Multi-Input Optimal Control Problems for Combined Tumor Anti-Angiogenic and Radiotherapy Treatments[1]

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Abstract. A cell-population based model for tumor growth under anti-angiogenic treatment with the tumor volume and its variable carrying capacity as variables is combined with the linear-quadratic model for damage done by radiation ionization. The resulting multi-input system is analyzed as an optimal control problem with the objective of minimizing the tumor volume subject to isoperimetric constraints that limit the overall amounts of anti-angiogenic agents, respectively the damage done to healthy tissue by radiotherapy. For various model formulations, explicit expressions for singular controls are derived for both the dosage of the anti-angiogenic therapeutic agent and the radiation dose schedule. Their role in the structure of optimal protocols is discussed.

Keywords. optimal control, totally singular controls, combination therapy, anti-angiogenic treatments, radiotherapy

AMS Subject Classification: 49K15, 92C50

1 Introduction

Tumor anti-angiogenic treatment is an indirect cancer therapy that aims at limiting a tumor's ability to grow by inhibiting the development of the vasculature that supplies it with nutrients and oxygen [21, 29]. There exist various treatment targets ranging from the signaling mechanisms of the tumor that stimulate angiogenesis to the endothelial cells that form the lining of the newly developing blood vessels and capillaries. These are healthy, genetically stable cell lines and so far no clonal resistance to angiogenic inhibitors has been observed in experimental cancer [1]. For this reason, there has been great hope in anti-angiogenic treatments as a cancer therapy [28]. However, with an increasing awareness of negative side effects, and also since the treatment only limits the tumor's support mechanism without actually killing the cancer cells, it soon became clear that it only achieves a temporary "therapeutic effect" that goes away with time as the tumor grows back once treatment is halted. While anti-angiogenic monotherapy by itself therefore is not considered a viable treatment option, it is still believed that in combination with treatment approaches that kill cancer cells, such as chemotherapy or radiotherapy, anti-angiogenic therapy can enhance the efficacy of these traditional approaches by normalizing the tumor's vasculature. For example, Jain and Munn argue that the normalization of a tumor's irregular and dysfunctional vasculature [10], which is achieved by prior anti-angiogenic treatment, enhances the delivery of chemotherapeutic agents and thus improves the effectiveness of chemotherapy [25, 26]. Combinations of classical treatment approaches with anti-angiogenic therapy have the advantage that they "simultaneously target two compartments, the cancer cells and the vascular cells that support the tumor" (Dr. Qian, John Hopkins Kimmel Cancer Center [43]).

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In combinations of anti-angiogenic therapy with chemo- or radiotherapy, the question how these treatments should be scheduled arises naturally and this leads to optimal control problems. Optimal control has a long history of applications to cancer treatments, but they are mostly concerned with traditional chemotherapy (for earlier work, see [16, 45, 46]; for, more recent work, see [7, 20, 31, 32, 34]). The model considered here combines a population based mathematical model for tumor angiogenesis whose principal variables are the tumor volume and its variable carrying capacity with the linear-quadratic model for radiation damage. In the dynamics for the tumor-vascular interactions we use both a previously biologically validated model by Hahnfeldt, Panigrahy, Folkman and Hlatky [23] and a modification of this model by Ergun, Camphausen and Wein [17] that was formulated and analyzed numerically in the context of combination with radiotherapy. In the paper here we consider both of these approaches that differ slightly in their modelling assumptions. Other models, like, for example, those considered in [44] that interpolate between these two systems, are equally feasible and for more general types of models for tumor-vascular interactions we refer the reader to [12, 13]. In the model for the radiation damage we follow [17].

Hahnfeldt's model has been the basis for several papers by ourselves [35, 15] and A. Swierniak [47, 48] in which both monotherapy and combinations with chemotherapy are analyzed as optimal control problems. While A. Swierniak considers the problem of scheduling therapies over a prescribed, fixed therapy horizon, in our research, and following the approach taken by Ergun et al. in [17], we have considered the problem of how to schedule a priori given amounts of therapeutic agents in order to achieve optimal effects. In the papers [35, 33, 30], we have given a complete mathematical solution in form of an optimal synthesis of controlled trajectories for both of these models for an objective function that minimizes the cancer volume. Intuitively, such a synthesis provides a complete 'road map' of how optimal protocols look like depending on the initial condition in the problem, both qualitatively and quantitatively. Based on these solutions, we then have considered extensions of the monotherapy model to the case when also the actions of a cytotoxic agent were taken into account in [15, 36]. It turned out that the optimal solutions for the single-input monotherapy model became the basis on which the optimal protocols for the multi-control combination therapy models could be constructed. We shall see that this is also true when combinations with radiotherapy are considered.

One of the main conclusions of our earlier research was that there exists a in a certain way 'optimal path' for the damage done to the vasculature (and this by no means is to destroy it completely) characterized by a so-called singular control for the administration of the anti-angiogenic agent in the monotherapy problem. For the model by Ergun et al. [17] this optimal path is preserved in identical functional form if the monotherapy model is augmented to include killing effects of a cytotoxic agent [36]. In this paper here, we shall see that this remains true for combination therapy with radiotherapy as well. This is quite remarkable since the damage for radiotherapy, the standard LQ-model [2, 27, 49], leads to quite a different mathematical formulation. For the model by Hahnfeldt et al. [23], in this paper simple modifications of the optimal monotherapy path will be computed if radiotherapy is added. The fact that such an optimal relation between tumor volume and carrying capacity of the vasculature is observed in so many versions of these mathematical models gives credibility to the belief that there exists some ideal relation between these two variables when the best tumor reductions can be achieved. Thus the question arises if these optimal paths can be characterized and computed, at least in a mathematical model. In the optimal control formulation these paths are given by so-called *singular arcs* and the dosages that keep them invariant are the so-called *singular controls*. Lie derivative based computations provide a powerful

means to perform these nonlinear calculations and to arrive at explicit formulas for singular controls and arcs. In this paper, we derive these relations for combinations of anti-angiogenic treatments with radiotherapy for both the underlying model from [23] and [17]. However, depending on how detailed an approach is taken to model the radiation damage (e.g., to what extent its effects on tumor cells, the vasculature and healthy cells are distinguished) systems of varying dimensions arise. The structure of singular controls depends on existing degrees of freedom and is closely related to the dimension of the state space. In this paper, we develop these relations and discuss the structure of optimal controls for the various scenarios.

The paper is organized as follows. In section 2 we formulate a general mathematical model that combines anti-angiogenic and radiotherapy treatments and phrase the problem of minimizing the tumor volume with a priori given amounts of anti-angiogenic agents and limited total radiation dose as an optimal control problem. The main necessary conditions for optimality will then be considered in section 3. Sections 4 and 5, respectively, address the structure of singular controls for two specific realizations of the general model, a 5-dimensional version with the dynamics for tumor-vascular interactions given by the one proposed by Ergun et al. [17] and a 6-dimensional model that differentiates radiation damage to the healthy tissue and is based on the model by Hahnfeldt et al. [23].

2 Combined Anti-angiogenic and Radiotherapy Treatment as Multi-Input Optimal Control Problem

The underlying mathematical model for the dynamics is a 2-compartment cell-population based model with the primary tumor volume, p, and the carrying capacity of the tumor vasculature, q, as variables. Tumor growth is modelled in the form

$$\dot{p} = pF\left(\frac{p}{q}\right) \tag{1}$$

where, in principle, F denotes an arbitrary growth function. With ξ denoting a tumor growth parameter, standard examples that are commonly used in cancer studies include (i) exponential growth where F is simply constant, $F(x) = \xi$, (ii) classical or generalized logistic growth of the form $F(x) = \xi\,(1 - x^{\alpha})$ with $\alpha > 0$ and $\alpha = 1$ the classical case, or (iii) a Gompertzian growth model of the form $F(x) = -\xi \ln x$. Depending on the stage of the tumor's development, one or the other of these models may be more adequate. Clearly, there is a stage when the simple exponential growth model is an excellent description, but it does not take into account saturation phenomena like logistic and Gompertzian growth models do. On the other hand, with its singularity at $x = 0$, a Gompertzian growth model is not an adequate description for small tumor volumes [8], but there exist several classical studies in the medical literature that support this model for large tumor volumes and more progressed stages (e.g., see [39, 40]) and this function is widely used for modelling cancer growth. These are the cases of interest here and for sake of definiteness we use a Gompertzian growth model in this paper, but logistic models are equally feasible.

2.1 Dynamics of tumor-vascular interactions

However, one main difference to classical models is that the carrying capacity q is not constant, but it is taken as a variable in the system with the dynamics for the change in the carrying capacity broadly understood as a balance equation between stimulatory and inhibitory effects in the form

$$\dot{q} = S(p, q) - I(p, q). \tag{2}$$

This modeling approach is based on the paper by Hahnfeldt et al. [23], a group of researchers then at the Harvard School of Medicine that included J. Folkman, who, back in the 1970s, first suggested anti-angiogenic treatments as a therapy possibility [21]. In their paper, based on an asymptotic analysis of an underlying consumption-diffusion equation, Hahnfeldt et al. proposed to choose the stimulation and inhibition terms as $S(p,q) = bp$ and $I(p,q) = dp^{\frac{2}{3}}q$ with b (birth) and d (death), respectively, endogeneous stimulation and inhibition parameters. Thus the stimulation is proportional to the tumor volume and inhibition is regulated through the interplay of the tumor surface (through which inhibitors are being released) with the surrounding vasculature. An alternative derivation of this model is given by Poleszczuk et al. in [41]. The model was biologically validated and parameters were estimated using medical data for Lewis lung carcinoma implanted in mice. This is a fast growing type of cancer and as a result, for the parameters specified in [23], the dynamics has a strong differential-algebraic character and the q-dynamics reaches its steady-state extremely fast. To mitigate this property, in 2003, Ergun, Camphausen and Wein, a group of researchers from NCI and Stanford, proposed a different approach in [17]. Working precisely on incorporating radiotherapy treatment into the model, they proposed to take the inhibition and stimulation terms as $I(q) = dq^{\frac{4}{3}}$ and $S(q) = bq^{\frac{2}{3}}$. In this modification the inhibition term is taken proportional to the tumor radius, not its surface area, and then, assuming the system is in steady state, the variables p and q are identified. Overall, this results in a better balance in the substitution of stimulation and inhibition and slows down the q-dynamics. Another advantage of the model is that it results in a significant mathematical simplification of the q-dynamics since the tumor volume p is eliminated from this equation. Naturally, this also has been a source of criticism for this model. While the model from [23] is closer to first principles, when analyzed as monotherapy optimal control problems, both models lead to qualitatively the same conclusions [35, 30]. A third model that obeys the principles laid out in [23] was considered by d'Onofrio and Gandolfi in [11] where the bahavior of these systems under constant infusion therapies was analyzed. But here we limit our analysis to the two models formulated above. For more detailed discussions of the modelling assumptions we refer the reader to [44, 41].

