Commun. Optim. Theory 2026 (2026) 38 https://doi.org/10.23952/cot.2026.38

MATHRES Communications in Optimization Theory
Available online at http://cot.mathres.org

CONTROLLED LOTKA-VOLTERRA COMPETITION MODELS IN ADAPTIVE THERAPY OF PROSTATE CANCER

ELLINA GRIGORIEVA[1,*], EVGENII KHAILOV[2]

[1]Department of Mathematics and Computer Sciences, Texas Woman's University, Denton, TX 76204, USA
[2]Faculty of Computational Mathematics and Cybernetics, Lomonosov Moscow State University, Moscow, 119991, Russia

Dedicated to Professor Terry Rockafellar on the occasion of his 90th birthday

Abstract. Current prostate cancer treatment protocols, based on continuous use of the maximum tolerated dose of an anticancer drug, rapidly destroy drug-sensitive cancer cells in the patient's body. As a result, they change the competition between drug-sensitive and drug-resistant cancer cells in favor of the latter. As drug-resistant cancer cells begin to dominate in the patient's body, continued therapy may become ineffective. A new direction in prostate cancer treatment is adaptive therapy. It allows a significant number of drug-sensitive cancer cells to survive using only minimally effective doses of drugs with temporary breaks in drug administration. As a result, drug-sensitive cancer cells compete for common limited resources and suppress the proliferation of drug-resistant cancer cells. Finding optimal moments for switching between dosing and resting intervals by monitoring patient characteristics in real time is critical for the success of adaptive therapy. In this paper, for a given time interval representing the total period of prostate cancer treatment, the corresponding Lotka-Volterra mathematical models describing the competition between drug-sensitive and drug-resistant cancer cells during adaptive therapy are investigated, taking into account both the direct and indirect effects of the targeted drug. These models contain time control functions that are responsible for switching between the stage of active adaptive therapy to the stage of its absence and vice versa. To find the optimal moments of switchings, it is necessary to minimize the total load of cancer cells both during the entire period of prostate cancer treatment and at its final moment. The optimal control problems are solved using the Pontryagin maximum principle and the non-oscillatory theory of differential equations. The optimal scenarios of drug administration are obtained analytically. The results are discussed.

Keywords. Controlled Lotka-Volterra competition model; Non-oscillation theory; Optimal control; Pontryagin maximum principle; Prostate cancer; Riccati equation; Switching function.

2020 Mathematics Subject Classification. 49J15, 49J30, 49N90, 58E25, 92D30.

*Corresponding author.
E-mail address: krasavizha@yahoo.com (E. Grigorieva), khailov@cs.msu.su (E. Khailov).
Received April 14, 2025; Accepted July 27, 2025.

1. INTRODUCTION

Prostate cancer is a malignant tumor that develops from the cells of the prostate gland. It occurs due to the uncontrolled growth and division of prostate cells. These abnormal cells can form a tumor that can spread to surrounding tissues and organs, and form metastases (secondary lesions) in other parts of the body. Treatment for prostate cancer depends on the stage of the disease, the patient's age, general health, and other factors. Treatment options include surgical removal of the prostate gland, radiation therapy, chemotherapy, and hormonal therapy. Prostate cancer is one of the most common cancers in men, especially in older men. Prostate cancer detected at an early stage has a favorable prognosis, and most men are successfully treated. With late diagnosis, the prognosis may be less favorable, but modern treatment methods can significantly prolong life and improve the quality of life of patients.

Mathematical modeling of prostate cancer helps to describe and predict the development of this disease. Such models include a description of tumor growth and take into account such factors as the rate of cell division, availability of nutrients, and the influence of the microenvironment. They also reflect the response to various treatment methods (radiation therapy, chemotherapy, hormonal therapy) and the spread of cancer cells to other organs and tissues (metastases). Mathematical controlled models are used to optimize treatment strategies, evaluate the effectiveness of various treatment methods, and personalize the approach to each patient.

Adaptive therapy in the context of mathematical models of prostate cancer treatment refers to an approach in which treatment is modified depending on the tumor's response to previous stages of therapy, which is monitored and analyzed using mathematical models. These models help predict optimal treatment strategies for a specific patient, taking into account the individual characteristics of the tumor and the body. The essence of adaptive therapy lies in regular monitoring of tumor parameters (volume, growth rate, sensitivity to drugs) using visualization and blood tests (determination of the PSA level). In this case, mathematical models are actively used that describe the dynamics of the tumor and its interaction with various types of treatment. Based on the results of such monitoring, the most effective treatment strategy is selected. This may include changing drug dosages, switching to another type of therapy, or adding new treatments. Thus, adaptive therapy using mathematical models is a promising approach to prostate cancer treatment, allowing to increase the effectiveness of treatment and improve the prognosis for patients.

Optimization in mathematical models of prostate cancer is aimed at improving treatment results, reducing side effects and increasing the quality of life of patients. In this regard, we will highlight the works [2, 3, 6, 8, 11, 12, 13, 14, 15, 17, 18] devoted to assessing the effectiveness of various treatment methods and treatment plans taking into account the individual characteristics of the patient. In our recent paper [6] we used mathematical optimization to identify effective and personalized treatment strategies for prostate cancer, particularly with regard to the timing of hormonal therapy, with the goal of maximizing tumor control and potentially improving patient outcomes. However, in [6] the anticancer drug was used indirectly, under the assumption that when the drug is administered, it is taken at the maximum dose. Some researchers have wondered whether this would be true if, instead of the maximum tolerated dose, there was an option to take a lower dose of the drug, as is done in metronomic treatment or with a gradual dose reduction over time. To answer these questions, in this paper we created a controlled model that contains direct drug use, the intensity of which varied from 0 (no drug) to M (maximum

tolerated dose), and compared our results with the control model that reflects indirect use of the drug. Although the two models are different, the optimal control type is similar in structure: it has a maximum of two switchings, between treatment at the maximum tolerated dose and rest intervals, and it always ends with drug administration. No other treatment protocol or use of a lower drug dose has been shown to be optimal.

