On the Optimality of Singular Controls for a Class of Mathematical Models for Tumor Anti-Angiogenesis*

Urszula Ledzewicz†
Dept. of Mathematics and Statistics,
Southern Illinois University at Edwardsville,
Edwardsville, Illinois, 62026-1653,
uledzew@siue.edu

Heinz Schättler
Dept. of Electrical and Systems Engineering,
Washington University,
St. Louis, Missouri, 63130-4899,
hms@wustl.edu

Revision, June 2008

Abstract

Anti-angiogenesis is a novel cancer treatment targeting the vasculature of a growing tumor. In this paper a metasystem is formulated and analyzed that describes the dynamics of the primary tumor volume and its vascular support under anti-angiogenic treatment. The system is based on a biologically validated model by Hahnfeldt et al. and encompasses several versions of this model considered in the literature. The problem how to schedule an a priori given amount of angiogenic inhibitors in order to achieve the maximum tumor reduction possible is formulated as an optimal control problem with the dosage of inhibitors playing the role of the control. It is investigated how properties of the functions defining the growth of the tumor and the vasculature in the general system affect the qualitative structure of the solution of the problem. In particular, the presence and optimality of singular controls is determined for various special cases. If optimal, singular arcs are the central part of a regular synthesis of optimal trajectories providing a full solution to the problem. Two specific examples of a regular synthesis including optimal singular arcs are given.

*This material is based upon research supported by the National Science Foundation under collaborative research grants DMS 0707404 and 0707410.

†U. Ledzewicz's research is also partially supported by SIUE 2007 Summer Research Fellowship.

Keywords: optimal control, cancer treatment, anti-angiogenesis, maximum principle, regular synthesis, singular control, Lie-bracket

1 Introduction

Mathematical modeling of cancer treatments is a growing interdisciplinary field stimulated by active developments in medical research. The models describe the dynamics of the growth of cancer cells and their reaction to various types of therapies applied. In this direction historically the most attention has been given to chemotherapy. Starting in the seventies and eighties (e.g., [10, 30]) and still continuing today (e.g., [31, 12]) a number of models have been formulated that describe the dynamics of cancer cells, normal cells, or a combination of both. Since chemotherapy affects not only the cancer, but also the healthy cells, it is natural to formulate the question of how to apply chemotherapy in the most effective way according to some a priori chosen criterion. This leads to the formulation of these models as optimal control problems with the drug dosage of chemotherapy playing the role of the control. Numerous models have been analyzed with the goal of finding optimal controls representing the "best" protocols for chemotherapy. In our research we consider L_1-type objectives for which necessary conditions for optimality result in two types of controls, so-called bang-bang and singular controls. Medically the first ones represent sessions of full doses with rest periods in between while singular controls correspond to a treatment with feedback type time-varying partial doses, not easily realizable in practice. Employing the tools of geometric optimal control, for many models we eliminated singular controls as candidates for optimality (e.g., [18, 19]) and gave a theoretical proof for the optimality of bang-bang controls, the type of protocols currently used in the medicine.

However, in view of substantial negative aspects of chemotherapy including severe side effects and drug resistance, there is a strong incentive in medical research to look for novel treatment approaches. One of these is tumor anti-angiogenesis. A solid tumor at the size of about 2mm in diameter starts the process of *angiogenesis* during which it recruits blood vessel capillaries of the host needed for its own supply of nutrients. Anti-angiogenic treatments bring in external angiogenic inhibitors (e.g., endostatin) that target endothelial cells which form the lining of the newly developing blood vessels. This indirectly effects the tumor which, deprived of necessary nutrition, regresses. Since, contrary to traditional chemotherapy, this treatment targets normal, not cancer cells, no resistance has been reported in experimental studies and thus there is hope that this is a treatment approach that can avoid the "curse" of drug resistance. As a therapy "resistant to resistance" anti-angiogenesis thus became an active area of medical research providing a new hope for the treatment of tumor type cancers [16].