2.2 Modeling anti-angiogenic treatment

Anti-angiogenic treatment is an indirect therapy approach that does not kill cancer cells, but disables their growth by targeting the vasculature of the tumor. Anti-angiogenic drugs, like, for example, endostatin inhibit the *vascular endothelial growth factor*, VEGF, disrupting the growth of endothelial cells which form the lining of the newly developed blood vessels. The action of anti-angiogenic treatments can be modelled by introducing a control variable, u, that represents the dosage of the anti-angiogenic agent. Mathematically, the control is taken as a Lebesgue-measurable function that represents the dose rate of the anti-angiogenic agent and takes values in a compact interval $[0, u_{\max}]$ with $u_{\max}$ denoting the full dose. Anti-angiogenic agents diminish the carrying capacity, for example, by disrupting the movement and growth of endothelial cells. Under the typical *log-kill hypotheses* it is assumed that therapeutic agents kill a certain proportion of the cells which implies that the number of cells eliminated by the treatment is proportional to both the dosage and to the size of the cell population. This gives rise to a term $-\gamma qu$ with γ representing the effectiveness of the treatment. Thus the dynamics for the carrying capacity of the vasculature under anti-angiogenic treatment will have the form

$$\dot{q} = S(p,q) - I(p,q) - \gamma qu. \tag{3}$$

Together with the dynamics for p in (1), this gives a general model for a monotherapy anti-angiogenic treatment. Models of this type, which, for example, are analyzed from a dynamical systems point of view in the work of d'Onofrio et al. [9, 14], then become the basis on which models for combination therapy are constructed. As it was mentioned in the introduction, the inhibitor-based treatment does not kill cancer cells and only provides more of a temporary "therapeutic effect" since the tumor will grow back once the treatment is halted. Thus it needs to be combined with traditional treatments focused on killing cancer cells like chemo- or radiotherapy. Combinations with chemotherapy were considered in previous research by us and other researchers [15, 47], but much less attention has been given to modeling of anti-angiogenic treatment with radiotherapy.

2.3 Modeling radiotherapy

While the log-kill hypothesis used to model the action of anti-angiogenic inhibitors also applies to the action of a chemotherapeutic agent, it is only a crude approximation for the effects of radiotherapy. Here the so-called linear-quadratic(LQ) model [22, 49] has become the accepted norm. It expresses the probability of cell death in the form $\exp\left(\alpha D + \beta D^2\right)$ where D denotes the total radiation dose and α and β are radiosensitive parameters that, respectively, are related to the probabilities of double-strand breaks in the DNA and their repair. In this molecular theory of radiation action [2], it is assumed that the damage to DNA made by the effects of ionization radiation consists of a linear and a quadratic component. The linear part corresponds to simultaneous breaks in both DNA strands caused by a single particle which are considered lethal in the sense that the cell is no longer able to proliferate. While a single strand breakage is not considered lethal since DNA has the ability to repair it, if there exists another adjacent break of the second strand before the first one can be repaired, that also will lead to cell death in this sense and these breakages are modelled by the quadratic term. There exist several derivations for the linear-quadratic model based on varying underlying principles, (e.g., see [27]), but all arrive at the same principal structure. In these derivations, it is assumed that the number of single or double strand breaks follows a Poisson distribution and, although recently there has been some valid criticism for large radiation doses [24], this still is the commonly used model for cell survival in radiotherapy.

Here we follow the approach by Ergun et al. who in [17] model the combination of radiotherapy with anti-angiogenic treatment as an optimization problem with the particular version of the linear-quadratic model employed there based on the paper by Wein et al. [50]. Denoting the radiation dose rate by w, the second control in the system, Ergun, Camphausen and Wein model the damage of radiation to the tumor in the form

$$-p(t)\left(\alpha + \beta \int_0^t w(s)\exp(-\rho(t-s))ds\right) w(t) \tag{4}$$

where α, β and ρ are positive constants. The linear component $-\alpha p w$ is equivalent to a log-kill term and represents the damage done by double-strand breaks with α the corresponding probability. The coefficient β in the quadratic component is related to the probability that two single-strand breakages occur and the coefficient ρ in the exponential denotes the tumor repair rate. The probability that two such breaks occurring at times s and t will be lethal decays exponentially with the repair rates. The parameters α and β are related to the so-called tumor LQ parameters in the medical literature. For modeling details, we refer the reader to the papers by Wein et al. [50, 17] on which these equations are based. Note that the integral term in parenthesis in (4) is simply the solution to the first order linear differential equation

$$\dot{r} = -\rho r + w, \qquad r(0) = 0, \tag{5}$$

and thus the radiation damage can also be written in the form

$$-p(t)\left(\alpha+\beta r(t)\right)w(t). \tag{6}$$

For a constant dose rate $\bar{w}$ we have in the steady state that $\bar{r}=\frac{\bar{w}}{\rho}$ and thus the damage term becomes the standard linear-quadratic expression $-p\left(\alpha\bar{w}+\frac{\beta}{\rho}\bar{w}^2\right)$. Equation (4) better models the transient behavior and the structure of the overall model becomes clearer if we replace the integral with the differential equation (5).

A small tumor repair rate implies a larger influence of the integral term in the quadratic component and thus a greater effectiveness of the therapy, whereas for large repair rates the integral may be replaced with its steady-state value. In the model, we distinguish three different type of tissues, cancer cells, endothelial cells that determine the carrying capacity of the vasculature, and healthy cells which endure the side effects of treatments. The parameters that describe the damage of radiotherapy are tissue specific and thus, incorporating a linear-quadratic model into the dynamical system that describes the tumor-vascular interactions, we arrive at the following general five-dimensional system:

$$\begin{aligned}
\dot{p} &= pF\left(\frac{p}{q}\right)-\left(\alpha+\beta r_p\right)pw, && p(0)=p_0\\
\dot{q} &= S(p,q)-I(p,q)-\gamma qu-\left(\eta+\delta r_q\right)qw && q(0)=q_0\\
\dot{r}_i &= -\rho_i r_i+w, && i=p,q,z,
\end{aligned}$$

with the parameters α and η accounting for the linear damage caused by radiation to the tumor and the vasculature, respectively, and β and δ the parameters associated with the quadratic part of the damage. The three equations for r_p, r_q and r_z represent the effects of tissue repair with the coefficients ρ_p, ρ_q and ρ_z denoting the *repair rates* for the tumor, the vasculature and the healthy cells, accordingly.

2.4 Formulation as an optimal control problem

An optimal control problem now arises since the amounts of anti-angiogenic agents and the cumulative radiation dose are limited. Angiogenic inhibitors are biological agents that need to be grown in a lab and thus are very expensive. Furthermore, recently some of these agents have shown severe side effects. For example, in the US FDA approval for Bevacizumab for advanced breast cancer has been revoked and there are indications of increased side effects in combination with chemotherapy as well. For all these reasons, the amount of anti-angiogenic agents that will be administered is limited. Chemotherapeutic agents or radiotherapy, on the other hand, are widely available at reasonable cost, but both treatments have serious side-effects. Thus, and possibly for different reasons, it is important to limit both the amount of the anti-angiogenic agents and the damage to the healthy cells caused by the radiation ionization. Mathematically, this gives rise to two isoperimetric constraints of the form

$$\int_0^T u(t)dt\le y_{\max} \qquad \text{and} \qquad \int_0^T (1+\theta r_z(t))w(t)dt\le z_{\max}. \tag{7}$$

The first integral simply measures the total amount of all angiogenic agents administered and in the second integral the toxicity of the radiation treatment is characterized in terms of its biologically equivalent dose (BED). In [17], in addition a constraint on the early-responding tissue [50] is considered that is related to the behavior of these tissues between fractionated dosages to take into account repopulation. In this paper, we consider a continuous-time formulation and it is our aim to show that such a model leads to

effective and simple procedures to arrive at formulas for singular treatment schedules. In such a simplified model we do not distinguish between early- and late responding tissue and thus for the time being the early-responding tissue constraint is omitted. We shall discuss the issue of fractionated dosages in the conclusion.