This paper is organized as follows. Section 2 contains a description of the control system based on the Lotka-Volterra competition model that describes the interaction between drug-sensitive and drug-resistant cancer cell populations and that does not directly consider the effect of the drug on the patient's body during adaptive therapy for prostate cancer. It also includes the formulation of the corresponding optimal control problem and the discussion of the existence of an optimal solution to such a problem. Section 3 demonstrates the application of the necessary optimality condition in the form of the Pontryagin maximum principle to these optimal control problem. Section 4 presents the properties of the switching function that determines the behavior of the corresponding optimal control, as well as its possible types. Section 5 describes a more complex control system, also based on the Lotka-Volterra competition model, which uses the relationships between populations of drug-sensitive and drug-resistant cancer cells and directly takes into account the effect of the drug on the patient's body during adaptive therapy for prostate cancer. It also contains the formulation of the corresponding optimal control problem and the discussion of the existence of an optimal solution to such a problem. Section 6 again shows the application of the Pontryagin maximum principle to such an optimal control problem. Section 7 describes the properties of the switching function that determines the behavior of the corresponding optimal control, as well as its possible types. Finally, Section 8 contains conclusions and discussion based on our analytical investigation.

2. Optimal control problem for Lotka-Volterra competition model without the direct influence of the targeted drug

For a mathematical description of the interaction between populations of drug-sensitive and drug-resistant cancer cells during adaptive therapy for prostate cancer without taking into account the direct influence of the targeted drug in [12, 13] the following Lotka-Volterra competition model is used:

$$\begin{cases} T_1'(\tau) = \lambda_1 T_1(\tau)\left(1-(1+\kappa v(\tau))\dfrac{(a_{11}T_1(\tau)+a_{12}T_2(\tau))}{K_1}\right)-\mu_1 T_1(\tau), \\ T_2'(\tau) = \lambda_2 T_2(\tau)\left(1-\dfrac{(a_{21}T_1(\tau)+a_{22}T_2(\tau))}{K_2}\right)-\mu_2 T_2(\tau), \end{cases} \tag{2.1}$$

in which:

- $T_1(\tau)$ is population size of drug-sensitive cancer cells;
- $T_2(\tau)$ is population size of drug-resistant cancer cells;
- λ_i, $i=1,2$ are the intrinsic growth rates of drug-sensitive and drug-resistant cancer cells, respectively;
- K_i, $i=1,2$ are drug-sensitive cancer cells carrying capacity and drug-resistant cancer cells carrying capacity, respectively;
- μ_i, $i=1,2$ are the death rates of drug-sensitive and drug-resistant cancer cells, respectively;

- a_{ij}, $i,j=1,2$ are elements of the competition matrix of drug-sensitive and drug-resistant cancer cells;
- κ is patient sensitivity to the maximum tolerated dose of the targeted drug;
- $v(\tau)\in\{0;1\}$ is the control function that shows in what sequence the medication regimen $v(\tau)=1$ and the non-medication regimen $v(\tau)=0$ should alternate, and how long each of them should last.

We assume that

- elements a_{ij}, $i,j=1,2$ of the competition matrix are positive and $a_{11},a_{22}<1$;
- parameters λ_i, μ_i and K_i, $i=1,2$ are positive;
- inequality $a_{21}/a_{11}\neq K_2/K_1$ is true.

Remark 2.1. Taking a medication leads to a decrease of the carrying capacity of drug-sensitive cancer cells K_1.

We add initial conditions to the system (2.1):

$$T_1(0)=T_1^0,\ \ T_2(0)=T_2^0;\ \ T_1^0\in(0,K_1),\ \ T_2^0\in(0,K_2), \tag{2.2}$$

and consider system (2.1), (2.2) for a given period of time $[0,\Theta]$, which is the total period of prostate cancer treatment.

Let us perform scaling of variables, time, as well as parameters and initial conditions in this system:

$$\begin{aligned}
&x=(a_{11}T_1)/K_1,\quad y=(a_{22}T_2)/K_2,\quad x_0=(a_{11}T_1^0)/K_1,\quad y_0=(a_{22}T_2^0)/K_2,\\
&t=\tau/\lambda_2,\qquad T=\Theta/\lambda_2,\qquad m_1=\mu_1/\lambda_2,\qquad m_2=\mu_2/\lambda_2,\\
&r=\lambda_1/\lambda_2,\qquad \gamma_{12}=(a_{12}/a_{22})\cdot(K_2/K_1),\qquad \gamma_{21}=(a_{21}/a_{11})\cdot(K_1/K_2).
\end{aligned}$$

As a result, we have the control system:

$$\begin{cases}
x'(t)=rx(t)\Big(1-(1+\kappa v(t))(x(t)+\gamma_{12}y(t))\Big)-m_1x(t),\ t\in[0,T],\\
y'(t)=y(t)\Big(1-(\gamma_{21}x(t)+y(t))\Big)-m_2y(t),\\
x(0)=x_0,\ \ y(0)=y_0;\ \ x_0\in(0,1),\ \ y_0\in(0,1),
\end{cases} \tag{2.3}$$

in which $\gamma_{21}\neq 1$. In addition, values x and y become concentrations of drug-sensitive and drug-resistant cancer cells, respectively. The value r represents the growth rate of drug-sensitive cancer cells relative to drug-resistant cancer cells.

By the set of admissible controls $\Omega(T)$ we mean all possible Lebesgue measurable functions $v(t)$ which, for almost all $t\in[0,T]$, satisfy the inclusion $v(t)\in V=\{0;1\}$. Here V is a control set.

Let us introduce the set:

$$\Lambda=\{(x,y):0<x<1,\ 0<y<1\}$$

that is an invariant set of the system (2.3).

Then, following the arguments from [5], the validity of the following lemma can be established.

Lemma 2.2. *For an arbitrary admissible control $v(t)$, the corresponding absolutely continuous solution $(x(t),y(t))$ of the system (2.3) is defined on the entire interval $[0,T]$ and satisfies the inclusion:*

$$(x(t),y(t)) \in \Lambda, \quad t \in [0,T]. \tag{2.4}$$

For system (2.3) on the set of admissible controls $\Omega(T)$, we consider the objective function:

$$J(v) = \alpha(x(T)+y(T)) + \beta \int_0^T (x(t)+y(t))dt, \;\; \alpha > 0, \;\; \beta > 0, \tag{2.5}$$

which is a weighted sum of the concentrations of drug-sensitive and drug-resistant cancer cells both at the final moment T of the total treatment period $[0,T]$ and throughout its entire duration.

The medical meaning of this objective function is

- the cancer load in the patient's body both at the final moment T and over the entire interval $[0,T]$;
- the most effective tumor marker (PSA), showing the severity of the disease and having a direct relation to the sum $(x(t)+y(t))$.

