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Optimal Protocols for the Anti-VEGF Tumor Treatment

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Abstract. Cancer treatment using the antiangiogenic agents targets the evolution of the tumor vasculature. The aim is to significantly reduce supplies of oxygen and nutrients, and thus starve the tumor and induce its regression. In the paper we consider well established family of tumor angiogenesis models together with their recently proposed modification, that increases accuracy in the case of treatment using VEGF antibodies. We consider the optimal control problem of minimizing the tumor volume when the maximal admissible drug dose (the total amount of used drug) and the final level of vascularization are also taken into account. We investigate the solution of that problem for a fixed therapy duration. We show that the optimal strategy consists of the drug-free, full-dose and singular (with intermediate values of the control variable) intervals. Moreover, no bang-bang switch of the control is possible, that is the change from the no-dose to full-dose protocol (or in opposite direction) occurs on the interval with the singular control. For two particular models, proposed by Hahnfeldt et al. and Ergun et al., we provide additional theorems about the optimal control structure. We investigate the optimal controls numerically using the customized software written in MATLAB ®, which we make freely available for download. Utilized numerical scheme is based on the composition of the well known gradient and shooting methods.

Keywords and phrases: angiogenesis, bevacizumab, optimal control, cancer

Mathematics Subject Classification: 49J15, 49N90

1. Introduction

Conventional cancer therapies, such as radiotherapy or chemotherapy, are designed to induce large amount of cell death in rapidly proliferating cancer cells. Although such therapies are capable of shrinking the tumor many orders of magnitude, the complete tumor eradication is often unachievable [16]. In addition, cancer cells may acquire drug resistance, because of their fast duplications combined with high genetic instability. Novel treatment approaches shift focus away from the cancer cells and instead target the environment that supports the tumor [2]. An example of such approach is the antiangiogenic therapy postulated by Folkman [8], which is designed to inhibit the vascular support of the tumor, and thus induce

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the tumor starvation and regression. It holds the promise of being less patient specific, because it targets genetically stable host vasculature and not the constantly mutating tumor cells [4]. Moreover, it has been proposed that the proper dose of the antiangiogenic drugs might significantly improve chemotherapy efficacy [11, 12]. Namely, without the treatment, tumor has the ability to recruit new blood vessels in a process called tumor angiogenesis. However, it has been discovered that tumor angiogenesis is highly pathological-incorrect structure and poor efficiency of newly formed vessels are common tumor features [11, 12]. Some trials revealed that those vasculature pathologies result in significant impairment of the chemotherapy delivery since most of the administered drug dose is not even absorbed by the tumor and the successfully delivered part is not distributed uniformly in the tumor region [11]. The hypothesis is that the proper amount of antiangiogenic drugs may cause in the removal of abberant neovessels (in a process called vascular pruning) what would result in the increase of the overall vasculature quality, and thus in the boost of chemotherapy efficacy through its increased delivery. Of course too high dose of the agents may destroy too much of the tumor vasculature, leading to the poor drug delivery. Hence, the effort is to identify the dosage and the timing of the normalization window caused by the antiangiogenic therapy in order to increase the efficacy of chemotherapy.

In the paper we address the problem of designing optimal protocols for the antiangiogenic treatment. We focus our attention on the therapeutic agents directly blocking angiogenesis inducing proteins which are secreted by the cancer cells (compare bevacizumab, trademark Avastin®, that inhibits vascular endothelial growth factor VEGF). We base our analysis on the well established family of mathematical models originating from the Hahnfeldt *et al.* model of tumor angiogenesis [10]. However, we consider the models with the modification proposed in [20] which was introduced in order to better reflect the effect of considered drugs and, to our knowledge, has never been analyzed from the optimal control point of view. We consider the optimal control problem of minimizing the tumor volume for a fixed therapy duration and when the maximal admissible drug dose, the total amount of used drugs, and the final level of vascularization (ratio of the carrying capacity to the tumor volume) are also taken into account. We explicitly introduce the part of the payoff functional describing the level of final vascularization in order to capture the concept of vasculature related to chemotherapy efficacy, what, to our knowledge, is also a novelty. Our main aim is to formulate as much detailed description of the optimal control as possible.

2. Considered family of tumor angiogenesis models

In the seminal paper [10], Hahnfeldt *et al.* proposed a mathematical model resulting from the theoretical concept postulating that the tumor growth is a bidirectional control process. The tumor regulates associated vascular growth or suppression, and in turn, the tumor vasculature controls the tumor growth through its usual nutritive function. The tumor volume (p) and the effective vascular support (q), which defines the environmental carrying capacity, are time-dependent variables described by coupled ordinary differential equations (ODEs). The tumor growth is assumed to be governed by the Gompertz law [9],