In medical practice the limits $y_{\max}$ and $z_{\max}$ typically are decided upon at the beginning of one specific therapy period, possibly to be increased later on. The question thus becomes how given amounts of therapeutic agents and total radiation dose can best be administered to have an "optimal" effect. If we choose as objective to minimize the tumor volume, this gives an optimal control problem of Meyer type with the objective $p(T)$ and with free terminal time T. We incorporate the constraints (7) into the problem by adding extra states y and z that keep track of the total amounts of anti-angiogenic agents given, respectively, the total damage done by radiotherapy. We then arrive at the following formulation:

[AR-gen] for a free terminal time T, minimize the objective $J(u,w) = p(T)$ subject to the dynamics

$$\dot{p} = pF\left(\frac{p}{q}\right) - (\alpha + \beta r_p)\, pw, \qquad p(0) = p_0, \tag{8}$$

$$\dot{q} = S(p,q) - I(p,q) - \gamma q u - (\eta + \delta r_q)\, qw, \qquad q(0) = q_0, \tag{9}$$

$$\dot{r}_i = -\rho_i r_i + w, \qquad i = p, q \text{ or } z \qquad r(0) = 0, \tag{10}$$

$$\dot{y} = u, \qquad y(0) = 0, \tag{11}$$

$$\dot{z} = (1 + \theta r_z)w, \qquad z(0) = 0, \tag{12}$$

over all Lebesgue measurable functions $u : [0,T] \to [0, u_{\max}]$ and $w : [0,T] \to [0, w_{\max}]$ for which the corresponding trajectory satisfies the end-point constraints $y(T) \leq y_{\max}$ and $z(T) \leq z_{\max}$.

We only remark that under any assumptions on the general functions F, S and I that define a reasonable model for the tumor-vascular interactions, and for any admissible controls u and w, the solutions p and q to the dynamics will remain positive for all times and there is no need to impose a non-negativity constraint on p and q.

3 Necessary Conditions for Optimality

The dynamics (8)-(12) underlying the optimal control problem can be written in the form

$$\dot{x} = f(x) + ug_1(x) + wg_2(x) \tag{13}$$

where $x = (p, q, r_p, r_q, r_z, y, z)^T$ a 7-dimensional state vector and the vector fields f, g_1 and g_2 describe the dynamics. We call f the *drift* and the vector fields g_1 and g_2 are the *control vector fields*. Thus, in its full generality, [AR-gen] is a seven-dimensional system with two controls u and w.

First-order necessary conditions for optimality are given by the *Pontryagin Maximum Principle* ([42], for a recent textbook on the subject, see [6]): if u_* and v_* are optimal controls defined over an interval $[0,T]$, then there exist a constant $\lambda_0 \geq 0$ and an absolutely continuous co-vector, $\lambda : [0,T] \to (\mathbb{R}^7)^*$, (which we write as row-vector) such that (i) $(\lambda_0, \lambda(t)) \neq (0,0)$ for all $t \in [0,T]$, (ii) λ satisfies the adjoint equations

$$\dot{\lambda}(t) = -\left\langle \lambda(t), Df(x(t)) + u_*(t)Dg_1(x(t)) + w_*(t)Dg_2(x(t)) \right\rangle, \tag{14}$$

with terminal condition

$$\lambda(T) = (\lambda_0, 0, 0, 0, 0, \lambda_6, \lambda_7)^T,$$

transversality conditions

$$\lambda_6 = \begin{cases} 0 & \text{if } y(T) < y_{\max} \\ \geq 0 & \text{if } y(T) = y_{\max} \end{cases} \qquad \text{and} \qquad \lambda_7 = \begin{cases} 0 & \text{if } z(T) < z_{\max} \\ \geq 0 & \text{if } z(T) = z_{\max} \end{cases}$$

and (iii) the controls $u_*(t)$ and $v_*(t)$ minimize the Hamiltonian H,

$$H = \left\langle \lambda, f(x) + ug_1(x) + wg_2(x) \right\rangle,$$

along $(\lambda(t), x(t))$ over the control set $[0, y_{\max}] \times [0, z_{\max}]$ with the minimum value given by 0.

Note that the multipliers λ_6 and λ_7 are constant since the right hand side of the dynamics does not depend on the variables y and z. The inequality conditions $\lambda_6 \geq 0$ and $\lambda_7 \geq 0$ are complementary

slackness conditions that are generated by the terminal point restrictions on these variables. We also note that the multiplier $\lambda = \lambda(t)$ is always non-zero. For, λ is a solution to a homogenous linear differential equation and if $\lambda(\tau) = 0$ for some time τ, then λ vanishes identically and thus also $\lambda_0 = 0$. This contradicts the non-triviality condition (i) for the multipliers.

Since the control sets are compact intervals and the Hamiltonian H is linear in the controls, typically the minimizing controls are given by the boundary values of the control sets. Defining the so-called *switching functions* Φ_1 and Φ_2 as,

$$\Phi_1(t) = \langle \lambda(t), g_1(x(t)) \rangle \qquad \text{and} \qquad \Phi_2(t) = \langle \lambda(t), g_2(x(t)) \rangle \,, \tag{15}$$

it follows that optimal controls u_* and w_* satisfy

$$u_*(t) = \begin{cases} 0 & \text{if } \Phi_1(t) > 0 \\ u_{\max} & \text{if } \Phi_1(t) < 0 \end{cases} \qquad \text{and} \qquad w_*(t) = \begin{cases} 0 & \text{if } \Phi_2(t) > 0 \\ w_{\max} & \text{if } \Phi_2(t) < 0 \end{cases} . \tag{16}$$

A priori the controls are not determined by the minimum condition on H at times when the switching functions vanish. Clearly, if $\Phi_i(\tau) = 0$, but its time-derivative, $\dot{\Phi}_i(\tau)$, does not vanish, then the control switches between the endpoints of the corresponding control interval at time τ. In the other extreme, if $\Phi_i(t) \equiv 0$ on an open interval I, then also all derivatives of $\Phi_i(t)$ vanish on I and this may determine the controls. Controls of this kind are called *singular* while we refer to the constant controls at maximum or zero value as *bang* controls. These two classes are the canonical candidates for optimal controls and there exists a wealth of literature, both classical and modern, analyzing their optimality status (e.g., [3, 4, 18, 19, 37, 38]). Optimal controls then need to be synthesized from these candidates through an analysis of the switching function.

In the monotherapy problem, singular controls for the anti-angiogenic agents are essential to the solution of the corresponding optimal control problem [35]. For a combination therapy model that included chemotherapy these relations are preserved and administration of the cytotoxic agent is in one full dose session at the end of treatment [15]. For the model that includes radiotherapy, the radiation dose rate will be singular as well and so-called totally singular controls when both controls u and w are singular emerge. The following proposition is elementary, but fundamental for the computation of the derivatives of the switching functions that determine the singular controls.

Proposition 3.1 *Let h be a continuously differentiable vector field and define*

$$\Psi(t) = \langle \lambda(t), h(x(t)) \rangle \,.$$

Then the derivative of Ψ along a solution x to the system equation (13) for the controls u and v and a solution λ of the corresponding adjoint equations (14) of the maximum principle is given by

$$\dot{\Psi}(t) = \langle \lambda(t), [f + ug_1 + wg_2, h](x(t)) \rangle \,, \tag{17}$$

where $[k, h]$ denotes the Lie bracket of the vector fields k and h. □

Recall that the Lie bracket can be computed in local coordinates as

$$[k, h](x) = Dh(x)k(x) - Dk(x)h(x)$$

with Dk and Dh denoting the Jacobian matrices of the partial derivatives of k and h, respectively.

Proof. The proposition is verified by a simple explicit computation. Dropping the argument t we have that:

$$\begin{aligned}\dot{\Psi} &= \left\langle \dot{\lambda}, h(x) \right\rangle + \langle \lambda, Dh(x)\dot{x} \rangle \\ &= -\lambda \left(Df(x) + uDg_1(x) + wDg_2(x) \right) h(x) + \lambda(t) Dh(x(t)) \left(f(x) + ug_1(x) + wg_2(x) \right) \\ &= \langle \lambda(t), [f + ug_1 + wg_2, h](x) \rangle \,. \end{aligned}$$ □

A further analysis of the problem requires the computation of iterated Lie brackets whose forms depend on the choice of the growth function F and the choices for the stimulation and inhibition terms, $S(p,q)$ and $I(p,q)$. In this paper, we consider both the underlying dynamics from Ergun et al. [17] and the one from Hahnfeldt et al. [23]. Furthermore, in order to elucidate the roles of singular controls, we first consider a model where we identify the repair rates for the various types of tissue resulting in a simplified five-dimensional system and then increase the dimension as we differentiate these rates for healthy and tumor cells.

4 A 5-dimensional Model with Equal Repair Rates

We use a Gompertzian function, $F(x) = -\xi \ln x$, to model tumor growth and employ the terms $S(p,q) = bq^{\frac{2}{3}}$ and $I(p,q) = dq^{\frac{4}{3}}$ proposed in [17] for the stimulation and inhibition term in the dynamics for the carrying capacity. Also, in this first model, rather than distinguishing between the repair rates ρ_p, ρ_q and ρ_z for the tumor, vasculature and healthy cells, we take them all equal and thus instead of having three equations for r_p, r_q and r_z that enter the quadratic effects we only have one equation, $\dot{r} = -\rho r + w$, reducing the dimension by 2. Thus we consider the following optimal control problem with five-dimensional state space $x = (p, q, r, y, z)^T$ and two controls u and w:

[AR5] for a free terminal time T, minimize the objective $J(u,w) = p(T)$ subject to the dynamics

$$\dot{p} = -\xi p \ln\left(\frac{p}{q}\right) - (\alpha + \beta r)\, pw, \qquad p(0) = p_0, \tag{18}$$

$$\dot{q} = bq^{\frac{2}{3}} - dq^{\frac{4}{3}} - \gamma q u - (\eta + \delta r)\, qw, \qquad q(0) = q_0, \tag{19}$$

$$\dot{r} = -\rho r + w, \qquad c(0) = 0, \tag{20}$$

$$\dot{y} = u, \qquad y(0) = 0, \tag{21}$$

$$\dot{z} = (1 + \theta r) w, \qquad z(0) = 0, \tag{22}$$

over all Lebesgue measurable functions $u : [0,T] \to [0, u_{\max}]$ and $w : [0,T] \to [0, w_{\max}]$ for which the corresponding trajectory satisfies the end-point constraints $y(T) \le y_{\max}$ and $z(T) \le z_{\max}$.