Following these advances in medical research, several mathematical models describing the dynamics of angiogenesis have been proposed, e.g., [2, 28, 1, 15, 11, 9], many of them, however, more suitable for large scale simulations than mathematical analysis. In [15] Hahnfeldt, Panigrahy, Folkman and Hlatky, a group of researchers then at Harvard Medical School, developed and biologically validated a two-dimensional model of ordinary differential equations for the interactions between the primary tumor volume, p, and the carrying capacity of the vasculature, q, or endothelial support for short. Based on this model and the underlying spatial analysis carried out in that research two modifications of the original model have also been formulated since then, one by d'Onofrio (at the European Institute of Oncology in Milan) and Gandolfi [9] (at the National Research Council in Rome, Italy,) the other by Ergun, Camphausen and Wein at the Cancer Research Institute at NIH [11]. In each formulation a Gompertzian model with variable carrying capacity q is chosen to model tumor growth, but the dynamics for the endothelial support differ in their inhibition and stimulation terms, $I(p,q)$ and $S(p,q)$. The dynamics of these models, as well as the important problem of how to schedule an a priori given amount of angiogenic inhibitors in such a way as to realize the maximum tumor reduction possible was analyzed in several papers [11, 9, 32]. In our work on this topic, [20, 21, 22, 23], we utilized tools of optimal control theory similar to those that had been applied by us to chemotherapy models to determine the optimal solutions for the original model by Hahnfeldt et al. and its two modifications. It turned out that, contrary to the chemotherapy models discussed earlier, the models from [11, 15] have optimal singular controls and these along with bang-bang controls played an important role in the synthesis of the solutions for the problem. Since this phenomenon appeared in two of the three related models, while singular controls did not even exist for the the third one [9, 32], this raised the natural question how changes in the models effect the qualitative structure of solutions. This question was even more intriguing because the two models that shared the same structure of optimal solutions were somewhat different in their formulations and assumptions while the third one that resulted in a different structure for its solutions was based on the same modelling premises as the model in [15]. What variations in the dynamics cause the singular arc to disappear? For biomedical systems in general it is still true that there is great uncertainty about how biological characteristics should be translated into modeling assumptions and are reflected in the model. It is thus important to investigate various possible scenarios, as long as they are biologically supported, and determine how the structure of solutions changes.

In this paper we address these questions by pursuing this analysis for a general structure i.e., a meta-system which encompasses the three models under consideration. The dynamics of this general system allows for different than Gompertzian growth of the tumor volume (for example, logistic growth [13]) as long as some general qualitative properties are satisfied and for a fairly general dynamics of the endothelial support q with arbitrary inhibition and stimulation functions, $I(p,q)$ and $S(p,q)$, respectively.

This model is presented in section 2 and in section 3 its dynamics is incorporated into the optimal control problem to minimize the primary tumor volume with a given amount of angiogenic inhibitors. In section 4 then the optimality of singular controls resulting from an application of the maximum principle to the problem is analyzed in its full generality. In the following sections 5-8 the general problem then is narrowed down by taking into account various additional characteristics for the dynamics of the tumor, the endothetial support, or both. The similarities and differences in the qualitative structure of solutions will be discussed and results obtained earlier in [20] and [22] are used to illustrate some of this analysis. A full synthesis of optimal controls and trajectories with singular controls playing an essential role for the original model by Hahnfeldt et al. [15] and its modification from [11] are presented. Overall, the analysis of this general system provides a theoretical background that explains various phenomena observed in particular models considered before. For other models for anti-angiogenesis that share the same general characteristics it provides information about their solutions without a need for a detailed separate analysis.

While applications of optimal control to mathematical models arising in biomedical problems have had a long history with the early focus on models in cancer chemotherapy, there has been a strong resurgence of this methodology in the analysis of newer models. This especially holds for novel treatment approaches to cancer like anti-angiogenesis discussed above but also for models describing the immune response and resulting immunotherapies (e.g., [6, 7, 8]), a second approach currently intensively pursued in medical cancer research. Especially when the overall interactions are difficult to gauge a priori, a theoretical analysis of models can become of practical value.

2 Mathematical Models of Tumor Angiogenesis

The dynamical systems we consider in this paper are based in their structure on a model formulated and biologically validated by Hahnfeldt, Panigrahy, Folkman and Hlatky in [15]. The principal variables considered in this model are the primary tumor volume, p, and the carrying capacity of the vasculature, q. The latter is defined as the maximum tumor volume sustainable by the vascular network. Henceforth we also refer to this as the endothelial support of the tumor for short. In this section we give a formulation of the underlying model in general terms that encompasses a large number of specific models that have been considered in the literature as well as new formulations.