$$\dot{p}(t) = -\varepsilon p(t) \ln \frac{p(t)}{q(t)} \,. \tag{2.1}$$

With the constant effective vascular support $q(t) = q_{max}$, the initial rapid tumor growth is followed by a slowdown as the tumor volume approaches environmental carrying capacity q_{max}. To account reciprocal interaction of the tumor with the host vasculature the vascular support can be described by the following relation

$$\dot{q}(t) = -\mu q(t) + bS(p(t), q(t)) - dI(p(t), q(t)) \,, \tag{2.2}$$

where $-\mu q(t)$ represents the spontaneous loss of functional vasculature, the term $bS(p(t), q(t))$ represents the stimulation of vessels growth, while $-dI(p(t), q(t))$ describes the endogenous inhibition of previously generated vasculature. To derive the relationship between the functions $I(p, q)$ and $S(p, q)$ Hahnfeldt *et al.*

considered the partial differential equation for the concentration of angiogenic stimulators/inhibitors from which the following relationship between $I(p,q)$ and $S(p,q)$ was derived

$$\frac{I(p,q)}{S(p,q)} = p^{\alpha}q^{\beta}\,, \quad \text{where } \alpha+\beta = 2/3\,,$$

see [21] for further details. Hahnfeldt *et. al* proposed to consider $\alpha = -1/3$ and $\beta = 1$, that is the stimulatory capacity and the endogenous inhibition functions given by $p(t)$ and $q(t)p^{2/3}(t)$, respectively. However, other forms of those functions were considered by other authors, compare Tab. 1, and hence one can consider the whole family of the tumor angiogenesis models. Introduction of other stimulation/inhibition

$S(p(t),q(t))$	$I(p(t),q(t))$	Ref.
$p(t)$	$q(t)p^{2/3}(t)$	Hahnfeldt *et al.* [10]
$q^{2/3}(t)$	$q^{4/3}(t)$	Ergun *et al.* [7]
$q(t)$	$q(t)p^{2/3}(t)$	d'Onofrio and Gandolfi [6]

TABLE 1. Formulas for the stimulatory capacity function $S(p,q)$ and the endogenous inhibition function $I(p,q)$ considered in the literature.

functions was motivated by the biological evidences [6] or it was dictated by easier tractability of the associated optimal control problem [7]. However, it can be shown (see e.g. [18]) that for all formulas presented in Tab. 1 and arbitrary positive initial conditions $p_0 > 0$ and $q_0 > 0$, the corresponding solution (p,q) of Eqs. (2.1) and (2.2) exists for all $t \geq 0$, is unique and both p and q remain positive. In addition, there are only two possible scenarios depending on the parameter values: there exists a unique positive globally asymptotically stable steady state in $\mathbb{R}^2_+$ or there is no positive steady state and the solution (p,q) tends to $(0,0)$ as $t \to +\infty$.

The model described by Eqs. (2.1) and (2.2) captures the tumor growth without any therapeutic intervention. The equation describing the evolution of vessels carrying capacity has originally been adapted to include antiangiogenic treatment effect as follows

$$\dot{q}(t) = -\mu q(t) + bS(p(t),q(t)) - dI(p(t),q(t)) - eq(t)u(t)\,, \tag{2.3}$$

where $u(t)$ is the time dependent concentration of administered inhibitor. What is important, the model predictions for the S and I proposed by Hahnfeldt *et al.* were successfully compared with experimental data on the treatment with TNP-470, Angiostatin and Endostatin [10]. However, in [20] Poleszczuk *et al.* argued that the original model, although successful in predicting the response to many therapeutic agents, might insufficiently describe the effect of antiangiogenic drugs that directly inhibit angiogenic stimulating molecules. Bevacizumab (trademark Avastin®), a humanized monoclonal antibody, that inhibits vascular endothelial growth factor A (VEGF-A), was provided as an example of such agent [20]. For the antiangiogenic agents with the course of action comparable to bevacizumab, the following modification of the original model (Eqs. (2.1) and (2.3)) was proposed

$$\begin{aligned}
\dot{p}(t) &= -\varepsilon p(t)\ln\frac{p(t)}{q(t)}\,,\\
\dot{q}(t) &= -\mu q(t) + \frac{l}{a+u(t)}S(p(t),q(t)) - dI(p(t),q(t))\,,
\end{aligned} \tag{2.4}$$

where all parameters are non-negative and, as above, $u(t)$ represents the concentration of the administered agent. Note that in comparison to the original model the treatment does not induce gross reduction of vasculature but selectively inhibits the formation of tumor-stimulated neovasculature. What is important, comparisons of the modified and original models predictions with the experimental data show that when bevacizumab is applied as the therapeutic agent, then the quality of fit is higher (data approximation error is lower) for the modified model [19, 22].