If we allow that the coefficients β, δ and θ are zero, this model reduces to the mathematical model for combination of anti-angiogenic therapy with chemotherapy considered in [36]. For this model, the drift vector field f and the control vector fields g_1 and g_2 are given by

$$f(x) = \begin{pmatrix} -\xi p \ln\left(\frac{p}{q}\right) \\ bq^{\frac{2}{3}} - dq^{\frac{4}{3}} \\ -\rho r \\ 0 \\ 0 \end{pmatrix}, \quad g_1(x) = \begin{pmatrix} 0 \\ -\gamma q \\ 0 \\ 1 \\ 0 \end{pmatrix} \quad \text{and} \quad g_2(x) = \begin{pmatrix} -(\alpha + \beta r)\, p \\ -(\eta + \delta r)\, q \\ 1 \\ 0 \\ 1 + \theta r \end{pmatrix}. \tag{23}$$

The vector fields g_1 and g_2 commute, $[g_1, g_2] = 0$, and somewhat longer, but direct and elementary calculations verify that

$$[f, g_1](x) = \gamma \begin{pmatrix} \xi p \\ -\frac{1}{3}\left(bq^{\frac{2}{3}} + dq^{\frac{4}{3}}\right) \\ 0 \\ 0 \\ 0 \end{pmatrix}, \tag{24}$$

$$[f, g_2](x) = \begin{pmatrix} (\eta + \delta r)\,\xi p - (\alpha + \beta r)\,\xi p + \beta\rho r p \\ -\frac{1}{3}(\eta + \delta r)\left(bq^{\frac{2}{3}} + dq^{\frac{4}{3}}\right) + \delta\rho r q \\ \rho \\ 0 \\ -\rho\theta r \end{pmatrix} = \frac{\eta + \delta r}{\gamma}[f, g_1](x) + \begin{pmatrix} -(\alpha + \beta r)\,\xi p + \beta\rho r p \\ \delta\rho r q \\ \rho \\ 0 \\ -\rho\theta r \end{pmatrix}, \tag{25}$$

$$[g_1, [f, g_1]](x) = -\frac{1}{9}\gamma^2 \begin{pmatrix} 0 \\ bq^{\frac{2}{3}} - dq^{\frac{4}{3}} \\ 0 \\ 0 \\ 0 \end{pmatrix}, \qquad [g_2, [f, g_1]](x) = -\frac{1}{9}\gamma(\eta + \delta r) \begin{pmatrix} 0 \\ bq^{\frac{2}{3}} - dq^{\frac{4}{3}} \\ 0 \\ 0 \\ 0 \end{pmatrix}. \tag{26}$$

and

$$[g_2, [f, g_2]](x) = \begin{pmatrix} (\delta - \beta)\,\xi p + 2\rho\beta p \\ -\frac{1}{9}(\eta + \delta r)^2\left(bq^{\frac{2}{3}} - dq^{\frac{4}{3}}\right) - \frac{\delta}{3}\left(bq^{\frac{2}{3}} + dq^{\frac{4}{3}}\right) + 2\rho\delta q \\ 0 \\ 0 \\ -2\rho\theta \end{pmatrix}. \tag{27}$$

The formulas for the second-order Lie brackets with f, especially $[f, [f, g_2]]$, become rather unwieldy and will not be listed. These brackets collectively determine explicit analytical formulas for singular controls u and v. If a control u or w is singular on an open interval $I = (\alpha, \beta)$, then the corresponding switching function $\Phi_i(t) = \langle \lambda(t), g_i(x(t)) \rangle$, $i = 1, 2$, and all its derivatives vanish identically on I. Since the control vector fields g_1 and g_2 commute, $[g_1, g_2](x) \equiv 0$, applying Proposition 3.1 to $\Phi_i(t)$ results in

$$\dot{\Phi}_i(t) = \langle \lambda(t), [f + ug_1 + wg_2, g_i](x(t)) \rangle = \langle \lambda(t), [f, g_i]\,(x(t)) \rangle \tag{28}$$

and thus, once more applying Proposition 3.1, the second derivatives are given by

$$\ddot{\Phi}_i(t) = \langle \lambda(t), [f + ug_1 + wg_2, [f, g_i]]\,(x(t)) \rangle \equiv 0.\ i = 1, 2 \tag{29}$$

4.1 Singular control u

Singular controls u can be computed quite simply explicitly and regardless of the structure of the control w, i.e., it does not matter whether w is singular or bang-bang. The reason lies in the following relation that is satisfied between second-order Lie brackets. Simple inspection of (26) shows that

$$[g_2, [f, g_1]](x) = \frac{\eta + \delta r}{\gamma}[g_1, [f, g_1]](x). \tag{30}$$

This relation is central to the argument since it allows to eliminate the Lie bracket $[g_2, [f, g_1]]$ from equation (29) for $\ddot{\Phi}_1$. In fact,

$$\ddot{\Phi}_1(t) = \langle \lambda(t), [f, [f, g_1]]\,(x(t))\rangle + \frac{1}{\gamma}\left(\gamma u + (\eta + \delta r)\, w\right) \langle \lambda(t), [g_1, [f, g_1]]\,(x(t))\rangle\,. \tag{31}$$

If we set

$$\tilde{u} = u + \frac{\eta + \delta r}{\gamma} w, \tag{32}$$

then equation (31) is identical with the formula that defines the singular control in the monotherapy case considered in [30] and thus all the results directly carry over if we replace u with $\tilde{u}$,

$$\ddot{\Phi}_1(t) = \langle \lambda(t), [f + \tilde{u} g_1, [f, g_1]]\,(x(t))\rangle \equiv 0$$

More specifically, in the monotherapy case the effect of the anti-angiogenic agent on the carrying capacity q is given by $-\gamma q u$. Replacing u with $\tilde{u}$, this term becomes

$$-\gamma q \tilde{u} = -\gamma q u - (\eta + \delta r)\, q w \tag{33}$$

and thus for the combination therapy model [AR5] the *combined effect* that an optimal singular control u and a radiation dose rate w have on $\dot{q}$ *is identical to the monotherapy case*. Furthermore,

$$\langle \lambda(t), [g_1, [f, g_1]]\,(x(t))\rangle = -\gamma^2 b p \lambda_2(t).$$

For this model the conditions of the maximum principle imply that the multipliers λ_4 and λ_5 are constant and non-negative. Since the switching function vanishes on I, we have that $\lambda_2(t)\gamma q(t) \equiv \lambda_4 \geq 0$ and thus $\lambda_2(t) \geq 0$. Hence the Legendre-Clebsch condition for optimality is satisfied. Note that it is satisfied with strict inequality, i.e., the strengthened Legendre-Clebsch condition is satisfied, if and only if λ_4 is positive so that the amount of anti-angiogenic inhibitors must be fully used up. If $\lambda_4 = 0$, further derivatives of the switching function need to be computed. But in this case it follows from the formulas for the switching function and its derivative that both λ_1 and λ_2 vanish identically on I and this can be used to eliminate this case so that $\lambda_4 > 0$ along an optimal singular arc. Earlier computations made in [33] and [30] therefore imply the following result:

Proposition 4.1 *Suppose the optimal control u_* is singular on an open interval I, $u_*(t) = u_{sin}(t)$, and the radiotherapy schedule is given on I by $w(t)$. Then the quantity $\gamma u_{sin}(t) + (\eta + \delta r(t))\, w(t)$ is a smooth feedback control that only depends on the carrying capacity $q(t)$ in the form*

$$\gamma u_{sin}(t) + (\eta + \delta r(t))\, w(t) = \Psi\left(\sqrt[3]{q(t)}\right) \tag{34}$$

where

$$\Psi(x) = \frac{b - dx^2}{x} + 3\xi \frac{b + dx^2}{b - dx^2} \tag{35}$$

Fig. 1 shows the graph of the function Ψ over the interval $(0, \sqrt{\frac{b}{d}})$, the relevant set for the model based on [17]. The same result is true for the model of anti-angiogenic treatment in combination with chemotherapy considered in [36] and thus there is a strong robustness in the system pertaining to the u-singular control which is the defining element of the synthesis of optimal controlled trajectories both for the monotherapy and the combination therapy models. Like for combinations with chemotherapy [15], also in this case there is an immediate and mathematically simple extension of the formula that determines the optimal singular anti-angiogenic dose rate to the more structured and more complicated mathematical model that describes the combination treatment with radiotherapy. However, now the structure of the second control is very different.

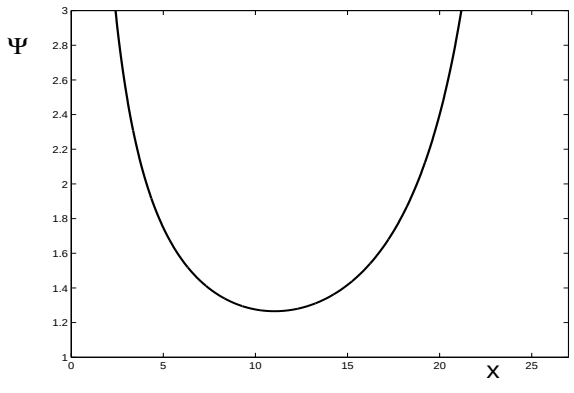

Figure 1: Graph of the function Ψ over the interval $(0, \sqrt{\frac{b}{d}})$ for $b = 5.85$, $d = 0.00873$ and $\xi = 0.192$.

4.2 Singular control w

Contrary to the case of combined anti-angiogenic treatment with chemotherapy, the radiation dose rate can, and if the bounds on the dosages permit, typically will be singular as well. The controls u and w are said to be *totally singular* on an open interval I if they are both singular simultaneously. This is not optimal for the model of anti-angiogenic inhibitors combined with chemotherapy [15], but it is the defining structure for the the combination of anti-angiogenic therapy with radiotherapy. For this we need a second equation that links u_{sin} with w_{sin}.

