0, \theta_*], \\ 0 & t \in (\theta_*, T], \end{cases}$$

where the moment of switching is $\theta_* = 27.3$ in Fig. 2 and $\theta_* = 27.9$ in Fig. 3. In Figs. 2, 3 and 4 the blue lines corresponds to the optimal solutions. The red lines are the continuations of the optimal solutions for a longer time interval (in this case, for

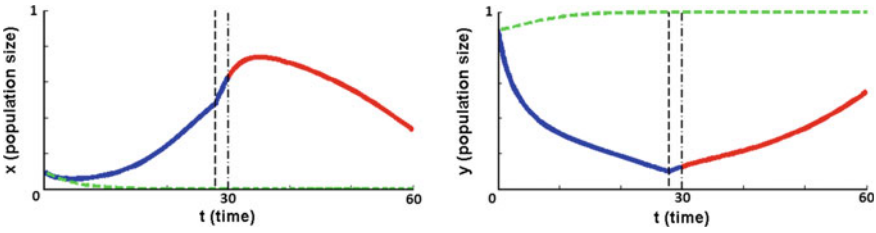

Fig. 3 Optimal solutions $x^*(t)$ and $y^*(t)$. Here, $x_0 = 0.1$, $y_0 = 0.9$, $\alpha = 1$, $u_{max} = 0.6$, $r = 0.6$, $a_{12} = 1.5$, $a_{21} = 0.9$, $\kappa_1 = 0.2$, $\kappa_2 = 0.7$, $m_1 = 0.2$, $m_2 = 0.4$, $T = 30$, and $w = 1$

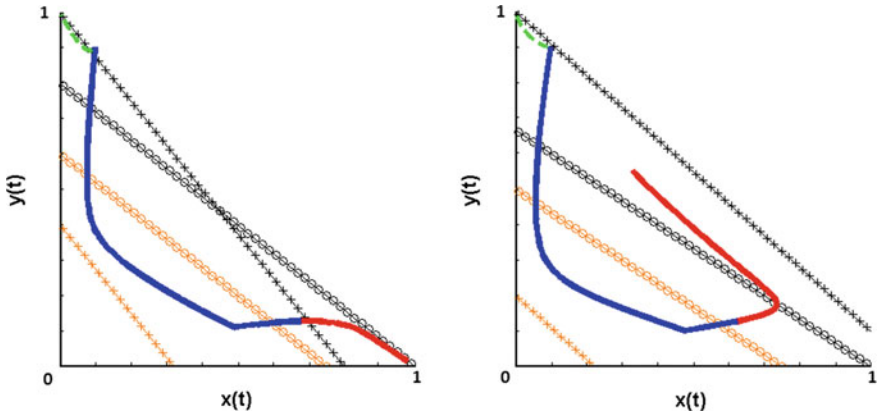

Fig. 4 Phase portraits corresponding to the optimal solutions in Figs. 2 and 3, respectively

$t \in [T, 2T]$). The green dashed curves represent the solutions in the absence of the control ($u(t) = 0$). The vertical dashed lines correspond to the switching moments, whereas the vertical dot-dashed lines correspond to $t = T$ (the end of the control interval). In Fig. 4, black lines are the nullclines of uncontrolled system ($u = 0$), while orange lines are the nullclines of the controlled system (in this case, $u = 0.6$).

Please note that in both these examples, the initial conditions are located in the domain of attraction of the point (0,1), which corresponds to the extinction of the normal cells. The phase portraits show that the behavior of the uncontrolled system match, respectively, Scenario 3 (the first example) and Scenario 2 (the second example) as shown in Fig. 1. The optimal control, when it is active (i.e., $u = u_{\max},\ t \in [0, \theta_*]$), transfers the system to Scenario 1. Thereafter, when the optimal control is passive (i.e., $u = 0,\ t \in (\theta_*, T]$), the system returns to its original scenario. In the first example, the optimal control is able to move the state of the system into the domain of attraction of the point (1,0), where cancer cell population goes to extinction. For this case, further treatment is not required. In the second example, while the therapy appears to be successful, and after the treatment, the system returns to the scenario where the cancer cell population continues to grow.

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