The *growth of the primary tumor volume* p is modeled as

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

where ξ denotes a tumor growth parameter and F is a general growth function defined in terms of the scalar variable $x = \frac{p}{q}$. We *assume* that

(F) the function $F : (0, \infty) \to \mathbb{R}$, $x \mapsto F(x)$, is twice continuously differentiable, strictly decreasing, and satisfies $F(1) = 0$.

Given the definition of the variables, these are natural conditions to impose: Since q is the carrying capacity, at $p = q$ the endothelial support and tumor volume are balanced and thus p should not change whereas the tumor volume should shrink for inadequate endothelial support ($p > q$) and increase if support is available ($p < q$). It is reasonable to assume that these processes are more pronounced the smaller the quotient x is. Standard examples of growth functions that have these properties are given by classical Gompertzian growth,

$$F(x) = -\ln x, \tag{2}$$

classical logistic growth,

$$F(x) = 1 - x, \tag{3}$$

or generalized logistic growth,

$$F(x) = 1 - x^{\theta}, \tag{4}$$

for some positive coefficient θ.

The *dynamics for the endothelial support* generally consists of a balance between stimulatory and inhibitory effects and its basic structure can be written in the form

$$\dot{q} = -\mu q + S(p, q) - I(p, q) - Guq \tag{5}$$

where I and S denote endogenous inhibition and stimulation terms and the terms μq and Guq that have been separated describe, respectively, loss to the endothelial cells through natural causes (death etc.), and loss of endothelial support due to additional outside inhibition. The variable u represents the control in the system and corresponds to the angiogenic dose rate while G is a constant that represents the anti-angiogenic killing parameter. Generally μ is small and often this term is negligible compared to the other factors and thus in the literature sometimes μ is set to 0 in this equation.

Clearly, the inhibition and stimulation terms need to be specified further to have a meaningful model. In this paper we consider three specifications that all are based on the paper by Hahnfeldt et al. [15] in which a spatial analysis of the underlying consumption-diffusion model was carried out that led to the following two principal conclusions for the relations between endogenous inhibition and stimulation:

1. *The inhibitor will impact endothelial cells in a way that grows like volume of cancer cells to the power $\frac{2}{3}$. (The exponent $\frac{2}{3}$ arises through the interplay of the surface of the tumor through which the inhibitor needs to be released with the volume of endothelial cells.)*

2. *The inhibitor term tends to grow at a rate of $q^{\alpha}p^{\beta}$ faster than the stimulator term with $\alpha+\beta = \frac{2}{3}$.*

Making standard modelling assumptions about the interactions of p and q, in [15] the inhibitor term is taken in the form

$$I(p,q) = dp^{\frac{2}{3}}q \tag{6}$$

with d a constant, the "death" rate. But there is some freedom in the choice of α and β and this has become a source of other models considered in the literature. In the original work [15] Hahnfeldt et al. select $\alpha = 1$ and $\beta = -\frac{1}{3}$ resulting in the simple stimulation term

$$S(p,q) = bp \tag{7}$$

with b a constant, the "birth" rate. This structure makes the stimulation exerted by the tumor proportional to its volume. Other choices are equally possible and, for example, taking $\alpha = 0$ and $\beta = \frac{2}{3}$ results in the equally simple form

$$S(p,q) = bq \tag{8}$$

chosen by d'Onofrio and Gandolfi in [9]. This choice generates a considerably simpler q-dynamics for the model that has q as a factor. For a Gompertzian growth function F, it is a feature of either model that the q-dynamics is much faster than the p-dynamics and these systems exhibit a behavior characteristic for differential-algebraic models. In fact, it is argued in [11] that the systems tend to reach their steady state too fast. Since p and q tend to move together in steady state, ideally $p = q$, there is some freedom in selecting the terms for inhibition and stimulation, and Ergun, Camphausen and Wein in [11] modify the $\dot{q}$ equation to