Then, we consider the problem of minimizing the objective function (2.5):

$$J(v) \to \min_{v(\cdot)\in\Omega(T)}. \tag{2.6}$$

The control set V is not convex that can lead to the absence of an optimal solution to the minimization problem (2.6) in the classes of admissible regimes traditional for applications. To avoid this problem, the convex hull of the control set V is taken. As a result, the two-point set V turns into the interval $U = [0,1]$. Then, instead of the set of admissible controls $\Omega(T)$, we consider the set of admissible controls $\Psi(T)$. It consists of all possible Lebesgue measurable functions $v(t)$ that satisfy the inclusion $v(t) \in U$ for almost all $t \in [0,T]$. Here U is a new control set.

As a consequence of this, the relaxed minimization problem arises, which consists in minimizing the objective function (2.5) for the control system (2.3) on the set of admissible controls $\Psi(T)$:

$$J(v) \to \min_{v(\cdot)\in\Psi(T)}, \tag{2.7}$$

which we will now consider.

Since the inclusion (2.4) remains valid for an arbitrary admissible control $v(t)$ from $\Psi(T)$, then together with the convexity of the control set U and linearity of the system (2.3) in control $v(t)$, they guarantee the existence of an optimal solution in the relaxed minimization problem (2.7) [9], which consists of the optimal control $v_*(t)$ and the optimal solution $(x_*(t),y_*(t))$ of the system (2.3) corresponding to it.

Remark 2.3. If the inclusions $v_*(t) \in V$ and $v_*(t) \in U$ are simultaneously satisfied for the optimal control $v_*(t)$, then the optimal solution in the relaxed minimization problem (2.7) is simultaneously the optimal solution in the original minimization problem (2.6).

3. Application of the Pontryagin maximum principle

To analyze the optimal control $v_*(t)$ and the corresponding optimal solution $(x_*(t), y_*(t))$ of the system (2.3) in the relaxed minimization problem (2.7), we apply the Pontryagin maximum principle [16]. First, we write the corresponding Hamiltonian:

$$H(x,y,v,\psi_1,\psi_2) = (r(1-(1+\kappa v)(x+\gamma_{12}y))-m_1)x\psi_1 + ((1-(\gamma_{21}x+y))-m_2)y\psi_2 - \beta(x+y),$$

where ψ_1 and ψ_2 are the adjoint variables. Second, we use it to calculate the required partial derivatives:

$$\begin{aligned}
H'_x(x,y,v,\psi_1,\psi_2) &= (r(1-(1+\kappa v)(x+\gamma_{12}y))-m_1)\psi_1 - r(1+\kappa v)x\psi_1 - \gamma_{21}y\psi_2 - \beta,\\
H'_y(x,y,v,\psi_1,\psi_2) &= ((1-(\gamma_{21}x+y))-m_2)\psi_2 - r\gamma_{12}(1+\kappa v)x\psi_1 - y\psi_2 - \beta,\\
H'_v(x,y,v,\psi_1,\psi_2) &= -r\kappa(x+\gamma_{12}y)x\psi_1.
\end{aligned}$$

Then, in accordance with the Pontryagin maximum principle, for the optimal control $v_*(t)$ and the optimal solution $(x_*(t), y_*(t))$ corresponding to it, there exits such a vector function $\psi(t) = (\psi_1(t), \psi_2(t))$ that

• $\psi(t)$ is a nontrivial solution of the adjoint system:

$$\begin{cases}
\psi'_1(t) = -(r(1-(1+\kappa v_*(t))(x_*(t)+\gamma_{12}y_*(t)))-m_1)\psi_1(t)\\
\qquad\qquad +r(1+\kappa v_*(t))x_*(t)\psi_1(t)+\gamma_{21}y_*(t)\psi_2(t)+\beta,\\
\psi'_2(t) = -((1-(\gamma_{21}x_*(t)+y_*(t)))-m_2)\psi_2(t)\\
\qquad\qquad +r\gamma_{12}(1+\kappa v_*(t))x_*(t)\psi_1(t)+y_*(t)\psi_2(t)+\beta,\\
\psi_1(T) = -\alpha,\ \ \psi_2(T) = -\alpha;
\end{cases} \tag{3.1}$$

• the control $v_*(t)$ maximizes the Hamiltonian $H(x_*(t), y_*(t), v, \psi_1(t), \psi_2(t))$ with respect to the variable $v \in [0,1]$ for almost all $t \in [0,T]$, and therefore it satisfies the relationship:

$$v_*(t) = \begin{cases}
1 & , \text{ if } \ -r\kappa(x_*(t)+\gamma_{12}y_*(t))x_*(t)\psi_1(t) > 0,\\
\text{any } v \in [0,1] & , \text{ if } \ -r\kappa(x_*(t)+\gamma_{12}y_*(t))x_*(t)\psi_1(t) = 0,\\
0 & , \text{ if } \ -r\kappa(x_*(t)+\gamma_{12}y_*(t))x_*(t)\psi_1(t) < 0.
\end{cases} \tag{3.2}$$

It is convenient to introduce new adjoint variables:

$$\phi_1(t) = -x_*(t)\psi_1(t), \quad \phi_2(t) = -y_*(t)\psi_2(t).$$

Then, there exits such a vector function $\phi(t) = (\phi_1(t), \phi_2(t))$ that the adjoint system (3.1) is transformed into a new adjoint system:

$$\begin{cases}
\phi'_1(t) = r(1+\kappa v_*(t))x_*(t)\phi_1(t)+\gamma_{21}x_*(t)\phi_2(t)-\beta x_*(t),\\
\phi'_2(t) = r\gamma_{12}(1+\kappa v_*(t))y_*(t)\phi_1(t)+y_*(t)\phi_2(t)-\beta y_*(t),\\
\phi_1(T) = \alpha x_*(T),\ \ \phi_2(T) = \alpha y_*(T),
\end{cases} \tag{3.3}$$

and the relationship (3.2) for the control $v_*(t)$ is rewritten as

$$v_*(t) = \begin{cases}
1 & , \text{ if } \ L_v(t) > 0,\\
\text{any } v \in [0,1] & , \text{ if } \ L_v(t) = 0,\\
0 & , \text{ if } \ L_v(t) < 0,
\end{cases} \tag{3.4}$$

where, due to Lemma 2.2, the function $L_v(t) = \phi_1(t)$ is the switching function. It describes the behavior of the control $v_*(t)$ using the formula (3.4).

4. Switching function and its properties

Since the switching function $L_v(t)$ is directly the function $\phi_1(t)$, then to determine the properties of the function $L_v(t)$, we study the equations of the system (3.3) and its initial conditions.

The analysis of the initial conditions of the system (3.3) and Lemma 2.2 lead to the relationship:

$$L_v(T) = \phi_1(T) = \alpha x_*(T) > 0,$$

which, due to the continuity of the switching function $L_v(t)$, ensures the validity of the following lemma.