In many recent studies it is usually assumed that the main goal of the antiangiogenic treatment is to minimize the tumor volume at the end of treatment, compare Świerniak *et al.* [25, 29] or Ledzewicz and Schättler [14, 15]. Various constraints on the treatment protocol are considered, among them: limited total amount of drug, maximal admissible dose or fixed therapy duration. For the original Hahnfeldt *et al.* model it has been shown that with limited amount of drug, fixed maximal drug dose and without fixed therapy duration the maximal minimization of tumor is achieved in a very non-trivial way [14, 15]. More precisely, the optimal treatment strategy might consist of a singular control interval in which the dosage depends on the temporal tumor volume and vasculature size. However, for a fixed duration of antiangiogenic therapy and for the Ergun *et al.* and d'Onofrio and Gandolfi forms of the model (see Tab. 1) the structure of optimal control is much simpler [25]. Namely, the intermediate doses of the drug are not optimal, and thus the optimal protocol has a bang-bang structure, that is it consists of switches between maximal dose and no drug intervals. Nowadays much effort is put into optimizing the combined treatments, *i.e* protocols in which antiangiogenic drugs are administered simultaneously with chemotherapy/radiotherapy. Various combined treatment protocols have been intensively studied through numerical simulations [5, 23] or from the optimal control point of view [13, 26, 27]. Numerical investigations show that there is an increase in the chemotherapy efficiency when antiangiogenic agents are simultaneously administered [23].

In the following, we consider only the family of models described by Eqs. (2.4) with continuously differentiable functions $S(p,q)$ and $I(p,q)$. For a particular kind of functions describing inhibition and stimulation, more precisely the functions such that $I(p,0) = 0$ and $S(p,0) \geq 0$ for all $p \geq 0$, we can show positivity of solutions of Eqs. (2.4). Indeed, the first equation of Eqs. (2.4) can be rewritten in the integral form

$$p(t) = p(0) \exp\left(-\varepsilon \int_0^t \ln \frac{p(s)}{q(s)} ds \right).$$

Hence, $p(0) > 0$ implies $p(t) > 0$ for all $t > 0$. Let us further assume that $q(t) \to 0$ as $t \to t_1$ for some $t_1 > 0$. However, from the second equation of Eqs. (2.4) we have that $\dot{q}(t_1) = \frac{l}{a+u} S(p,0) \geq 0$ due to the positivity of p. Hence, uniqueness of solutions yields their positivity for the positive initial data, and the following lemma holds.

Lemma 2.1. *If $I(p,0) = 0$ and $\forall p \geq 0$ $S(p,0) \geq 0$, then the solution of Eqs.* (2.4) *remains positive for positive initial data, independently of the maximal admissible dose $\tilde{A}$.*

Lemma 2.1 is crucial for the next Section, as the strict positivity of solutions of Eqs. (2.4) is constantly used. Notice, that the assumptions of Lemma 2.1 are fulfilled for all formulae presented in Tab. 1.

3. Results

The main part of the payoff functional that we consider in our minimization problem has a standard form and is consisted of the tumor volume at the end of therapy, $p(T)$, and the total amount of the used drug $\int_0^T u(t)dt$, where T is the fixed therapy duration. However, we would also like to tackle the problem of subsequent (after the antiangiogenic therapy) chemotherapy administration. According to the "vessels normalization" hypothesis, efficient treatment with chemotherapy is possible only when the cytotoxic agent can be distributed evenly, that is when vessels penetrate most of the tumor regions and have the proper structure and functionality [12]. In order to reflect that phenomena, we assume that

the higher the tumor vascularization (defined as the ratio of the vessels carrying capacity to the tumor volume, $q(t)/p(t)$) is, the larger the chemotherapy efficacy is. Hence, we take into account the tumor vascularization at the end of the treatment and we assume the following form of the payoff functional

$$P[u(\cdot)] = p(T) - k_1 \frac{q(T)}{p(T)} + k_2 \int_0^T u(t)dt\,, \tag{3.1}$$

where $T > 0$ is the treatment duration, and $k_1\,,\ k_2$ describe the trade-offs between separate treatment goals. Additionally, the cumulative side effects of the anti-angiogenic agents are taken into account to measure the side effects of the treatment. Hence, a penalty term in the form of integral to the terminal time T is present in the considered payoff functional. Clearly, $\int_0^T u(t)dt$ measures the total amount of the given anti-angiogenic agent u. Moreover, because of the high cost of anti-angiogenic agents one can not consider unlimited amount of available agents. Thus, we assume that the total amount of the anti-antiangiogenic agents is limited by A_{max}, i.e.

$$\int_0^T u(t)dt \leq A_{max}.$$

Our goal is to minimize $P[u(\cdot)]$ subject to the dynamics of Eqs. (2.4) for the fixed therapy duration T and over all measurable functions $u : [0, T] \to \left[0, \tilde{A}\right]$, where $\tilde{A}$ denotes the maximal drug dose that can be administered without making a harm to the patient. Clearly, we do not consider the model describing the influence of the chemotherapy and thus, although it seems biologically reasonable, we cannot claim that the usage of the final vascularization in the payoff functional is an optimal way for combined protocol in which we assume that the chemotherapy is administered after the antiangiogenic treatment. In fact, the optimality strongly depends on the way in which the chemotherapy is incorporated into the model.