$$\dot{q} = -\mu q + bq^{\frac{2}{3}} - dq^{\frac{4}{3}} - Guq \tag{9}$$

which eliminates any p-dependence. Their justification for this change or approximation lies in a different balance in the dynamics for the substitution of stimulation and inhibition, but compared with the underlying model of Hahnfeldt et al. the inhibitor term in this model is now only proportional to tumor radius and thus the premises of this model are not fully consistent with the implications of the analysis in [15]. As another justification for the choice $bq^{\frac{2}{3}}$ for the stimulation term, it could be argued that the necrotic core of the tumor does not interact with endothelial cells and thus the power $2/3$ could also be interpreted as scaling down the interactions from the tumor volume p to the surface area $p^{\frac{2}{3}}$ of the tumor and then interchanging p and q for the steady-state analysis, as it is done in [11]. The mathematical advantage of this approach is that the dynamics becomes a tremendous simplification in the sense that it eliminates a direct link between tumor volume p and endothelial support q. We summarize the q-dynamics of these three models in Table 1 and henceforth refer to these as models (A), (B) and (C).

Model	inhibition $I(p,q)$	stimulation $S(p,q)$	Reference
(A)	$dp^{\frac{2}{3}}q$	bp	Hahnfeldt et al., [15]
(B)	$dp^{\frac{2}{3}}q$	bq	d'Onofrio and Gandolfi, [9]
(C)	$dq^{\frac{4}{3}}$	$bq^{\frac{2}{3}}$	Ergun, Camphausen and Wein, [11]

Table 1: Models for inhibition and stimulation

3 An Optimal Control Formulation of Anti-Angiogenic Treatment

Due to limited resources and potential side effects of any kind of treatment, the problem of how to administer an a priori specified amount of inhibitors to achieve the "best possible" effect arises. A natural formulation suggested by Ergun et al. in [11] and then taken up by us in [20, 22, 23] is to maximize the tumor reduction achievable with a given amount of angiogenic inhibitors. Mathematically this becomes the following optimal control problem: for a free terminal time T, minimize the value $p(T)$ subject to the dynamics (1) and (5) over all Lebesgue measurable functions $u : [0,T] \to [0,a]$ that satisfy a constraint on the total amount of angiogenic inhibitors to be administered,

$$\int_0^T u(t)dt \leq A. \tag{10}$$

The upper limit a in the definition of the control set $U = [0,a]$ is a previously determined maximum dose at which inhibitors can be given. In this formulation arbitrary administration protocols are considered over the interval $(0,\infty)$ and the solution to the problem gives the protocol that achieves the smallest tumor volume achievable with the overall available amount A of inhibitors and T is the time when this minimum tumor volume is being realized. More general linear payoff functions of the form $c_1p(T) + c_2q(T)$ could easily be incorporated into our analysis below [25]. Alternatively, but this leads to a slightly different optimal control problem (see [32]), the same scheduling problem could be considered over an a priori prescribed therapy horizon T_{th} so that the final time T_{th} is fixed. Many of the results presented in this paper will remain valid for this formulation as well.

Mathematically it is more convenient to adjoin the isoperimetric constraint (10) as third variable and define the problem in $\mathbb{R}^3$. Hence we consider the following formulation:

[OC] For a free terminal time T, minimize the value $p(T)$ subject to the dynamics

$$\dot{p} = \xi pF\left(\frac{p}{q}\right), \qquad p(0) = p_0, \tag{11}$$

$$\dot{q} = -\mu q + S(p,q) - I(p,q) - Guq, \qquad q(0) = q_0, \tag{12}$$

$$\dot{y} = u, \qquad y(0) = 0, \tag{13}$$

over all Lebesgue measurable functions $u : [0, T] \to [0, a]$ for which the corresponding trajectory satisfies $y(T) \leq A$.

It is clear from the problem formulation that one precondition for the system to accurately reflect the underlying biological situation is that the variables p and q remain positive. This holds if the following simple and realistic assumption is satisfied:

(A) For $q = 0$ we either have $S(p, 0) \equiv I(p, 0)$ or $S(p, 0) > I(p, 0)$ for all $p > 0$.