Lemma 4.1. *There is a moment $t_0 \in (0,T)$ such that on the interval $(t_0,T]$ the switching function $L_v(t)$ is positive.*

Then, formula (3.4) implies the conclusion.

Corollary 4.2. *A neighborhood is defined adjacent to $t = T$, at which the optimal control $v_*(t)$ takes the value* 1.

An analysis of the equations of system (3.3) shows that the switching function $L_v(t)$ does not vanish identically on any subinterval of the interval $[0,T]$. Namely, the following lemma holds.

Lemma 4.3. *The switching function $L_v(t)$ cannot be zero on any subinterval of the interval $[0,T]$.*

Proof. We assume the contrary. Let the function $L_v(t)$ become zero everywhere on the interval $\Delta \subset [0,T]$. Then, it is obvious that $L_v'(t) = 0$ almost everywhere on this interval. Therefore, the first equation of system (3.3) and Lemma 2.2 imply the equality:

$$\gamma_{21}\phi_2(t) = \beta, \quad t \in \Delta. \tag{4.1}$$

Hence, the derivative $\phi_2'(t)$ becomes zero everywhere on the interval Δ. Therefore, the second equation of the system (3.3) and Lemma 2.2 lead to the expression $\phi_2(t) = \beta$, which together with (4.1) gives a contradictory equality $\gamma_{21} = 1$. Our assumption was wrong, and the switching function $L_v(t)$ does not vanish on any subinterval of the interval $[0,T]$. □

Lemma 4.3 implies the following conclusions.

Corollary 4.4. *The switching function $L_v(t)$ can vanish only at separate points of the interval $[0,T]$.*

Corollary 4.5. *Formula (3.4) shows that the optimal control $v_*(t)$ is a bang-bang function taking values $\{0;1\}$. This means that the control $v_*(t)$ obtained from the analysis of the minimization problem (2.7) is also the optimal control in the original minimization problem (2.6).*

Now we show how the number of zeros of the switching function $L_v(t)$ can be estimated. To do this, consider on the interval $[0,T]$ the linear homogeneous differential equation of the second order:

$$\begin{aligned} z''(t) + \Big(-\frac{x_*'(t)}{x_*(t)} - y_*(t) + r(1+\kappa v_*(t))x_*(t)\Big)z'(t) \\ - r\gamma_{12}\gamma_{21}(1+\kappa v_*(t))x_*(t)y_*(t)z(t) = 0. \end{aligned} \tag{4.2}$$

We extend by continuity the optimal control $v_*(t)$ to the interval $[0, T+2\varepsilon]$ [1], where ε is some given small positive number. Then the optimal solution $(x_*(t), y_*(t))$ is also extendable to this time interval. Thus, the equation (4.2) is defined on the interval $[0, T+2\varepsilon]$.

Let us consider the function $w(t) = 1$ on the interval $[0, T+2\varepsilon]$. It is positive and after its substitution into the left side of the equation (4.2) we have the inequality:

$$-r\gamma_{12}\gamma_{21}(1+\kappa v_*(t))x_*(t)y_*(t) < 0, \quad t \in [0, T+2\varepsilon].$$

Then, due to the de La Vallée-Poussin non-oscillation criterion [10], any non-zero solution of the equation (4.2) has at most one zero on the interval $[0, T+2\varepsilon]$. Let us take the solution $\eta(t)$ of this equation with initial conditions:

$$\eta(T+\varepsilon) = 0, \quad \eta'(T+\varepsilon) = -1. \tag{4.3}$$

Then, everywhere on the interval $[0, T]$ the function $\eta(t)$ is positive.

Let us define on the interval $[0, T]$ the following function:

$$h(t) = \frac{1}{\gamma_{21}x_*(t)} \cdot \frac{\eta'(t)}{\eta(t)}.$$

It is easy to see that this function on the entire interval $[0, T]$ satisfies the Riccati equation [7]:

$$q'(t) = -\gamma_{21}x_*(t)q^2(t) + (y_*(t) - r(1+\kappa v_*(t))x_*(t))q(t) + r\gamma_{12}(1+\kappa v_*(t))y_*(t). \tag{4.4}$$

The adjoint system (3.3) is the linear inhomogeneous system of differential equations. Let us make the following change of variables in it:

$$\chi_1(t) = \phi_1(t), \quad \chi_2(t) = \phi_2(t) - h(t)\phi_1(t) - \beta\gamma_{21}^{-1}.$$

Using the equations of the system (3.3), as well as equation (4.4), for the new variables $\chi_1(t)$ and $\chi_2(t)$ we find the following system:

$$\begin{cases} \chi_1'(t) = (r(1+\kappa v_*(t)) + \gamma_{21}h(t))x_*(t)\chi_1(t) + \gamma_{21}x_*(t)\chi_2(t), \\ \chi_2'(t) = (y_*(t) - \gamma_{21}x_*(t)h(t))\chi_2(t) + \beta\left(\gamma_{21}^{-1} - 1\right)y_*(t), \\ \chi_1(T) = \alpha x_*(T), \end{cases}$$

defined over the entire interval $[0, T]$. Involving the generalized Rolle's theorem [4] in it, one can show that the function $\phi_1(t) = \chi_1(t)$ has at most two different zeros on the interval $[0, T]$.

Using the definition of the switching function $L_v(t)$, we have shown that the following lemma is true.

Lemma 4.6. *The switching function $L_v(t)$ has at most two different zeros on the interval $[0, T)$.*

Combining the results of Lemmas 4.1 and 4.6, we arrive at the conclusion.

Corollary 4.7. *The switching function $L_v(t)$ is either positive for all $t \in [0, T]$;*
or it has one zero θ_* on the interval $(0, T)$ and

$$L_v(t)\begin{cases} < 0, & \text{if} \quad 0 \le t < \theta_*, \\ = 0, & \text{if} \quad t = \theta_*, \\ > 0, & \text{if} \quad \theta_* < t \le T, \end{cases}$$

or it has two distinct zeros θ_1^*, θ_2^* *on this interval and*

$$L_v(t)\begin{cases} >0, & if \quad 0\le t<\theta_1^*,\\ =0, & if \quad t=\theta_1^*,\\ <0, & if \quad \theta_1^*<t<\theta_2^*,\\ =0, & if \quad t=\theta_2^*,\\ >0, & if \quad \theta_2^*<t\le T. \end{cases}$$

Then, formula (3.4) implies the conclusion.