If w is singular on an open interval interval I, then also

$$\Phi_2(t) = \langle \lambda(t), g_2(x(t)) \rangle \equiv 0, \qquad \dot{\Phi}_2(t) = \langle \lambda(t), [f, g_2]\,(x(t) \rangle \equiv 0$$

and

$$\ddot{\Phi}_2(t) = \langle \lambda(t), [f + ug_1 + wg_2, [f, g_2]](x(t)) \rangle = 0. \tag{36}$$

Note that, since g_1 and g_2 commute, $[g_1, g_2] = 0$, it follows from the Jacobi-identity that $[g_1, [f, g_2]](x) = [g_2, [f, g_1]](x)$. In the set of interest, the vector fields g_1, g_2, $[f, g_1]$, $[f, g_2]$ and $[g_2, [f, g_2]]$ are linearly independent and form a basis for the state space. We write

$$[f, [f, g_2]] = a_1 g_1 + a_2 g_2 + a_3 [f, g_1] + a_4\,[f, g_2] + A\,[g_2, [f, g_2]] \tag{37}$$

$$[g_1, [f, g_2]] = b_1 g_1 + b_2 g_2 + b_3 [f, g_1] + b_4\,[f, g_2] + B\,[g_2, [f, g_2]] \tag{38}$$

where the coefficients a_i, b_i, A and B are functions of x. Note that with Cramer's rule it is possible, if desired, to give an explicit analytical description of all these functions in terms of determinants that only involve the vector fields in the dynamics and some of their iterated Lie brackets. Also, the fourth coordinate for the vector fields $[f, [f, g_2]]$ and $[g_1, [f, g_2]]$ is zero and this implies that the coefficients a_1 and b_1 vanish identically. If both controls are singular over an open interval I, then the multiplier $\lambda(t)$ vanishes against the vector fields g_1, g_2, $[f, g_1]$ and $[f, g_2]$ along the trajectory x. We therefore get that

$$\begin{aligned}
\langle \lambda(t), [f, [f, g_2]](x(t)) \rangle &= A(x(t)) \cdot \langle \lambda(t), [g_2, [f, g_2]](x(t)) \rangle \\
\langle \lambda(t), [g_1, [f, g_2]](x(t)) \rangle &= B(x(t)) \cdot \langle \lambda(t), [g_2, [f, g_2]](x(t)) \rangle\,.
\end{aligned}$$

Since the multiplier λ is non-trivial, it cannot vanish against $[g_2, [f, g_2]]$ along x and thus $\langle \lambda(t), [g_2, [f, g_2]](x(t)) \rangle \neq 0$. Equation (36) therefore reduces to the linear equation

$$0 = A(x(t)) + u_{\sin}(t)B(x(t)) + w_{\sin}(t).$$

Thus we have the following result:

Proposition 4.2 *If both the optimal anti-angiogenic dosage u and the radiation dose rate schedule w both follow singular regimens $u_{\sin}$ and $w_{\sin}$ on an open interval I, then in addition to equation (34), a second relation of the form*

$$A(x(t)) + B(x(t))u_{\sin}(t) + w_{\sin}(t) \equiv 0. \tag{39}$$

holds on I where A and B are the smooth functions defined in equations (37) and (38). □

Overall, $(u_{\sin}, w_{\sin})$ thus are the solutions of the 2×2 system of linear equations defined by (34) and (39) whose coefficients are determined solely by the equations defining the dynamics of the system. As already mentioned, it is possible to give explicit expressions for the functions A and B and thus also for the singular controls. These formulas depend on the second derivatives of the terms in the dynamics and they are long and unwieldy. On the other hand, for any particular value (p, q) of the state and specified values of the parameters, it is not difficult at all to compute these coefficients A and B numerically and solve for the controls. Fig. 2 shows two samples of singular controls u and w computed in this way for the parameter values given in Table 1. These values are based on the data in [23] and [17] and are only meant to illustrate the mathematical procedure.

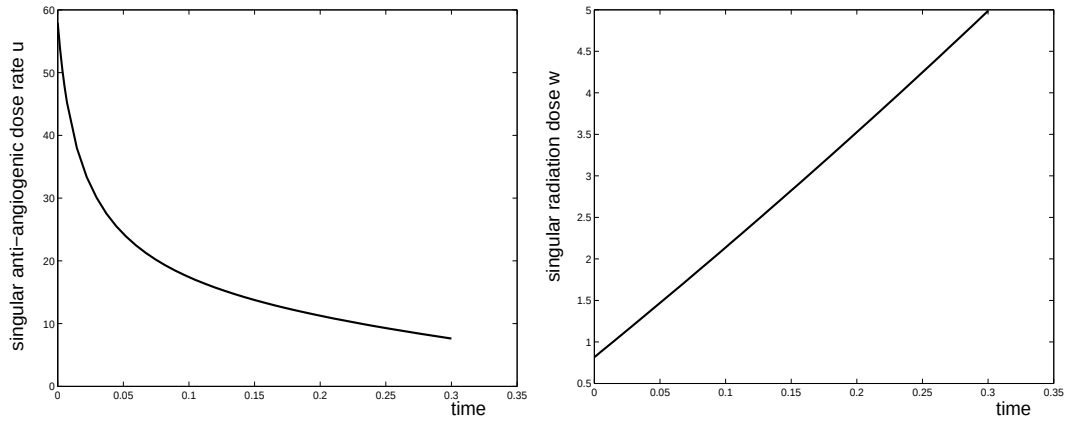

Figure 2: Examples for singular dose rates $u_{\sin}$ and $w_{\sin}$ for the values in Table 1

4.3 Singular Surface

If both controls u and w are singular over an interval I, then the multiplier λ vanishes vanishes against the vector fields g_1, g_2, $[f, g_1]$ and $[f, g_2]$ along the trajectory x. Furthermore,

$$H = \langle \lambda(t), f(x(t)) \rangle + u_{\sin}(t)\Phi_1(t) + w_{\sin}(t)\Phi_2(t) \equiv 0$$

and thus λ also vanishes against the vector field f. Since λ is non-trivial, these five vector fields must be linearly dependent along a singular arc. Hence totally singular controls are only optimal on a singular hyper-surface S defined by

Symbol		units	value used in computations	Reference
p	primary tumor volume	$[mm^3]$		
q	carrying capacity of the vasculature	$[mm^3]$		
r	variable related to quadratic radiation effects (repair)			
y	amount of anti-angiogenic agent used so far	$[mg]$		
z	cumulative radiation dose in BED	$[Gy]$		
x	state vector - $(p, q, r, y, z)^T$			
ξ	tumor growth parameter	$[\text{day}^{-1}]$	0.192	[23]
b	tumor-induced stimulation parameter	$[\text{day}^{-1}]$	5.85	[23]
d	tumor-induced inhibition parameter	$[\text{mm}^{-2}\ \text{day}^{-1}]$	0.00873	[23]
μ	baseline loss of vascular support through natural causes	$[\text{day}^{-1}]$	0 for [AR5] 0.02 for [AR6]	
u	anti-angiogenic agent dose rate	$\left[\frac{mg\,\text{of dose}}{kg}\right]\ \text{day}^{-1}$		
$u_{\max}$	maximum allowable dose for the anti-angiogenic agent	$\left[\frac{mg\,\text{of dose}}{kg}\right]\ \text{day}^{-1}$		
$y_{\max}$	available total amount for the anti-angiogenic agent	$\left[\frac{mg\,\text{of dose}}{kg}\right]$		
w	radiation dose	$[Gy]\ \text{day}^{-1}$		
$w_{\max}$	maximum allowable radiation dose	$[Gy]\ \text{day}^{-1}$		
$z_{\max}$	maximum allowable total BED	$[Gy]$		
γ	anti-angiogenic elimination parameter	$\left[\frac{kg}{mg\,\text{of dose}}\right]\ \text{day}^{-1}$	0.15	[23]
α	tumor LQ parameter	$\left[Gy^{-1}\right]$	0.7	[17]
β	tumor LQ parameter	$\left[Gy^{-2}\right]$	0.140	[17]
η	endothelial LQ parameter	$\left[Gy^{-1}\right]$	0.136	[17]
δ	endothelal LQ parameter	$\left[Gy^{-2}\right]$	0.086	[17]
θ	healthy tissue parameter	day^{-1}	0.5	[17]
ρ	tumor/endothelial repair rate	day^{-1}	$\frac{\ln(2)}{0.02}$	[17]
σ	healthy tissue repair rate	day^{-1}	$\frac{\ln(2)}{0.16}$	[17]

Table 1: Notations for the variables, controls and coefficients in the model

$$S = \{x : f(x) \wedge g_1(x) \wedge g_2(x) \wedge [f, g_1](x) \wedge [f, g_2](x) = 0\}, \tag{40}$$

where $\wedge$ denotes the wedge product, i.e., S is the set of all points x in the state-space where the determinant of the matrix whose columns are f, g_1, g_2, $[f, g_1]$ and $[f, g_2]$ vanishes. Note that the auxiliary variables y and z that only tell how much inhibitors are still available, respectively, how close to the maximum allowable total BED the radiation damage already is, do not enter into this computation and S becomes a surface in (p, q, r)-space. The values of the variables y and z only indicate whether it is still allowed to follow trajectories on this surface or not. A somewhat longer computation shows that this surface actually can be described as the graph of a function of q and r in the form

$$S: \qquad p = q\zeta(q, r)$$

with the defining relation given by

$$\ln\left(\frac{p}{q}\right) = 3\frac{b - dq^{\frac{2}{3}}}{b + dq^{\frac{4}{3}}} - \frac{\alpha r + \left[\beta\left(1 - \frac{\rho}{\xi}\right) + \theta\alpha\left(1 + \frac{\rho}{\xi}\right)\right] r^2 + \theta\beta r^3}{1 + 2\theta r} - 3\rho\left(\eta\theta - \delta\right)\frac{r^2}{1 + 2\theta r}\frac{q^{\frac{1}{3}}}{b + dq^{\frac{4}{3}}}.$$

Fig. 3 shows the surface S on the three-dimensional (p, q, r)-subspace. For $r = 0$ we obtain the curve representing the optimal singular arc in the case of monotherapy treatment [30]. We see that once the variable $r(t)$ that enters the quadratic terms for the radiation damage increases, both the tumor volume $p(t)$ and the vasculature $q(t)$ decrease. Fig. 4 shows a different view of the same surface with some of the responses corresponding to the totally singular flow shown on the surface and Figs. 5 and 6 show the values of the singular controls u_{sin} and w_{sin} on the singular surface as a function of the base variables q and r.