Before analyzing the problem in details, we discuss the optimal treatment protocol when there is no limitation on the total amount of used agent and the only goal is to minimize the tumor volume at the end of the therapy, i.e. when $k_i = 0$ for $i = 1, 2$. Suppose that the optimal control $u_*(t)$ for Eqs. (2.4) is less than $\tilde{A}$ on some interval of non-zero Lebesgue measure. Then there exists $t^* < T$ such that $q_*(t) > q_f(t)$ for $t > t^*$, where $q_*(t)$ and $q_f(t)$ are the solutions corresponding to the optimal control u_* and the full-dose protocol $u_f(t) \equiv \tilde{A}$, respectively. It easily follows that $p_*(T) > p_f(T)$, and hence $u_*(t)$ is not an optimal control. Therefore, we can formulate the following lemma.

Lemma 3.1. *If $k_1 = 0$ and $k_2 = 0$, then the optimal treatment protocol for Eqs. (2.4) is to give the maximal admissible dose through the whole treatment interval, that is $u_*(t) \equiv \tilde{A}$.*

Clearly, if we focus only on minimizing the tumor volume, then the structure of optimal treatment protocol is straightforward. This scenario can be utilized when the antiangiogenic treatment is administered just before the tumor resection. In such a case the final vascularization and the total amount of used drug can be omitted.

We consider now the structure of optimal control for strictly positive values of k_1 and k_2. Let us denote the right-hand side of Eqs. (2.4) by $F(p, q, u)$. The part of the payoff functional P that depends only on the endpoint can be treated as a function of $(p(T), q(T))$, that is $G(p(T), q(T)) = p(T) - k_1 \frac{q(T)}{p(T)}$. From the Pontryagin Minimum Principle it follows that if $u_*(t)$ is an optimal control and $(p_*(t), q_*(t))$ is the corresponding trajectory, then there exists a function (adjoint or co-state variable) $y : [0, T] \to \mathbb{R}^2$, which satisfies the adjoint system of equations $\dot{y} = -D^T_{(p,q)}F \cdot y$, where $D_{(p,q)}F$ describes the Jacobi matrix of F with respect to p and q, with the terminal condition $y(T) = \nabla G(p(T), q(T))$, and such that Hamiltonian $H(y, p, q, u) = y^{\mathrm{T}}F(p, q, u)$ is minimized [3, 24].

In our case the adjoint variables satisfy the following system of ordinary differential equations

$$\begin{aligned}\dot{y}_1 &= \varepsilon y_1\left(\ln\frac{p_*}{q_*}+1\right) - y_2\left(\frac{l}{a+u_*}\frac{\partial S(p,q)}{\partial p}\bigg|_{(p_*,q_*)} - d\frac{\partial I(p,q)}{\partial p}\bigg|_{(p_*,q_*)}\right),\\ \dot{y}_2 &= -\varepsilon y_1\frac{p_*}{q_*} + y_2\left(\mu - \frac{l}{a+u_*}\frac{\partial S(p,q)}{\partial q}\bigg|_{(p_*,q_*)} + d\frac{\partial I(p,q)}{\partial q}\bigg|_{(p_*,q_*)}\right),\end{aligned} \tag{3.2}$$

with the terminal conditions

$$\begin{aligned}y_1(T) &= 1 + k_1\frac{q_*(T)}{(p_*(T))^2} > 0\,,\\ y_2(T) &= -k_1\frac{1}{p_*(T)} < 0\,,\end{aligned} \tag{3.3}$$

and the optimal control $u_*(t)$ together with the corresponding trajectories $(p_*(t), q_*(t))$ and $(y_1(t), y_2(t))$ minimizes the Hamiltonian H given by

$$H(y_1,y_2,p,q,u) = -\varepsilon y_1 p\ln\frac{p}{q} - y_2\Big(\mu q - \frac{l}{a+u}S(p,q) + dI(p,q)\Big) + k_2 u\,.$$

Moreover, as the Hamiltonian does not depend explicitly on t, its value is constant on the optimal trajectory

$$H(y_1,y_2,p_*,q_*,u_*) \equiv \text{const}\,.$$

Through the minimization property on the Hamiltonian H the function

$$\Phi = \frac{\partial H}{\partial u} = H_u = k_2 - \frac{l}{(a+u)^2}y_2 S(p,q)\,, \tag{3.4}$$

determines the structure of the optimal control $u_*(t)$. Since the stimulation term $S(p,q)$ is positive for positive p and q, we have that if the co-state variable y_2 is negative or equal to zero, then $\Phi > 0$. Hence, from minimization property we have that $u_* = 0$ for $y_2 \le 0$. For positive values of y_2 there always exits $\bar{u} = \sqrt{\frac{l}{k_2}y_2 S(p,q)} - a$ such that $\Phi = 0$. If $\bar{u} \in [0, \tilde{A}]$, then $u_* = \bar{u}$, since $H_{uu} > 0$ for any value of u. Similarly, if $\bar{u} < 0$ ($\bar{u} > \tilde{A}$), then $u_* = 0$ ($u_* = \tilde{A}$). Thus, the values of the control are determined by the co-state y_2 and (p,q) as follows:

$$u_*(t) = \begin{cases} 0 & \text{for } y_2 \le 0\,,\\ \min\{\max\{\sqrt{\dfrac{l}{k_2}y_2 S(p,q)} - a\,,\ 0\}\,,\ \tilde{A}\} & \text{for } y_2 > 0\,.\end{cases} \tag{3.5}$$