Proposition 1 *Under assumption (A), for any admissible control u and arbitrary positive initial conditions p_0 and q_0, the corresponding trajectory (p, q), that is the solution to the differential equation (11)-(12) exists for some maximal interval $[0, \tau_+)$ and both p and q remain positive.*

Proof. Given any positive initial condition (p_0, q_0) and bounded control function $u : [0, \infty) \to [0, a]$, the solution to the dynamical system (11) and (12) exists on a maximal interval $[0, \tau_+)$ forward in time. If $S(p, 0) \equiv I(p, 0)$, then $q = 0$ is an equilibrium point for (12) and if $S(p, 0) > I(p, 0)$ for all $p > 0$, then we have $\dot{q}_{|q=0} > 0$. In either case, the solution $q(t)$ cannot cross from the region $q > 0$ into $q < 0$ and thus $q(t) > 0$ for $t \in [0, \tau_+)$. If F is continuous for $p = 0$, then $p = 0$ is an equilibrium point for (11) and this implies that $p(t)$ remains positive in this interval. If F has a singularity for $p = 0$, then it still follows from the definition of τ_+ that there cannot be any earlier escape times and thus $p(t)$ again remains positive in this interval. □

The three models (A)-(C) specified above satisfy condition (A) and it is not difficult to show that in these cases $\tau_+ = +\infty$, i.e. solutions exist for all times (see, [9, 20]). Naturally, for arbitrary functions I and S such a statement cannot be made a priori. Also, clearly both the growth function F and the inhibition and stimulation terms I and S need to be specified to fully solve problem $[OC]$, and the solutions may show different qualitative structures depending on the nature of these terms. Yet, there also are numerous results that only depend on general properties of the growth function F and other simple qualitative features of the system. We first analyze these in a common framework and later specify the models further. For this, we still need to make the following natural assumption that in steady state, i.e., on the diagonal $p = q$, the upper limit a on the control is large enough to overcome the net balance between endogenous stimulatory and inhibitory terms.

(B) For all $q > 0$ we have that

$$(Ga + \mu)\, q + I(q, q) > S(q, q). \tag{14}$$

It follows from the dynamics for p, (1), that regardless of the control used, p increases for $p < q$. As a result, for some degenerate initial conditions (p_0, q_0) it is possible that the (mathematically)

optimal solution to problem $[OC]$ is given by $T = 0$. This situation arises when the amount of available inhibitors simply is too small to reach a point that would have a lower p-value than p_0. In such a case it is not possible to decrease the tumor volume with the available amount of inhibitors and thus the mathematically "optimal" solution for problem $[OC]$ simply is to do nothing and take $T = 0$. It is still possible to slow down the tumor's growth, for example, by giving the full dose $u = a$ until all inhibitors run out (but this need not be the best way of doing this, [24]). However, this then becomes a different control problem and its formulation introduces a number of degeneracies into the analysis that we simply want to exclude here. We thus make the following definition.

Definition 1 *We say the initial condition* (p_0, q_0, A) *is* ill-posed *for the system under consideration if for no admissible control it is possible to reach a point* (p, q) *with* $p < p_0$*. In this case the optimal solution for the problem* [OC] *is given by* $T = 0$*. The initial condition* (p_0, q_0, A) *is* well-posed *if the final time* T *along the optimal control is positive.*

Clearly, whether or not a given initial condition (p_0, q_0, A) is well-posed depends on the specific system under consideration (growth function, inhibition and stimulation terms, values of the parameters etc.), but any initial condition that satisfies $p_0 \geq q_0$ is well-posed. Henceforth *we only consider well-posed initial conditions* (p_0, q_0, A).

4 Necessary Conditions for Optimality

First-order necessary conditions for optimality of a control u are given by the *Pontryagin Maximum Principle* [5, 27]: For a row-vector $\lambda = (\lambda_1, \lambda_2, \lambda_3) \in (\mathbb{R}^3)^*$, we define the Hamiltonian $H = H(\lambda, p, q, u)$ as

$$H = \lambda_1 \xi p F\left(\frac{p}{q}\right) + \lambda_2 \left(-\mu q + S(p,q) - I(p,q) - Guq\right) + \lambda_3 u.$$

Then, if u_* is an optimal control defined over the interval $[0, T]$ with corresponding trajectory (p_*, q_*, y_*), there exist a constant $\lambda_0 \geq 0$ and an absolutely continuous co-vector, $\lambda : [0, T] \to (\mathbb{R}^3)^*$, such that the following conditions hold:

(a) $(\lambda_0, \lambda(t)) \neq (0, 0)$ for all $t \in [0, T]$,

(b) λ_3 is constant, and λ_1 and λ_2 satisfy the adjoint equations

$$\dot{\lambda}_1 = -\frac{\partial H}{\partial p} = -\lambda_1 \xi \left(F\left(\frac{p}{q}\right) + \frac{p}{q} F'\left(\frac{p}{q}\right)\right) - \lambda_2 \left(\frac{\partial S}{\partial p}(p,q) - \frac{\partial I}{\partial p}(p,q)\right) \tag{15}$$

$$\dot{\lambda}_2 = -\frac{\partial H}{\partial q} = \lambda_1 \xi \left(\frac{p}{q}\right)^2 F'\left(\frac{p}{q}\right) + \lambda_2 \left(\mu - \frac{\partial S}{\partial q}(p,q) + \frac{\partial I}{\partial q}(p,q) + Gu\right) \tag{16}$$

with transversality conditions

$$\lambda_1(T) = \lambda_0 \quad \text{and} \quad \lambda_2(T) = 0, \tag{17}$$

(c) for almost every time $t \in [0,T]$ the optimal control $u_*(t)$ minimizes the Hamiltonian along $(\lambda(t), p_*(t), q_*(t))$ over the control set $[0,a]$ with minimum value given by 0.

We call a pair $((p,q,y),u)$ consisting of an admissible control u with corresponding trajectory (p,q,y) for which there exist multipliers (λ_0,λ) such that the conditions of the Maximum Principle are satisfied an *extremal* (pair) and the triple $((p,q,y),u,(\lambda_0,\lambda))$ is an extremal lift (to the cotangent bundle). Extremals with $\lambda_0 = 0$ are called abnormal while those with a positive multiplier λ_0 are called normal.

The following lemmas summarize some general properties of optimal controls and extremals for problem $[OC]$. Analogous results for the case of a Gompertzian growth function and special q-dynamics have already been given in [21] and with appropriate changes in the proofs these results carry over to the general case considered here.

Lemma 1 *Along an optimal trajectory (p_*,q_*,y_*), all available inhibitors are exhausted, $y_*(T) = A$, and $p_*(T) = q_*(T)$ at the final time.*

Proof. It follows from the general properties of the growth function F that the cancer volume is growing for $p < q$ and is shrinking for $p > q$. This implies that optimal trajectories can only terminate at times where $p_*(T) = q_*(T)$. For, if $p_*(T) < q_*(T)$, then it would simply have been better to stop earlier since p was increasing over some interval $(T-\varepsilon, T]$. (Recall that we are assuming that the initial condition is well-posed so that the optimal final time T is positive.) On the other hand, if $p_*(T) > q_*(T)$, then we can always add another small interval $(T, T+\varepsilon]$ with the control $u = 0$ without violating any of the constraints and p will decrease along this interval if ε is small enough. Thus at the final time necessarily $p_*(T) = q_*(T)$. If now $y_*(T) < A$, then we can still add a small piece of a trajectory for $u = a$ over some interval $[0,\varepsilon]$. By assumption (B) we have $\dot{q} < 0$ and since $p_*(T) = q_*(T)$ it follows that $\dot{p} = 0$. This implies that the trajectory enters the region $p > q$ where the tumor volume p is still decreasing further. Hence T was not the optimal time. □

Lemma 2 *Extremals are normal. The multipliers λ_1 and λ_2 cannot vanish simultaneously; λ_2 has only simple zeroes. The multiplier λ_3 is constant and non-negative.*

Proof. The multipliers λ_1 and λ_2 satisfy the homogeneous linear system (15) and (16) and thus they vanish identically if and only if they simultaneously vanish at some time t. This is the case if and only if $\lambda_0 = 0$ and thus in this case the nontriviality of $(\lambda_0, \lambda(t))$ implies that the constant multiplier λ_3 is not zero. The condition $H \equiv 0$ on the Hamiltonian therefore gives that $u \equiv 0$ and thus the initial condition is ill-posed. Hence, without loss of generality we may assume that $\lambda_0 = 1$ and thus λ_1 and λ_2 cannot vanish simultaneously. In particular, whenever $\lambda_2(t) = 0$, then $\dot{\lambda}_2(t) \neq 0$ since $F' \neq 0$ and thus λ_2 has only simple zeroes.