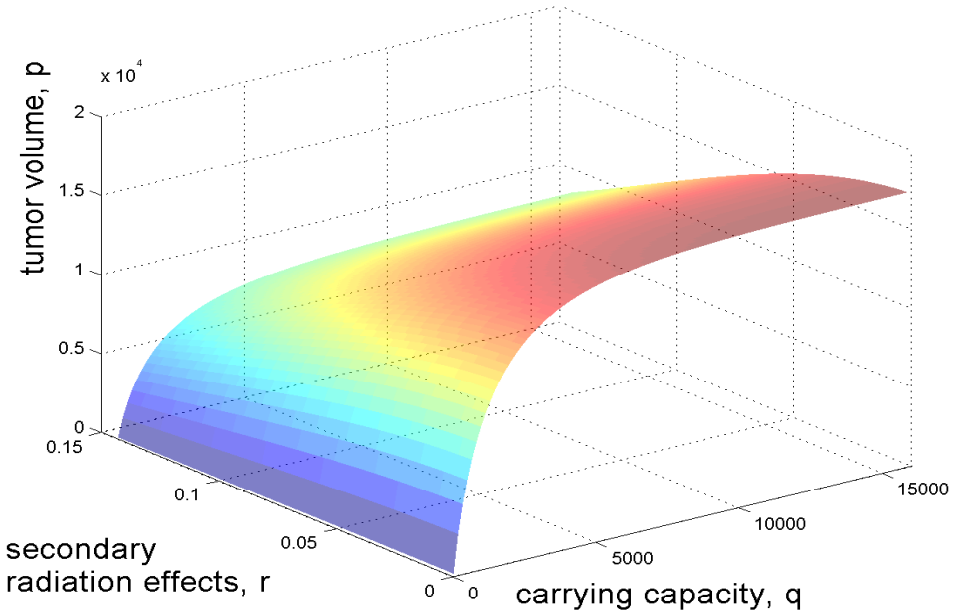

Figure 3: The totally singular surface $\mathcal{S}$ for model [AR5] and parameter values given in Table 1

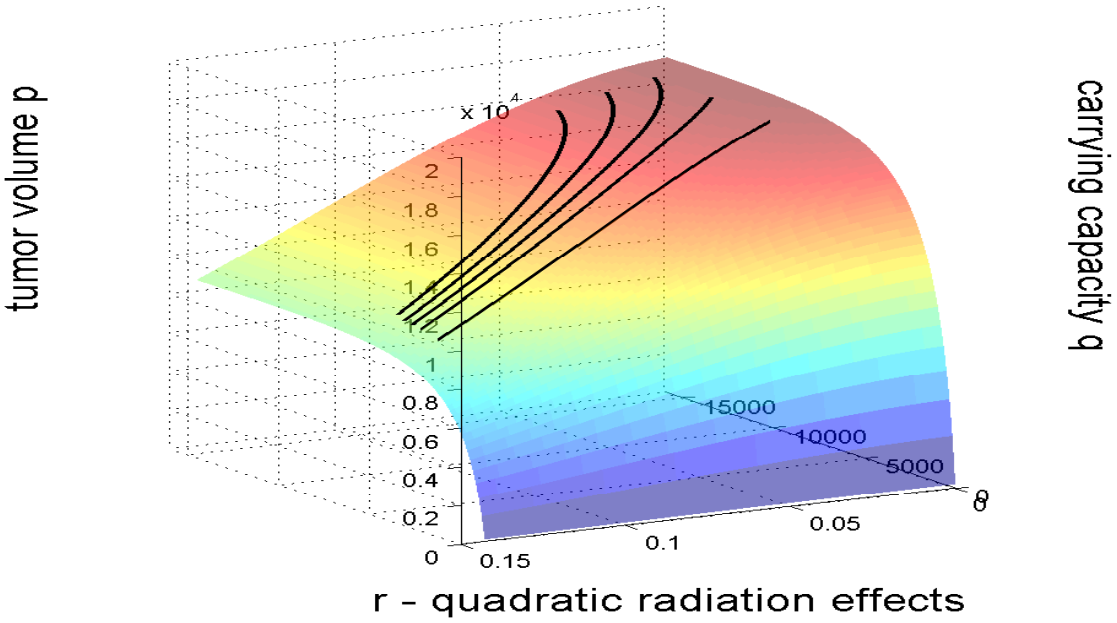

Figure 4: Samples of totally singular controlled trajectories on $\mathcal{S}$ for the parameter values in Table 1

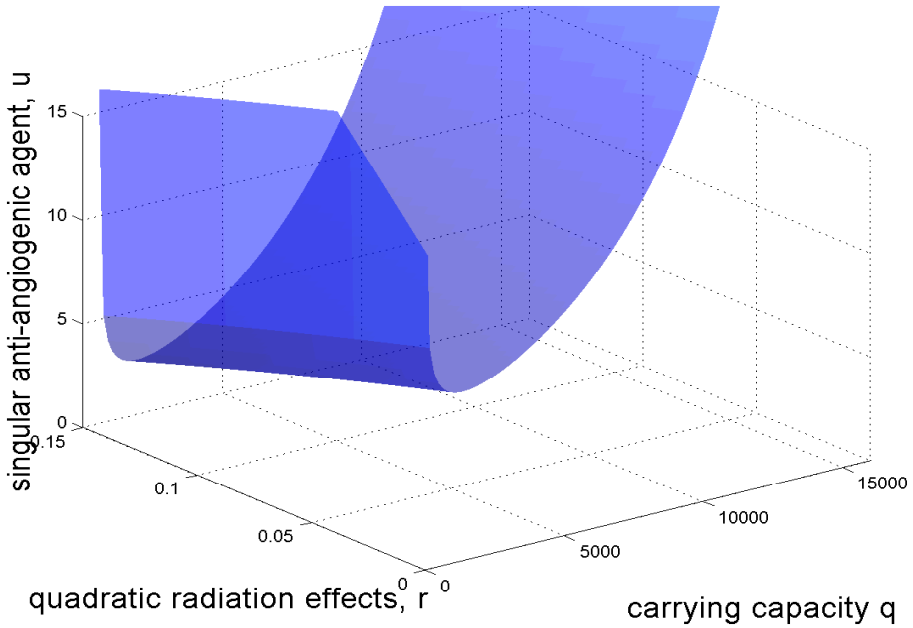

Figure 5: Values of the singular control u_{sin} on the singular surface $\mathcal{S}$ expressed as function of the base values q and r for the parameter values in Table 1

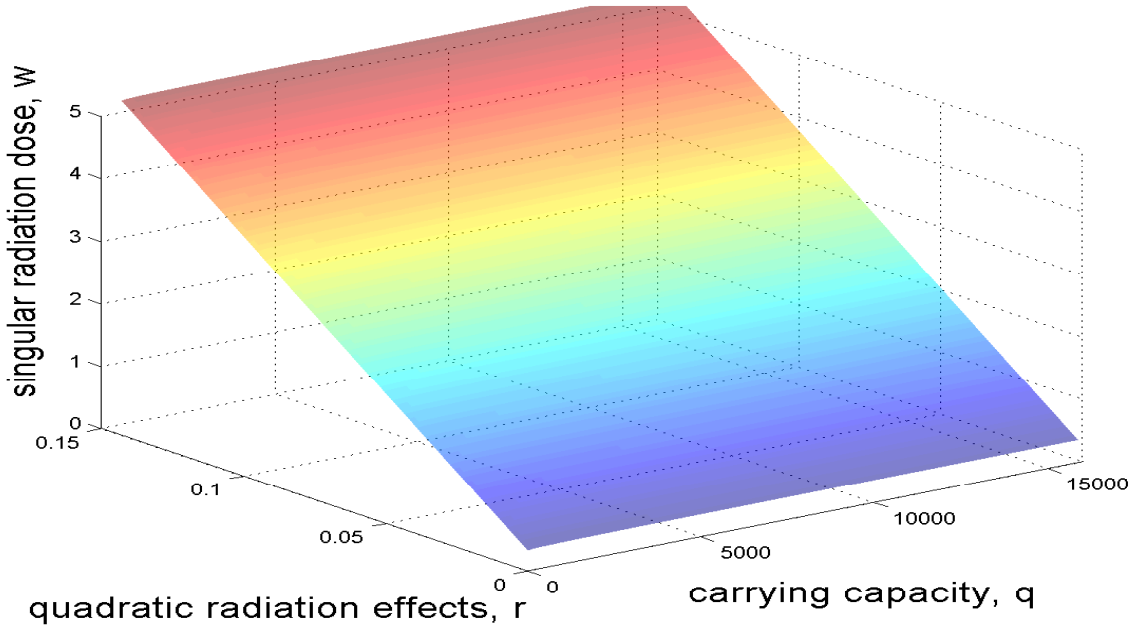

Figure 6: Values of the singular control w_{sin} on the singular surface $\mathcal{S}$ expressed as function of the base values q and r for the parameter values in Table 1