As it can be seen, there are singular parts of the control, but the intermediate values of the optimal u can be calculated explicitly. Moreover, it is clear that the switch from the full-dose to no-dose protocol (or in the opposite direction) can occur only through singular interval and not in a bang-bang manner. In addition, since the terminal condition for y_2 is negative, y_2 remains negative in some neighborhood of T. Formula (3.5) implies that this neighborhood is the drug free interval, and hence we may state the following lemma.

Lemma 3.2. *Optimal control for Eqs.* (2.4) *ends with the drug free interval* $(\tau, T]$.

In general, because of the constrains on the control value, we can have multiple intervals in which $u_* = 0$ or $u_* = \tilde{A}$ for $y_2 > 0$. However, in the next subsection we provide theorems limiting the number of points in which the change of the sign of y_2 occurs. Let us denote the intervals in which $y_2 > 0$ by "y" and in which $y_2 \le 0$ (drug free intervals) by "0".

3.0.1. Case of functions considered by Ergun et al.

For the stimulatory and inhibitory functions considered by Ergun et al. the adjoint equation for the co-state variable y_1 reduces to the following

$$\dot{y_1} = \varepsilon y_1 \left(\ln \frac{p_*}{q_*} + 1 \right) .$$

Hence, if y_1 vanishes at some $\bar{t}$, then $y_1 \equiv 0$ for all $t > \bar{t}$ as a consequence of the uniqueness of solutions of Eqs. (3.2). Therefore, it cannot change the sign and the terminal condition (3.3) implies that y_1 is strictly positive for all t. As the time derivative of the co-state variable $y_2(t)$ at point $y_2(t) = 0$ is equal to

$$\dot{y_2}(t)\Big|_{y_2(t)=0} = -\varepsilon y_1 \frac{p_*}{q_*} ,$$

and only the switch of the y_2 sign can occur. Thus, we may formulate the following theorem.

Theorem 3.3. *For Eqs.* (2.4) *with* $S(p,q) = q^{2/3}$ *and* $I(p,q) = q^{4/3}$ *there is at most one switch of the* y_2 *sign during the whole treatment interval, i.e. the optimal control is at most* $y\,0$.

3.0.2. Case of functions considered by Hahnfeldt et al.

Assume that $l - \mu a > 0$. This means that for the therapy free model considered by Hahnfeldt *et al.* [10], that is when $u \equiv 0$ in Eqs. (2.4), there exists a single globally asymptotically stable positive steady state $(\bar{p}, \bar{q})$, cf. [1,6]. Thus, we consider a successfully growing tumor, which cannot be eliminated without the treatment. Phase portrait analysis (see Fig. 2) allows to prove the following lemma.

Lemma 3.4. *In the absence of therapy* ($u = 0$), *the set* $\mathcal{D} = \{(p,q) \in \mathbb{R}^+ : p < \bar{p}\,, q < \bar{q}\}$, *where* $(\bar{p}, \bar{q})$ *is the positive steady state, is positively invariant for Eqs.* (2.4) *with* $S(p,q) = p$, $I(p,q) = qp^{2/3}$ *and* $l > \mu a$.

The number of points in which the change in the y_2 sign can occur is limited by the following theorem.

Theorem 3.5. *For Eqs.* (2.4) *with* $S(p,q) = p$, $I(p,q) = qp^{2/3}$, $(p(0), q(0)) \in \mathcal{D}$ *and* $l > \mu a$ *there are at most two switches of the* y_2 *sign during the whole treatment interval, that is the optimal control is at most* $0\,y\,0$.