For the final time T it follows from $p_*(T) = q_*(T)$, the transversality condition $\lambda_2(T) = 0$, and the condition $H(T) \equiv 0$ that $\lambda_3 u_*(T) = 0$. If $\lambda_3 < 0$, then the function $\lambda_3 - \lambda_2(t)Gq_*(t)$ will be negative on some interval $(T - \varepsilon, T]$ and thus by the minimization condition (c) on the Hamiltonian the control must be given by $u_*(t) = a$ on this interval. Contradiction. Hence $\lambda_3 \geq 0$. $\square$

For almost any time t the optimal control $u_*(t)$ minimizes the Hamiltonian $H(\lambda(t), p_*(t), q_*(t), u)$ over the interval $[0, a]$. Since H is linear in u, and defining the so-called *switching function* Φ as

$$\Phi(t) = \lambda_3 - \lambda_2(t)Gq_*(t), \tag{18}$$

it follows that

$$u_*(t) = \begin{cases} 0 & \text{if } \Phi(t) > 0 \\ a & \text{if } \Phi(t) < 0 \end{cases} . \tag{19}$$

The minimum condition in itself does not determine the control at times when $\Phi(t) = 0$. However, if $\Phi(t) \equiv 0$ on an open interval, then also all derivatives of $\Phi(t)$ must vanish and this typically allows to compute the control. Controls of this kind are called *singular* [3] while we refer to the constant controls $u = 0$ and $u = a$ as *bang* controls. For example, if $\Phi(\tau) = 0$, but $\dot{\Phi}(\tau) \neq 0$, then the control switches between $u = 0$ and $u = a$ depending on the sign of $\dot{\Phi}(\tau)$. Optimal controls then need to be synthesized from these candidates through an analysis of the switching function.

In general singular controls play a major role in this synthesis and in this paper we analyze their local optimality for the problem $[OC]$ under rather general assumptions. If the control u is singular on some open interval J, we call the corresponding trajectory (p, q, y) a singular arc and the triple $((p, q, y), u, \lambda)$ a singular extremal. The following fact is an immediate corollary of the adjoint system.

Lemma 3 *If $((p, q, y), u, \lambda)$ is a singular extremal over an open interval J, then $\lambda_3 > 0$ and $\lambda_2(t)$ is positive over J.*

Proof. The switching function $\Phi(t)$ vanishes identically on J and thus $\lambda_3 = \lambda_2(t)Gq_*(t)$. If $\lambda_3 = 0$, then $\lambda_2(t) \equiv 0$ on J and by the adjoint equation for λ_2 also $\lambda_1(t)$ must vanish identically on J. Contradiction. Hence $\lambda_3 > 0$ and thus also $\lambda_2(t)$ is positive over J. $\square$

In order to compute singular controls we need to analyze the switching function and its derivatives. These computations can be expressed concisely within the framework of geometric optimal control theory and we therefore now write the state as $z = (p, q, y)^T$ and express the dynamics in the form

$$\dot{z} = f(z) + ug(z) \tag{20}$$

where

$$f(z) = \begin{pmatrix} \xi p F\left(\frac{p}{q}\right) \\ -\mu q + S(p, q) - I(p, q) \\ 0 \end{pmatrix} \quad \text{and} \quad g(z) = \begin{pmatrix} 0 \\ -Gq \\ 1 \end{pmatrix} . \tag{21}$$

Note that the switching function simply is the inner product of the multiplier λ with the control vector field g,

$$\Phi(t) = \lambda_3 - \lambda_2(t)Gq_*(t) = \lambda(t)g(z(t)). \tag{22}$$

Derivatives of the switching function are computed using the following well-known result that can be verified by a direct calculation.

Proposition 2 *Let h be a continuously differentiable vector field, $h \in \mathbb{R}^3$, and define*

$$\Psi(t) = \lambda(t)h(z(t)). \tag{23}$$

Then the derivative of Ψ along a solution to the system equation (20) for control u and a solution λ to the corresponding adjoint equations is given by

$$\dot{\Psi}(t) = \lambda(t)[f + ug, h](z(t)), \tag{24}$$

where $[f, h]$ denotes the Lie bracket of the vector fields f and h. In local coordinates the Lie bracket is expressed as $[f, h](z) = Dh(z)f(z) - Df(z)h(z)$ with Df and Dh denoting the matrices of the partial derivatives of f and h, respectively. □