Corollary 4.8. *The optimal control* $v_*(t)$ *is either of the type* $v_*(t)=1$ *for all* $t\in[0,T]$, *or*

$$v_*(t)=\begin{cases} 0 & ,if \quad 0\le t\le\theta_*,\\ 1 & ,if \quad \theta_*<t\le T, \end{cases}$$

or

$$v_*(t)=\begin{cases} 1 & ,if \quad 0\le t\le\theta_1^*,\\ 0 & ,if \quad \theta_1^*<t\le\theta_2^*,\\ 1 & ,if \quad \theta_2^*<t\le T, \end{cases}$$

where $\theta_*\in(0,T)$ *and* $\theta_1^*,\theta_2^*\in(0,T)$ *are moments of switching.*

5. Optimal control problem for Lotka-Volterra competition model with the direct influence of the targeted drug

In cancer treatment, the term "drug" presents the dose of the drug. The controlled model (2.1) takes into account the effect of drug dose. After the treatment, the number of drug-sensitive cancer cells decreases, which influences drug-resistant cancer cells. In turn, the concentration of the drug means the constant accumulation of doses of the drug in the patient's body. When the concentration of the drug is too low, it may not be enough to kill enough drug-sensitive cancer cells. When the concentration of the drug is too high, it can affect normal cells and cause harm to the human body. Therefore, it is important to consider the effect of drug concentration on the treatment. Within the framework of the above, to mathematically describe the interaction between populations of drug-sensitive and drug-resistant cancer cells during adaptive therapy for prostate cancer with taking into account the direct influence of the targeted drug, the paper [14] presents the following Lotka-Volterra competition model:

$$\begin{cases} T_1'(\tau)=\lambda_1T_1(\tau)\left(1-(1+\kappa z(\tau))\dfrac{(a_{11}T_1(\tau)+a_{12}T_2(\tau))}{K_1}\right)-\mu_1T_1(\tau),\ \tau\in[0,\Theta],\\ T_2'(\tau)=\lambda_2T_2(\tau)\left(1-\dfrac{(a_{21}T_1(\tau)+a_{22}T_2(\tau))}{K_2}\right)-\mu_2T_2(\tau),\\ z'(\tau)=-\gamma z(\tau)+u(\tau), \end{cases} \tag{5.1}$$

in which we additionally have:

- $z(\tau)$ is drug concentration in the patient's body;
- $u(\tau)\in[0,M]$ is the control function that reflects the intensity of drug entry into the patient's body;
- κ is patient's sensitivity to the targeted drug;
- γ is dissipation coefficient.

By performing a transformation in the system (5.1) similar to that carried out in the system (2.1), we obtain the following control system:

$$\begin{cases} x'(t) = rx(t)\Big(1-(1+\kappa z(t))(x(t)+\gamma_{12}y(t))\Big) - m_1x(t),\ t\in[0,T], \\ y'(t) = y(t)\Big(1-(\gamma_{21}x(t)+y(t))\Big) - m_2y(t), \\ z'(t) = -\delta z(t)+u(t), \\ x(0)=x_0,\ \ y(0)=y_0,\ \ z(0)=0;\ \ x_0\in(0,1),\ \ y_0\in(0,1). \end{cases} \tag{5.2}$$

By the set of admissible controls $\Phi(T)$ we mean all possible Lebesgue measurable functions $u(t)$ which, for almost all $t\in[0,T]$, satisfy the inclusion $u(t)\in\Pi=[0,M]$. Here M is a given positive constant and Π forms a control set.

We consider the interval $[0,T]$ that determines the duration of the treatment period. Let us fix an arbitrary control $u(\cdot)\in\Phi(T)$. Then, due to the third equation of the system (5.2) and its initial condition, the solution $z(t)$ is determined on the entire interval $[0,T]$ and is expressed by the formula:

$$z(t) = e^{-\delta t}\int\limits_0^t e^{\delta s}u(s)ds, \quad t\in[0,T]. \tag{5.3}$$

Constraints on the control $u(t)$ and formula (5.3) yield the inequalities:

$$0\le z(t)\le M\delta^{-1}(1-e^{-\delta t})\le M\delta^{-1}, \quad t\in[0,T].$$

Now we substitute the function $z(t)$ into the first equation of the system (5.2). After which, carrying out in this system the same reasoning as used to substantiate Lemma 2.2, we arrive at the validity of the following lemma.

Lemma 5.1. *For an arbitrary admissible control $u(t)$, the corresponding absolutely continuous solution $(x(t),y(t),z(t))$ of the system (5.2) is defined on the entire interval $[0,T]$ and satisfies the inclusion:*

$$(x(t),y(t),z(t))\in\Sigma, \quad t\in[0,T], \tag{5.4}$$

where the set:

$$\Sigma=\left\{(x,y,z): 0<x<1,\ 0<y<1,\ 0\le z\le M\delta^{-1}\right\}$$

is an invariant set of the system (5.2).

For system (5.2) on the set of admissible controls $\Phi(T)$, we consider the objective function similar to the objective function (2.5):

$$J(u)=\alpha(x(T)+y(T))+\beta\int\limits_0^T(x(t)+y(t))dt,\ \ \alpha>0,\ \ \beta>0,$$

and the minimization problem similar to the minimization problem (2.6):

$$J(u)\to\min_{u(\cdot)\in\Phi(T)}. \tag{5.5}$$

Due to the inclusion (5.4), the reasoning carried out in Section 2 to justify the existence of the optimal solution in the relaxed minimization problem (2.7) is also valid in this section for the minimization problem (5.5) that we consider for the control system (5.2). Therefore, an

optimal solution is defined, consisting of the optimal control $u_*(t)$ and the optimal solution $(x_*(t), y_*(t), z_*(t))$ of the system (5.2) corresponding to it.