5 A 6-dimensional Model with a Different Repair Rate for the Healthy Tissue

Naturally, the repair rates for tumor cells, endothelial cells and healthy cells are not the same and, in principle, thus should be modelled by separate equations (20) with different parameters ρ_i. This leads to similar formulations, but in spaces of varying dimension. Mathematically, this generates different behaviors since the degrees of freedom that come with higher dimensional state-spaces no longer force singular flows to be constrained to lower dimensional submanifolds. In the literature, often the effects of radiation therapy on the tumor cells and its vasculature are modelled by one equation (for example, see [17] where equal numerical values are used for these repair rates that are based on [5]) and here we take this approach as well. As before, we then include separate states y and z that keep track of the total amounts of anti-angiogenic agents given, respectively the total damage done by radiotherapy measured in terms of its biologically equivalent dose (BED). In this section, we also change equation (20) for the carrying capacity from the model used in [17] to the model from [23]. We then arrive at the following 6-dimensional optimal control formulation:

[AR6] for a free terminal time T, minimize the objective $J(u,w) = p(T)$ subject to the dynamics

$$\dot{p} = -\xi p \ln\left(\frac{p}{q}\right) - (\alpha + \beta r)\, pw, \qquad p(0) = p_0, \tag{41}$$

$$\dot{q} = bp - \left(\mu + dp^{\frac{2}{3}}\right) q - \gamma q u - (\eta + \delta r)\, qw, \qquad q(0) = q_0, \tag{42}$$

$$\dot{r} = -\rho r + w, \qquad r(0) = 0, \tag{43}$$

$$\dot{y} = u, \qquad y(0) = 0, \tag{44}$$

$$\dot{z} = (1 + \theta s)w, \qquad z(0) = 0, \tag{45}$$

$$\dot{s} = -\sigma s + w, \qquad s(0) = 0, \tag{46}$$

over all Lebesgue measurable functions $u : [0,T] \to [0, u_{\max}]$ and $w : [0,T] \to [0, w_{\max}]$ for which the corresponding trajectory satisfies the end-point constraints $y(T) \leq y_{\max}$ and $z(T) \leq z_{\max}$.

The meaning of the parameters is the same as before (see Table 1). The only new parameter is a different repair rate σ for healthy tissue in (46). We also are interested to see what implications the changes in the q-dynamics have on the system. The state of the system is now given by $x = (p, q, r, y, z, s)^T$ and the drift vector field f and the control vector fields g_1 and g_2 are given by

$$f(x) = \begin{pmatrix} -\xi p \ln\left(\frac{p}{q}\right) \\ bp - (\mu + dp^{\frac{2}{3}})q \\ -\rho r \\ 0 \\ 0 \\ -\sigma s \end{pmatrix}, \quad g_1(x) = \begin{pmatrix} 0 \\ -\gamma q \\ 0 \\ 1 \\ 0 \\ 0 \end{pmatrix} \quad \text{and} \quad g_2(x) = \begin{pmatrix} -(\alpha + \beta r)\, p \\ -(\eta + \delta r)\, q \\ 1 \\ 0 \\ 1 + \theta s \\ 1 \end{pmatrix}.$$

The control vector fields g_1 and g_2 still commute and like for the five-dimensional model considered above, iterated Lie brackets that involve the vector field g_1 only have non-zero terms in the first two coordinates. If we introduce the notation $\frac{\partial}{\partial p}$ and $\frac{\partial}{\partial q}$ (common in differential geometry) for these first two coordinate fields, respectively, then we can express these vector fields more concisely in the form

$$[f, g_1](x) = \gamma p \left(\xi \frac{\partial}{\partial p} - b \frac{\partial}{\partial q}\right), \tag{47}$$

$$[g_1, [f, g_1]](x) = -\gamma^2 bp \frac{\partial}{\partial q}, \tag{48}$$

$$[g_2, [f, g_1]](x) = ((\alpha + \beta r) - (\eta + \delta r))\, \gamma bp \frac{\partial}{\partial q}. \tag{49}$$

The formulas for the Lie brackets with g_2 generally are full, only having a zero value in the fourth coordinate corresponding to the variable y. For example, we have that

$$[f,g_2](x) = \begin{pmatrix} [(\eta+\delta r)-(\alpha+\beta r)]\,\xi p+\beta\rho r p \\ -[(\eta+\delta r)-(\alpha+\beta r)]\,bp-\frac{2}{3}dp^{\frac{2}{3}}q\,(\alpha+\beta r)+\delta\rho r q \\ \rho \\ 0 \\ -\sigma\theta s \\ \sigma \end{pmatrix}$$

$$= \frac{(\eta+\delta r)-(\alpha+\beta r)}{\gamma}[f,g_1](x) + \begin{pmatrix} \beta\rho r p \\ -\frac{2}{3}dp^{\frac{2}{3}}q\,(\alpha+\beta r)+\delta\rho r q \\ \rho \\ 0 \\ -\sigma\theta s \\ \sigma \end{pmatrix}.$$

5.1 Singular control u

Similar to the five-dimensional model, we have the relation

$$[g_2,[f,g_1]](x) = \frac{(\eta+\delta r)-(\alpha+\beta r)}{\gamma}[g_1,[f,g_1]](x) \tag{50}$$

that allows to eliminate the Lie bracket $[g_2,[f,g_1]]$ from equation (29):

$$\begin{aligned}\ddot{\Phi}_1(t) &= \langle\lambda(t),[f+ug_1+wg_2,[f,g_1]]\,(x(t))\rangle \\ &= \langle\lambda(t),[f,[f,g_1]]\,(x(t))\rangle + \left(u+\frac{(\eta+\delta r)-(\alpha+\beta r)}{\gamma}w\right)\langle\lambda(t),[g_1,[f,g_1]]\,(x(t))\rangle\end{aligned}$$

Also, as for model [AR5], we have that

$$\langle\lambda(t),[g_1,[f,g_1]]\,(x(t))\rangle = -\gamma^2 bp\lambda_2(t)$$

and $\lambda_2(t)$ is non-negative along a singular arc since $\gamma q(t)\lambda_2(t)\equiv\lambda_4\geq 0$. Hence the Legendre-Clebsch condition for local optimality of a singular arc is satisfied. If we now set

$$\tilde{u} = u+\frac{(\eta+\delta r)-(\varphi+\beta r)}{\gamma}w, \tag{51}$$

then we once more have exactly the monotherapy case considered in [35] and as for problem [AR5] all the formulas directly carry over with u replaced by $\tilde{u}$.

Proposition 5.1 *If the optimal anti-angiogenic dosage u follows a singular control $u_{\sin}(t)$ on an open interval I and the radiotherapy schedule is given by w, then we have the following relation between the controls u and w:*

$$\gamma u_{\sin}(t)+[(\eta+\delta r)-(\alpha+\beta r)]\,w(t) = \Psi(p(t),q(t)) \tag{52}$$

with Ψ the function defining the singular feedback control for the optimal anti-angiogenic monotherapy given by

$$\Psi(p,q) = \xi\ln\left(\frac{p}{q}\right)+b\left(\frac{p}{q}\right)-(\mu+dp^{\frac{2}{3}})+\frac{2}{3}\frac{d}{b}\xi p^{-\frac{1}{3}}q. \tag{53}$$

□

Note that, whenever the anti-angiogenic control u follows a singular regimen, then the quotient $\frac{p}{q}$ follows the simple dynamics

$$\begin{aligned}\frac{d}{dt}\left(\frac{p}{q}\right) &= \frac{\dot{p}q - p\dot{q}}{q^2} = \\ &= -\xi\frac{p}{q}\ln\left(\frac{p}{q}\right) - (\alpha+\beta r)\frac{p}{q}w - \left[b\left(\frac{p}{q}\right)^2 - \left(\mu + dp^{\frac{2}{3}}\right)\frac{p}{q} - \gamma\frac{p}{q}u_{\sin} - (\eta+\delta r)\frac{p}{q}w\right] \\ &= \left(\frac{p}{q}\right)\left[-\Psi(p,q) + \gamma u_{\sin} + [(\eta+\delta r) - (\alpha+\beta r)]\,w + \frac{2}{3}\frac{d}{b}\xi p^{-\frac{1}{3}}q\right] \\ &= \frac{2}{3}\xi\frac{d}{b}p^{\frac{2}{3}}. \end{aligned} \tag{54}$$

For the parameter values used in [23] and [17] and for realistic values for p, this quotient is in fact very small and varies little. Thus the corresponding controlled trajectories follow an almost linear relation between p and q. Also note that for this model, replacing u with $\tilde{u}$, the combined effect of a singular anti-angiogenic and radiotherapy treatment is given by

$$-\gamma q u - (\eta+\delta r)\,qw = -\gamma q\tilde{u} - (\alpha+\beta r)qw$$

with the $-(\alpha+\beta r)w$ the same term that determines the damage to the tumor. One can view this in a way that anti-angiogenic treatment compensates for radiotherapy in a sense to make the effects of radiotherapy on tumor and vasculature equal.

5.2 Singular control w

We need a second equation to determine totally singular protocols ($u_{\sin}$,$w_{\sin}$). If w is singular as well, then

$$\Phi_2(t) = \langle\lambda(t), g_2(x(t))\rangle \equiv 0, \qquad \dot{\Phi}_2(t) = \langle\lambda(t), [f,g_2]\,(x(t))\rangle = 0$$

and

$$\ddot{\Phi}_2(t) = \langle\lambda(t), [f+ug_1+wg_2, [f,g_2]]\,(x(t))\rangle \equiv 0. \tag{55}$$

Since the dimension is increased by one, we need one more vector field to represent the second order Lie brackets and thus include f in our basis. Note that it follows from the maximum principle that

$$0 \equiv H = \langle\lambda(t), f(x) + ug_1(x) + wg_2(x)\rangle = \langle\lambda(t), f(x)\rangle$$

so that λ vanishes against the vector fields f, g_1, g_2, $[f,g_1]$ and $[f,g_2]$ along a totally singular trajectory x. If we now express the second-order brackets in the form

$$[f,[f,g_2]] = a_0 f + a_1 g_1 + a_2 g_2 + a_3\,[f,g_1] + a_4\,[f,g_2] + A\,[g_2,[f,g_2]], \tag{56}$$

$$[g_1,[f,g_2]] = b_0 f + b_1 g_1 + b_2 g_2 + b_3\,[f,g_1] + b_4\,[f,g_2] + B\,[g_2,[f,g_2]], \tag{57}$$

with coefficients that are smooth functions of x (assuming that the vector fields on the right are linearly independent), then, as above, we get that

$$\langle\lambda(t), [f,[f,g_2]](x(t))\rangle = A(x(t))\cdot\langle\lambda(t), [g_2,[f,g_2]](x(t))\rangle$$

and

$$\langle\lambda(t), [g_1,[f,g_2]](x(t))\rangle = B(x(t))\cdot\langle\lambda(t), [g_2,[f,g_1]](x(t))\rangle\,.$$

The non-triviality of the multiplier implies that $\langle \lambda(t), [g_2, [f, g_1]](x(t)) \rangle$ cannot vanish and thus, as before, we get from (55) that

$$A(x(t)) + B(x(t))u_{\sin}(t) + w_{\sin}(t) \equiv 0.$$

Of course, the coefficients A and B are not the same as in model [AR5], but formally we have the identical statement and conclusions.