Proof. Assume that there are three or more switches of the y_2 sign in the whole treatment interval. The derivative of the co-state variable y_2 at the switch point is expressed as

$$\dot{y_2}(t)\Big|_{y_2(t)=0} = -\varepsilon y_1 \frac{p_*}{q_*} .$$

Hence, if $y_1 > 0$, then the y_2 switches from positive to negative values. If $y_1 < 0$, then the switch occurs in the opposite direction. In order to get more than one switch of the optimal control, y_1 needs to change the sign from negative to positive in the interval in which $y_2 > 0$, compare Fig. 1. At the switching

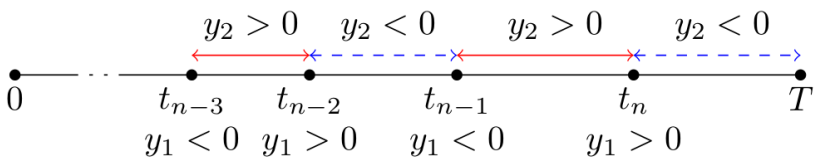

FIGURE 1. Structure of the optimal control. Moments t_i denote the y_2 switching points. Blue dashed lines denote no-dose intervals.

points, that is when $y_2 = 0$, we have

$$H(y_1, 0, p_*, q_*, u_*) = -\varepsilon y_1 p_* \ln \frac{p_*}{q_*},$$

and as the Hamiltonian is constant, we obtain that if at any switching point $y_1 < 0$ and $p_* > q_*$ ($p_* < q_*$), then $p_* < q_*$ ($p_* > q_*$) if $y_1 > 0$ at any other switching point.

Let us focus now on the switch from the singular to no-dose protocol that occurs before the last one of that type (t_{n-2} in Fig. 1). In order to have that switch, y_1 should change its sign from positive to negative during the treatment free interval, that is in the interval in which $y_2 < 0$ (the interval (t_{n-2}, t_{n-1}) in Fig. 1). Hence, at some point inside this interval the following inequality should be satisfied

$$\dot{y_1}\Big|_{y_1=0} = -y_2 \left(\frac{l}{a} - d\frac{2}{3}\frac{q_*}{p_*^{1/3}} \right) < 0\,.$$

This inequality is equivalent to

$$q_* > \frac{3l}{2ad} p_*^{1/3}. \tag{3.6}$$

In the treatment free model (Eqs. (2.4) with $u(t) \equiv 0$), the null-cline for the variable q is described by the following equation

$$q = \frac{\frac{l}{a}p}{\mu + dp^{2/3}},$$

and if Inequality (3.6) is satisfied at some (p_*, q_*), then it is easy to see that (p_*, q_*) lies above the null-cline for the variable q, that is (p_*, q_*) is placed in the area C in Fig. 2, while we consider only the set $\mathcal{D}$. On the other hand, from the structure of the optimal control we have that during the same therapy free

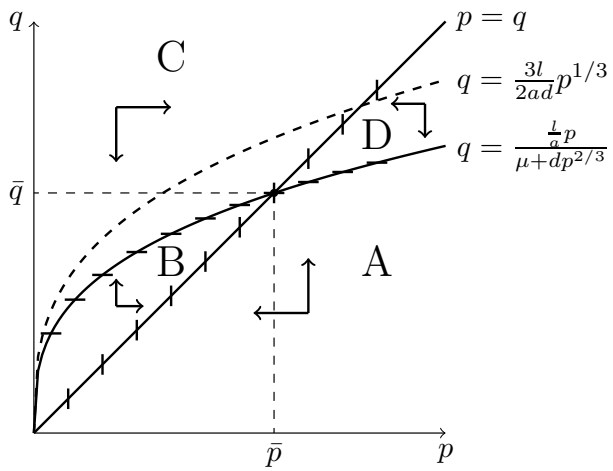

FIGURE 2. Sketch of the phase portrait.

interval the ratio of the tumor volume to the carrying capacity p_*/q_* should start below (above) 1 and end above (below) 1. Looking at the phase portrait in Fig. 2 we see that if the solution starts below the null-cline $q = p$, that is from the area A, then it either remains in the same area or moves from A to B and remains in B. In that case Inequality (3.6) cannot be fulfilled and there cannot be a second switch of the optimal control from the full-dose to no-dose protocol. If the solution starts above the null-cline $q = p$, that is initially $q_* > p_*$, then it remains above that null-cline and it is impossible to have $q_* < p_*$ at the end of the interval. This completes the proof. □

For the stimulatory and inhibitory functions considered by d'Onofrio and Gandolfi [6], that is for $S(p,q) = q$ and $I(p,q) = qp^{2/3}$, we were unable to formulate any theorem limiting the number of y_2 sign switches.

4. Numerical results

There are various methods that allow to approximate numerically the optimal control for given parameters and initial conditions [17, 30]. For the purpose of this paper we implemented numerical scheme based on two well known methods: gradient (steepest descent) method and shooting method. The former one uses the information about the derivative of the Hamiltonian with respect to the control and can be summarized in the following steps:

1. Pick a control $\tilde{u}$ and solve the model equations (2.4) for $(\tilde{p}(t), \tilde{q}(t))$.
2. Integrate adjoint equations (3.2) backwards using terminal conditions (3.3) with $(\tilde{p}(T), \tilde{q}(T))$. Calculate simultaneously $\frac{\partial H}{\partial u}$.
3. Pick k such that the control $\bar{u} = \tilde{u} - k\frac{\partial H}{\partial u}$ gives a smaller value of the payoff functional. Proceed to 1 with $\tilde{u} = \bar{u}$.