6. Using the Pontryagin maximum principle

To study the optimal control $u_*(t)$ and the corresponding optimal solution $(x_*(t), y_*(t), z_*(t))$ of the system (5.2) in the minimization problem (5.5), we again use the Pontryagin maximum principle. To do this, first, we write down the corresponding Hamiltonian:

$$\begin{aligned} H(x,y,z,u,\psi_1,\psi_2,\psi_3) = &(r(1-(1+\kappa z)(x+\gamma_{12}y))-m_1)x\psi_1 \\ &+((1-(\gamma_{21}x+y))-m_2)y\psi_2+(-\delta z+u)\psi_3-\beta(x+y), \end{aligned}$$

where ψ_1, ψ_2 and ψ_3 are the adjoint variables. Second, we apply it to calculate the desired partial derivatives:

$$\begin{aligned} H'_x(x,y,z,u,\psi_1,\psi_2,\psi_3) &= (r(1-(1+\kappa z)(x+\gamma_{12}y))-m_1)\psi_1 - r(1+\kappa z)x\psi_1 - \gamma_{21}y\psi_2 - \beta, \\ H'_y(x,y,z,u,\psi_1,\psi_2,\psi_3) &= ((1-(\gamma_{21}x+y))-m_2)\psi_2 - r\gamma_{12}(1+\kappa z)x\psi_1 - y\psi_2 - \beta, \\ H'_z(x,y,z,u,\psi_1,\psi_2,\psi_3) &= -r\kappa(x+\gamma_{12}y)x\psi_1 - \delta\psi_3, \\ H'_u(x,y,z,u,\psi_1,\psi_2,\psi_3) &= \psi_3. \end{aligned}$$

Then, according to the Pontryagin maximum principle, for optimal control $u_*(t)$ and the optimal solution $(x_*(t), y_*(t), z_*(t))$ corresponding to it, there exists such a vector function $\psi(t) = (\psi_1(t), \psi_2(t), \psi_3(t))$ that

• $\psi(t)$ is a nontrivial solution of the adjoint system:

$$\begin{cases} \psi'_1(t) = -(r(1-(1+\kappa z_*(t))(x_*(t)+\gamma_{12}y_*(t)))-m_1)\psi_1(t) \\ \qquad\quad +r(1+\kappa z_*(t))x_*(t)\psi_1(t)+\gamma_{21}y_*(t)\psi_2(t)+\beta, \\ \psi'_2(t) = -((1-(\gamma_{21}x_*(t)+y_*(t)))-m_2)\psi_2(t) \\ \qquad\quad +r\gamma_{12}(1+\kappa z_*(t))x_*(t)\psi_1(t)+y_*(t)\psi_2(t)+\beta, \\ \psi'_3(t) = r\kappa(x_*(t)+\gamma_{12}y_*(t))x_*(t)\psi_1(t)-\delta\psi_3(t), \\ \psi_1(T) = -\alpha, \;\; \psi_2(T) = -\alpha, \;\; \psi_3(T) = 0; \end{cases} \tag{6.1}$$

• the control $u_*(t)$ maximizes the Hamiltonian $H(x_*(t), y_*(t), z_*(t), u, \psi_1(t), \psi_2(t), \psi_3(t))$ with respect to the variable $u \in [0, M]$ for almost all $t \in [0, T]$, and therefore it satisfies the formula:

$$u_*(t) = \begin{cases} M & , \text{ if } \;\; L_u(t) > 0, \\ \text{any } u \in [0,M] & , \text{ if } \;\; L_u(t) = 0, \\ 0 & , \text{ if } \;\; L_u(t) < 0, \end{cases} \tag{6.2}$$

where function $L_u(t) = \psi_3(t)$ is a switching function that describes the behavior of the control $u_*(t)$ according to the relationship (6.2).

It is convenient to introduce into the adjoint system (6.1) new adjoint variables:

$$\phi_1(t) = x_*(t)\psi_1(t), \quad \phi_2(t) = y_*(t)\psi_2(t)$$

and then rewrite it taking into account the definition of the switching function $L_u(t)$ as follows

$$\begin{cases} L_u'(t) = \delta L_u(t) + r\kappa(x_*(t) + \gamma_{12} y_*(t))\phi_1(t), \\ \phi_1'(t) = r(1+\kappa z_*(t))x_*(t)\phi_1(t) + \gamma_{21} x_*(t)\phi_2(t) + \beta x_*(t), \\ \phi_2'(t) = r\gamma_{12}(1+\kappa z_*(t))y_*(t)\phi_1(t) + y_*(t)\phi_2(t) + \beta y_*(t), \\ L_u(T) = 0, \;\; \phi_1(T) = -\alpha x_*(T), \;\; \phi_2(T) = -\alpha y_*(T). \end{cases} \tag{6.3}$$

This system will be useful in subsequent arguments.

7. Properties of the switching function

To clarify the properties of the switching function $L_u(t)$, we study the equations of the system (6.3) and its initial conditions.

Analysis of the initial conditions of the system (6.3) and its first equation, as well as the use of Lemma 5.1, lead to relationships:

$$L_u(T) = 0, \quad L_u'(T) = -\alpha r\kappa x_*(T)(x_*(T) + \gamma_{12} y_*(T)) < 0$$

that, due to the continuous differentiability of the switching function $L_u(t)$, ensure the validity of the following lemma.

Lemma 7.1. *There is a moment $t_0 \in (0,T)$, when the switching function $L_u(t)$ is positive on the interval $(0,T)$.*

Then, formula (6.2) gives the conclusion.

Corollary 7.2. *A neighborhood is defined adjacent to $t = T$, at which the optimal control $u_*(t)$ takes the value M.*

Studying the equations of the system (6.3) demonstrates the impossibility of identical vanishing of the switching function $L_u(t)$ on any subinterval of the interval $[0,T]$. Indeed, the following lemma is satisfied.

Lemma 7.3. *The switching function $L_u(t)$ cannot be identically equal to zero on any subinterval of the interval $[0,T]$.*

Proof. We assume the opposite. Let the function $L_u(t)$ be identically zero on the interval Δ. Then its derivative $L_u'(t)$ is also zero everywhere on this interval. Therefore, the first equation of the system (6.3) and Lemma 5.1 lead to the equality $\phi_1(t) = 0$ that holds on the interval Δ. Then the derivative $\phi_1'(t)$ also vanishes identically on this interval and the second equation of the system (6.3) together with Lemma 5.1 give the equality:

$$\gamma_{21}\phi_2(t) = -\beta, \quad t \in \Delta. \tag{7.1}$$

Hence, the derivative $\phi_2'(t)$ is zero on the interval Δ. Then the third equation of the system (6.3) together with Lemma 5.1 provide the equality $\phi_2(t) = -\beta$, which together with the formula (7.1) implies a contradictory equality $\gamma_{21} = 1$. Therefore, the original assumption was incorrect, and the switching function $L_u(t)$ does not vanish identically on any subinterval of the interval $[0,T]$. □

Lemma 7.3 leads to the following conclusions.