Proposition 5.2 *If the optimal anti-angiogenic dosage u and the radiotherapy schedule w both follow singular regimens $u_{\sin}$ and $w_{\sin}$ on an open interval I, then in addition to equation (52) a second relation of the form*

$$A(x(t)) + B(x(t))u_{\sin}(t) + w_{\sin}(t) \equiv 0 \tag{58}$$

holds on I where A and B smooth functions defined by (56) and (57). □

As before, $(u_{\sin}, w_{\sin})$ thus are the solutions of a 2×2 system of linear equations whose coefficients are determined solely by the equations defining the dynamics of the system and it is possible to give explicit expressions for the functions A and B and thus also for the totally singular controls. As before, these formulas are long and unhandy, but numerically the controls are easily computed.

Different from the five-dimensional model [AR5], in this case the number of constraints defining totally singular controls matches the degrees of freedom in the model. Along a totally singular controlled trajectory the multiplier $\lambda(t)$ vanishes against the vector fields f, g_1, g_2, $[f, g_1]$ and $[f, g_2]$. Now these conditions uniquely determine the multiplier (up to a positive scalar multiple that does not matter in the necessary conditions for optimality) and thus there exists a well-defined totally singular flow for the system. Rather than only being able to use totally singular controls on a hypersurface, as it is the case for the five-dimensional version of this model, now at every point in the state space totally singular controls computed as solutions to (52) and (58) are available, provided they do not violate the control limits.

Fig. 7 gives an example of a totally singular anti-angiogenic dose rate u and a radiotherapy schedule w that have been computed in this way for parameter values taken from [17]. Part (a) shows the graph of the radiation schedule if no upper limit on the dosage is imposed. If we set the radiation limit to $w_{max} = 4$, then this upper bound is initially exceeded and part (b) shows the control that has been computed by saturating this schedule at w_{max}. Since equation (52) is valid regardless of the structure of w, the calculations easily adjust. The corresponding graph of the singular control u is given in part (c) and part (d) shows the corresponding trajectory. Note that in accordance with our earlier observation, since the anti-angiogenic dose rate is always singular, this trajectory is almost linear. For this simulation, the right-hand side of (54) only varies between 0.0306 and 0.0764, i.e., is almost constant.

The controls given in this figure were not computed to be optimal, but they only illustrate a totally singular control structure for the combined anti-angiogenic and radiotherapy model. Based on our theoretical analysis, it is clear that these controls will play an essential part in the structure of optimal protocols. This is seconded by the structure of optimal protocols computed in [17] where all the solutions are totally singular, but no hard limits on the dosage rates were imposed. In order to solve the overall optimal control problem, however, it is necessary to take these constraints into account and to establish the structure of optimal controls before and after the singular segments. Different from the monotherapy problem described earlier, in this case there exists a vector field whose integral curves are the trajectories for totally singular controls everywhere, but it matters which of these trajectories is taken. Research on determining an optimal synthesis is ongoing.

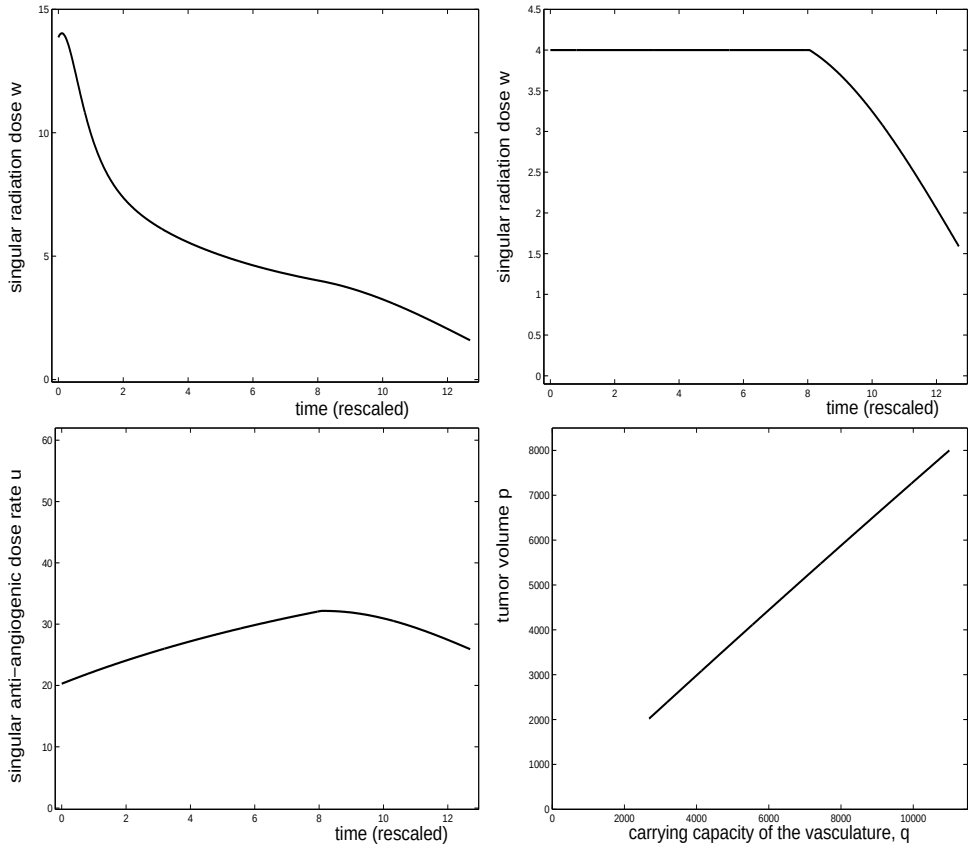

Figure 7: Examples of a totally singular controls for initial conditions $(p_0, q_0) = (8000, 11000)$ and values of the parameters in Table 1: (a, top left) the unsaturated singular radiation schedule w, (b, top right) the radiation schedule w with upper limit w_{max} enforced, (c, bottom left) corresponding singular anti-angiogenic agent u and (d, bottom right) corresponding trajectory (p, q) with p plotted vertically and q horizontally.

6 Conclusion and Discussion

In the paper, we formulated a model for the combination of anti-angiogenic treatment with radiotherapy and considered two particular realizations of it, a five-dimensional model when we identified the repair rates for the various tissues and used the model by Ergun et al. [17] to describe the tumor vascular interactions, and a six-dimensional model when we differentiated between the repair rates for the tumor and the healthy tissues and used the model by Hahnfeldt et al. [23]. In the past we have given complete solutions for each of these models for the monotherapy optimal control problem to minimize the tumor volume with a priori given amounts of anti-angiogenic agents [35, 30]. For both models, optimal singular controls are at the center of the solutions and we have seen earlier that the structure of these singular arcs prevails if combinations with chemotherapy are considered. In this paper, we have shown that this also holds for combinations with radiotherapy. There exist simple extensions of the earlier computations that determine totally singular controls for the anti-angiogenic agents and the radiotherapy dosage. One of the main points we want to make in the paper is that it is indeed possible to compute explicit formulas, if wanted, and that numerical computations to determine these controls are straightforward. Clearly, the

overall analysis of these problems is not finished, and we do not claim that our computations give the optimal controls. But based on our earlier analysis of the related problems, we have a strong expectation that they are closely connected with the optimal structures. A second aspect that needs to be clarified is the relation of the computed controls with fractionated dosages that give radiation only for a brief instant in time, the standard in medical practice. Clearly, the continuous-time model has mathematical advantages over a purely optimization based algorithm and one can also obtain some insights into the structure of optimal protocols from explicit formulas. Our hope is that it will be possible to come up with suboptimal fractionization schedules that are close to the solutions of the continuous-time models. However, a challenge in doing so is to properly relate the values of the parameters for these two vastly different models.

These are just some specific challenges for this particular problem. More general ones appear, regardless of the treatment type, when optimal control is applied to design optimal protocols for cancer treatments. First, there is always the issue to choose the "right"model. Large models that involve many variables are clearly biologically more precise (provided the parameters values or at least some ranges for them are known), but many analytic tools of optimal control, like for example the ones based on the geometric approach used in our paper, become very difficult, if not impossible to apply because of the system size. Thus, for these models often the only approach left is numerical analysis and simulations over a large range of parameters. This gives us information about the performance of various controls, but not much insights into the underlying mechanisms. Especially, given the uncertainty of any medical parameters, the question how reliable the numerical results are always remains. Another common challenge in modeling of an optimal control approach is the choice of the objective. One clearly should try to be biologically relevant, but in many approaches the objective is chosen so that it simplifies the analysis. Overall, although there are clearly many obstacles, difficulties and limitations, optimal control theory can help to shed some light on how protocols for cancer treatments should be administered. This research may thus lead to some guidelines that could become an additional aid in the organization of clinical trials for which exhaustive and expensive trial-and-error approaches currently are the norm.

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