The above procedure ends when the change in the payoff functional reaches prescribed tolerance. What is important, the gradient method gives rapid initial convergence. However, much faster final convergence is obtained with the shooting method, which is also less computationally intensive [17] and can be summarized in the following steps:

1. Pick an initial condition for the adjoint equations (3.2) and solve them together with the model equations (2.4) with the control u calculated using information about the $\frac{\partial H}{\partial u}$.
2. Calculate the error between the obtained terminal conditions and the ones that should be fulfilled (3.3).
3. Adjust the initial condition in order to decrease the absolute value of the calculated error (use for example the Newton-Raphson method) and proceed to 1.

We decided to use the combination of those two methods. Namely, we utilize the gradient method with relatively large prescribed tolerance to generate initial condition for the shooting method. All procedures are written in MATLAB® computing language and we share their source code on our personal websites and the sourceforge.net repository. What is important, we already implemented angiogenesis models (see Tab. 1) in both modified and original forms. Moreover, necessary modifications of the code in case of other stimulation and inhibition functions are simple and straightforward. Hence, the code gives a good basis for other numerical investigations of optimal antiangiogenic treatment protocols.

4.1. Numerical approximation of the optimal controls

Values of the parameters associated with the optimal control settings were taken arbitrary and the only criterion was that all of the terms in the payoff functional should be significant. For the therapy duration T equal to 30 days and the initial condition $(p(0), q(0)) = (3000\,mm^3, 4000\,mm^3)$ we set $k_1 = 10^3$ and $k_2 = 5$ or $k_2 = 100$ depending on the simulation. For the maximal admissible dose we set $\tilde{A} = 20\,mg/kg$ since it was the maximal dose used in one of the bevacizumab related experiments [19]. In the numerical simulations we consider the stimulation and inhibition functions considered by Hahnfeldt *et al.* and Ergun *et al.* as both of them were fitted to bevacizumab data in [19, 22] and we take the estimated parameters values as presented in Tab.2.

First, we numerically investigate the optimal control problem for the Ergun *et al.* form of the modified model (2.4). We take the smaller value of k_2, that is we consider the case in which the influence of the total amount of used drug on the overall performance is smaller, compare Eq. (3.1). Numerical solution to that optimization problem is presented in the Fig. 3. It can bee seen that, as stated in Lemma 3, the optimal control ends with a short drug-free interval. Moreover, for the rest of the treatment interval it

Parameter	Description	Unit	**Ergun** *et al.*	**Hahnfeldt** *et al.*
ε	*tumor growth rate*	day^{-1}	0.2032	0.074
μ	*rate of spontaneous loss of functional vasculature*	day^{-1}	0	0.002
l	*l/a is the rate of vessels growth stimulation*	$\text{day}^{-1}\text{conc}$	10.39	2.8109
a		conc	4.598	2.1008
d	*rate of endogenous inhibition of previously generated vasculature*	$\text{day}^{-1}\text{vol}^{-2/3}$	0.0028	0.002

TABLE 2. Model parameters used in all numerical simulations. Values for Hahnfeldt *et al.* and Ergun *et al.* models are taken from [19] and [22], respectively.

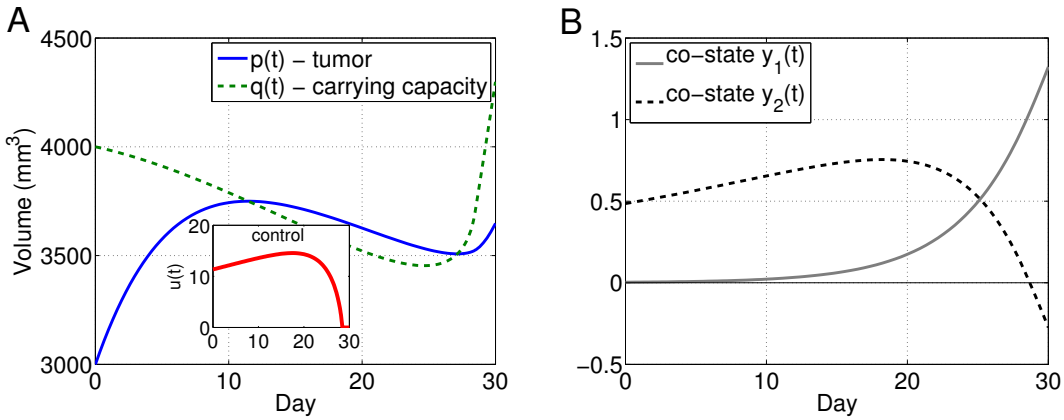

FIGURE 3. Optimal treatment strategy for the Ergun *et al.* model. (A) Solution to the model (2.4) with the optimal control u presented in the inset. (B) Corresponding dynamics of the co-state (adjoint) variables (3.2).

is singular, that is u takes the intermediate dose values. This result completely agrees with the analysis carried out in the previous section. Interestingly, singular control never reaches the maximal admissible dose ($\tilde{A} = 20\,mg/kg$) and one can see that the shape of the optimal control is similar to the dynamics of the y_2 co-state variable, compare panel A and B in Fig. 3. The later behavior of the control is related to the relatively small changes in the tumor volume during the treatment course, and hence the changes in y_2 have larger impact on the formula used to calculate u, compare Eq. (3.5).