Corollary 7.4. *The switching function $L_u(t)$ vanishes only at separate points of the interval $[0,T]$.*

Corollary 7.5. *The formula (6.2) shows that optimal control $u_*(t)$ is a bang-bang function that takes values $\{0;M\}$.*

Now we introduce new variables:

$$\widetilde{\phi}_1(t)=\phi_1(t),\quad \widetilde{\phi}_2(t)=\phi_2(t)+\beta\gamma_{21}^{-1},$$

after which we rewrite the system (6.3) in a more convenient form:

$$\begin{cases} L_u'(t)=\delta L_u(t)+r\kappa(x_*(t)+\gamma_{12}y_*(t))\widetilde{\phi}_1(t),\\ \widetilde{\phi}_1'(t)=r(1+\kappa z_*(t))x_*(t)\widetilde{\phi}_1(t)+\gamma_{21}x_*(t)\widetilde{\phi}_2(t),\\ \widetilde{\phi}_2'(t)=r\gamma_{12}(1+\kappa z_*(t))y_*(t)\widetilde{\phi}_1(t)+y_*(t)\widetilde{\phi}_2(t)+\beta\left(1-\gamma_{21}^{-1}\right)y_*(t),\\ L_u(T)=0,\ \ \widetilde{\phi}_1(T)=-\alpha x_*(T). \end{cases} \tag{7.2}$$

Now let us estimate the number of zeros of the switching function $L_u(t)$. To do this, we consider again on the interval $[0,T]$ a linear homogeneous differential equation of the second order:

$$\omega''(t)+\left(-\frac{x_*'(t)}{x_*(t)}-y_*(t)+r(1+\kappa z_*(t))x_*(t)\right)\omega'(t) \\ -r\gamma_{12}\gamma_{21}x_*(t)y_*(t)(1+\kappa z_*(t))\omega(t)=0. \tag{7.3}$$

We extend by continuity the optimal control $u_*(t)$ to the interval $[0,T+2\varepsilon]$, where ε is some given small positive number. Then the optimal solution $(x_*(t),y_*(t),z_*(t))$ is also extendable to this time interval. Thus, the equation (7.3) is defined on the interval $[0,T+2\varepsilon]$.

Let us consider the function $v(t)=1$ on the interval $[0,T+2\varepsilon]$. It is positive and after its substituting into the left side of the equation (7.3) we have the inequality:

$$-r\gamma_{12}\gamma_{21}x_*(t)y_*(t)(1+\kappa z_*(t))<0,\quad t\in[0,T+2\varepsilon].$$

Then, again, due to the de La Vallée-Poussin non-oscillation criterion, any non-zero solution of the equation (7.3) has at most one zero on the interval $[0,T+2\varepsilon]$. Let us take the solution $\eta(t)$ of this equation with initial conditions (4.3). Then, the function $\eta(t)$ is positive everywhere on the interval $[0,T]$.

Next, let us define on the interval $[0,T]$ the following function:

$$h(t)=-\frac{1}{\gamma_{21}x_*(t)}\cdot\frac{\eta'(t)}{\eta(t)}\,.$$

It is easy to check that this function on the entire interval $[0,T]$ satisfies the Riccati equation:

$$q'(t)=\gamma_{21}x_*(t)q^2(t)+(y_*(t)-rx_*(t)(1+\kappa z_*(t)))q(t)-r\gamma_{12}y_*(t)(1+\kappa z_*(t)). \tag{7.4}$$

The system (7.2) is the linear inhomogeneous system of differential equations. Let us perform in its second and third equations the following change of variables:

$$\chi_1(t)=\widetilde{\phi}_1(t),\quad \chi_2(t)=\widetilde{\phi}_2(t)+h(t)\widetilde{\phi}_1(t).$$

Using the corresponding equations of the system (7.2), as well as equation (7.4), for the variables $L_u(t)$, $\chi_1(t)$ and $\chi_2(t)$ we find the following system:

$$\begin{cases} L_u'(t) = \delta L_u(t) + r\kappa(x_*(t) + \gamma_{12} y_*(t))\chi_1(t), \\ \chi_1'(t) = (r(1+\kappa z_*(t)) - \gamma_{21} h(t))x_*(t)\chi_1(t) + \gamma_{21} x_*(t)\chi_2(t), \\ \chi_2'(t) = (y_*(t) + \gamma_{21} x_*(t) h(t))\chi_2(t) + \beta\left(1 - \gamma_{21}^{-1}\right) y_*(t), \\ L_u(T) = 0, \;\; \chi_1(T) = -\alpha x_*(T), \end{cases}$$

defined over the entire interval $[0,T]$. Involving again the generalized Rolle's theorem in it, we conclude that the switching function $L_u(t)$ has no more than three different zeros on the interval $[0,T]$. Considering the presence of zero for this function at $t = T$, we have the following lemma.

Lemma 7.6. *The switching function $L_u(t)$ has at most two different zeros on the interval $[0,T)$.*

Combining the results of Lemmas 7.1 and 7.6, we arrive at the conclusion.

Corollary 7.7. *The switching function $L_u(t)$ is either positive for all $t \in [0,T)$;*
or it has one zero ξ_* on the interval $(0,T)$ and

$$L_u(t) \begin{cases} < 0, & if \;\; 0 \le t < \xi_*, \\ = 0, & if \;\; t = \xi_*, \\ > 0, & if \;\; \xi_* < t < T, \\ = 0, & if \;\; t = T, \end{cases}$$

or it has two distinct zeros ξ_1^*, ξ_2^* on this interval and

$$L_u(t) \begin{cases} > 0, & if \;\; 0 \le t < \xi_1^*, \\ = 0, & if \;\; t = \xi_1^*, \\ < 0, & if \;\; \xi_1^* < t < \xi_2^*, \\ = 0, & if \;\; t = \xi_2^*, \\ > 0, & if \;\; \xi_2^* < t < T, \\ = 0, & if \;\; t = T. \end{cases}$$

Then, formula (6.2) implies the conclusion.

Corollary 7.8. *The optimal control $u_*(t)$ is either of the type $u_*(t) = M$ for all $t \in [0,T]$,*
or

$$u_*(t) = \begin{cases} 0 & , if \;\; 0 \le t \le \xi_*, \\ M & , if \;\; \xi_* < t \le T, \end{cases}$$

or

$$u_*(t) = \begin{cases} M & , if \;\; 0 \le t \le \xi_1^*, \\ 0 & , if \;\; \xi_1^* < t \le \xi_2^*, \\ M & , if \;\; \xi_2^* < t \le T, \end{cases}$$

where $\xi_* \in (0,T)$ and $\xi_1^*, \xi_2^* \in (0,T)$ are moments of switching.

8. Conclusions and Discussion

It is known that standard prostate cancer treatment methods, which rely on using the maximum tolerated dose of an anti-cancer drug throughout the treatment, often expose patients to toxic chemicals that suppress their immune systems. Moreover, cancer cells are divided into two main populations: those that die when exposed to the drug, and those that perceive it as food and

begin to proliferate even faster. Although using only the maximum dose of an anti-cancer drug can cure some patients, it can also lead to an increase in drug-resistant cells and the suppression of drug-sensitive cells, and in fact, many patients die despite treatment. So how should a doctor treat a patient? There are various cancer treatment protocols, including metronomic treatment, in which a lower concentration of a drug is given periodically over a long period of treatment by switching between periods of receiving chemotherapy ("drug on") and periods of not receiving it ("drug off"). Some physicians practice alternating the maximum tolerated dose with periods of rest from any drug, and there are also some methods of continuous drug administration by gradually reducing the dose, similar to how one would take prednisone or an antibiotic (e.g., 4 tablets for 3 days, 3 tablets for 3 more days, 2 tablets for the next 3 days, and finally one tablet for each of the remaining 3 days. The only difference is that the cancer drug is usually given by injection.)

Which method is optimal for a cancer patient? In this paper, we attempt to answer this question by modeling the interactions of drug-sensitive and drug-resistant cells under different drug dosing regimens. In our first model (2.1), we model the behavior of drug-sensitive and drug-resistant cells when the maximum tolerated dose of a drug is alternated with drug-free intervals. In the second model (5.1), we also consider the dynamics of competition between two types of cancer cells, when the drug dose can continuously change from 0 (no treatment) to M (maximum tolerated dose).

We considered and studied in detail using the Pontryagin maximum principle two optimal control problems with the same objective function, but for different control systems. The first control system (2.3), based on the Lotka-Volterra competition model, describes adaptive therapy of prostate cancer without taking into account the direct influence of the targeted drug. Its effect on the patient is carried out through the parameter κ. The second control system (5.2), also based on the Lotka-Volterra competition model and also defining adaptive therapy of prostate cancer, on the contrary, takes into account the direct influence of the targeted drug. Indeed, the control function $u(t)$ represents the limited intensity of its intake into the patient's body.

What is important here is that despite the obvious differences in the control systems, the corresponding optimal controls have the same structure: in both models, the optimal treatment protocols have no more than two switchings between the maximum tolerated dose and rest intervals, with the drug intake required at the end of the treatment period. We found that no other drug administration scenario can be optimal.

Mathematical models play an important role in optimizing prostate cancer treatment, allowing to increase the effectiveness of therapy, reduce side effects and improve the quality of life of patients. The development and application of these models in cooperation with doctors is a promising direction in the fight against prostate cancer. Depending on the patient's health condition, the model parameters will differ in each specific case, so it is possible to numerically find the exact positions of the switchings and, therefore the optimal treatment protocol for a specific cancer patient.

REFERENCES

[1] G. Birkoff, G.-C. Rota, Ordinary Differential Equations, John Wiley & Sons, New York, 1989.

[2] J.J. Cunningham, J.S. Brown, R.A. Gatenby, K. Staňková, Optimal control to develop therapeutic strategies for metastatic castrate resistant prostate cancer, J. Theor. Biol. 459 (2018) 67-78.

[3] J. Cunningham, F. Thuijsman, R. Peeters, Y. Viossat, J. Brown, R. Gatenby, K. Staňková, Optimal control to reach eco-evolutionary stability in metastatic castrate-resistant prostate cancer, PLoS ONE 15, e0243386 (2020) 1-24.

[4] A.V. Dmitruk, A generalized estimate on the number of zeros for solutions of a class of linear differential equations, SIAM J. Control Optim. 30 (1992) 1087-1091.

[5] N.L. Grigorenko, E.N. Khailov, E.V. Grigorieva, A.D. Klimenkova, Optimal strategies in the treatment of cancers in the Lotka-Volterra mathematical model of competition, P. Steklov Inst. Math. 312, suppl. 1 (2021) S1-S17.

[6] E. Grigorieva, E. Khailov, Bilinear controlled model in adaptive cancer therapy, Discrete Cont. Dyn.-B 30 (2025) 4324-4339.

[7] P. Hartman, Ordinary Differential Equations, John Wiley & Sons, New York, 1964.

[8] I. Irurzun-Arana, A. Janda, S. Ardanza-Trevijano, I.F. Trocóniz, Optimal dynamic control approach in a multiobjective therapeutic scenario: Application to drug delivery in the treatment of prostate cancer, PLoS Comput. Biol. 14, e1006087 (2018) 1-16.

[9] E.B. Lee, L. Marcus, Foundations of Optimal Control Theory, John Wiley & Sons, New York, 1967.

[10] A.Yu. Levin, Non-oscillation of solutions of the equation $x^{(n)} + p_1(t)x^{(n-1)} + \cdots + p_n(t)x = 0$, Russian Math. Surveys 24 (1969) 43-99.

[11] M.-C. Litzinger, Y. Todorov, M. Föller-Nord, M.K. Chaudhary, A.S. Bratus, On optimal therapy protocols in the mathematical model of prostate cancer progression, Adv. Syst. Sci. Appl. 20 (2020) 83-104.

[12] R. Liu, S. Wang, X. Tan, X. Zou, Identifying optimal adaptive therapeutic schedules for prostate cancer through combining mathematical modeling and dynamic optimization, Appl. Math. Model. 107 (2022) 688-700.

[13] W. Luo, X. Tan, J. Shen, Optimal treatment strategy for cancer based on mathematical modeling and impulse control theory, Axioms 12, 916 (2023) 1-18.

[14] W. Luo, X. Tan, X. Zou, Q. Tan, Optimal treatment of prostate cancer based on state constraint, Mathematics 11, 4025 (2023) 1-17.

[15] T. Phan, S.M. Crook, A.H. Bryce, C.C. Maley, E.J. Kostelich, Y. Kuang, Review: Mathematical modeling of prostate cancer and clinical application, Appl. Sci. 10, 2721 (2020) 1-29.

[16] L.S. Pontryagin, V.G. Boltyanskii, R.V. Gamkrelidze, E.F. Mishchenko, Mathematical Theory of Optimal Processes, John Wiley & Sons, New York, 1962.

[17] T. Suzuki, K. Aihara, Nonlinear system identification for prostate cancer and optimality of intermittent androgen suppression therapy, Math. Biosci. 245 (2013) 40-48.

[18] J.B. West, M.N. Dinh, J.S. Brown, J. Zhang, A.R. Anderson, R.A. Gatenby, Multidrug cancer therapy in metastatic castrate-resistant prostate cancer: An evolution-based strategy, Clin. Cancer Res. 25 (2019) 4413-4421.