Similar shape of the optimal control can bee also seen for the Hahnfeldt *et al.* model, compare Fig. 4(A). However, for the same value of the parameter k_2 there is an additional interval in which the full-dose protocol is realized, showing that the additional non-singular intervals are possible. Another non-singular no-dose interval appears in the case of $k_2 = 100$, that is when there is higher penalty for using antiangiogenic drugs, see Fig. 4(B). Interestingly, the additional no-dose interval occurring before the singular one is realized with $y_2 > 0$ and on its left there is a tiny interval with the singular control appearing again (not visible in the plot inset).

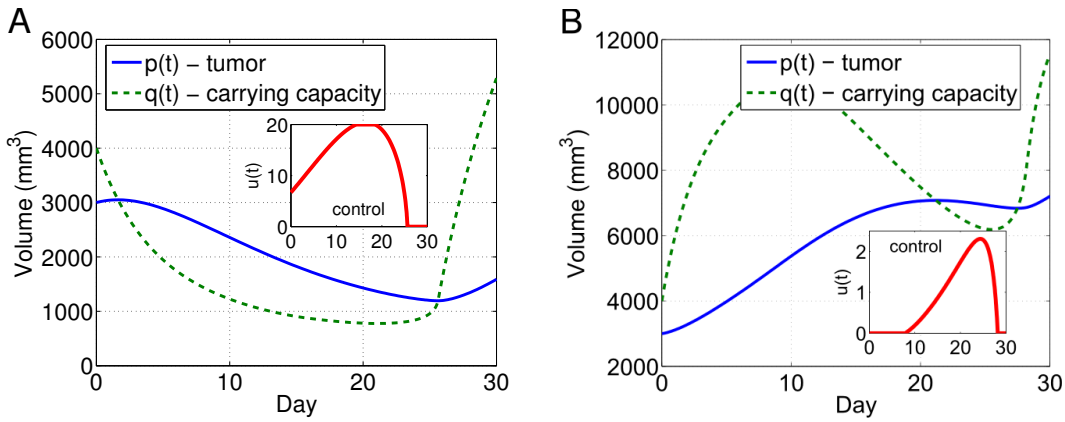

FIGURE 4. Optimal treatment strategy for the Hahnfeldt *et al.* model with $k_2 = 5$ (A) and $k_2 = 100$ (B). Presented are the solutions to the model (2.4) together with the corresponding optimal controls u presented in the insets.

5. Conclusions

Investigating the influence of new cancer therapies on tumor development is of the great importance. Their effects, both when used as supportive and stand alone therapies, need to be verified. In the paper we addressed the problem of designing optimal protocols for the antiangiogenic treatment using therapeutic agents directly blocking angiogenesis inducing proteins, such as VEGF. We based our analysis on the well established family of mathematical models originating from the Hahnfeldt *et al.* model of tumor angiogenesis [10]. We considered those models with the modification proposed in [20] which, to our knowledge, has never been analyzed from the optimal control point of view. Moreover, we introduced additional part to the standard payoff functional that describes the level of final vascularization, what, to our knowledge, is also a novelty. Proposed modification of the payoff functional tackles the "vessels normalization" hypothesis, which states that efficient treatment with chemotherapy is possible only when the cytotoxic agent can be distributed evenly, that is when vessels penetrate most of the tumor regions and they have proper structure and functionality. Namely, if the chemotherapy is administered after the antiangiogenc treatment, then it seems biologically reasonable to have as much vascularized tumor as possible before chemotherapy.

We showed that the optimal strategy consists of the drug-free, full-dose and singular (with intermediate values of the control variable) intervals. What is important, we showed that even for the fixed treatment duration T the singular controls are the common feature of the whole considered family of models. Singular controls in cancer treatment were previously obtained only for particular angiogenesis models [14, 15] and for some chemotherapy models [28]. From the structure of the optimal controls it follows that no bang-bang switch of the control is possible, i.e. there is no change from the no-dose to full-dose protocol (or in opposite direction) on the interval with the singular control. For Hahnfeldt *et al.* and Ergun *et al.* models, we provided additional theorems about the optimal control structure.

Finally, we investigated the optimal controls numerically using the customized software written in MATLAB ®, which we made freely available for download from our personal websites and sourceforge.net. Utilized numerical scheme is based on the composition of the well known gradient (steepest descent) and shooting methods. Numerical simulations showed clearly that the structure of the optimal controls are far from being simple and they can have multiple switches from the no-dose to singular to full-dose regimes.

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