For the switching function Φ, $\Phi(t) = \lambda(t)g(z(t))$, we therefore have that

$$\dot{\Phi}(t) = \lambda(t)[f, g](z(t)), \tag{25}$$

$$\ddot{\Phi}(t) = \lambda(t)[f + ug, [f, g]](z(t)). \tag{26}$$

These formulas are crucial in the analysis of singular controls: If u_* is singular on some open interval J, then the switching function and all its derivatives vanish on J. Note that since $[g, g] = 0$ the control does not appear in the first derivative, but if $\lambda(t)[g, [f, g]](z(t)) \neq 0$ on J, then (26) can be solved for u as

$$u_{\sin}(t) = -\frac{\lambda(t)[f, [f, g]](z(t))}{\lambda(t)[g, [f, g]](z(t))} \tag{27}$$

and this determines the singular control as a function on the cotangent bundle, i.e., as a function of the state $z(t)$ and the multiplier $\lambda(t)$. In this case the singular control is said to be of *order 1* on the interval J. Singular controls of higher order can arise if the term $\lambda(t)[g, [f, g]](z(t))$ does vanish on some subintervals, but these cases are not generic [3] and here we only consider singular controls of order 1. For singular controls of order 1 it is a second-order necessary condition for minimality, the so-called *strengthened Legendre-Clebsch condition* [3, 17], that

$$\lambda(t)[g, [f, g]](z(t)) < 0. \tag{28}$$

Thus the determination of singular controls and analysis of their local optimality reduces to the computations of the Lie brackets $[f,[f,g]]$ and $[g,[f,g]]$ and their inner products with the multiplier λ.

A special situation arises in dimension 3, as we have it in problem$[OC]$, if the vector field g and the Lie brackets $[f,g]$ and $[g,[f,g]]$ are linearly independent. In this case the Lie bracket $[f,[f,g]]$ can be written as a linear combination of this basis with coefficients that are smooth functions of the state z,

$$[f,[f,g]](z) = \rho(z)g(z) + \varphi(z)[f,g](z) + \psi(z)[g,[f,g]](z). \tag{29}$$

For a singular extremal (z,u,λ) the switching function $\Phi(t) = \lambda(t)g(z(t))$ and its derivative $\dot{\Phi}(t) = \lambda(t)[f,g](z(t))$ vanish and thus

$$\begin{aligned}\lambda(t)[f,[f,g]](z(t)) &= \lambda(t)\left\{\rho(z(t))g(z(t)) + \varphi(z(t))[f,g](z(t)) + \psi(z(t))[g,[f,g]](z(t))\right\}\\ &= \psi(z(t))\cdot\lambda(t)[g,[f,g]](z(t)).\end{aligned}$$

Hence, if $\lambda(t)[g,[f,g]](z(t)) \neq 0$, the singular control is given as a feedback function (i.e., in a form that does NOT depend on the multiplier) by

$$u_{\sin}(t) = -\psi(z(t)). \tag{30}$$

Clearly, whether this feedback is admissible, that is whether it takes values in the control set $[0,a]$ needs to be determined for each problem under consideration and cannot be asserted in general. However, even when admissible, this feedback does not define a singular control everywhere, but only on a thin subset. For, the conditions of the Maximum principle need to be satisfied and the extra condition that $H \equiv 0$ requires that also

$$\lambda(t)f(z(t)) = 0 \qquad \text{for all} \quad t \in J. \tag{31}$$

If $\lambda(t) \neq 0$, and in our case this is guaranteed by the positivity of λ_2 and λ_3 along a singular extremal, it follows that the vector fields f, g and their Lie bracket $[f,g]$ must be linearly dependent along the singular arc and thus (30) defines the singular control, but only on the surface

$$\mathcal{S} = \{z \in \mathbb{R}^3 : f(z) \wedge g(z) \wedge [f,g](z) = 0\}. \tag{32}$$

If the strengthened Legendre-Clebsch condition is satisfied along these arcs, then it follows from a classical construction of Gardner-Moyer [14] that these arcs are indeed locally optimal in $\mathbb{R}^3$. For more general results about the optimality of singular arcs in $\mathbb{R}^n$, see [3, 29].

Proposition 3 *Suppose the feedback (30) takes values in the interior of the control set. If the strengthened Legendre-Clebsch condition is satisfied on the singular surface $\mathcal{S}$, then a local synthesis of extremals around $\mathcal{S}$ can be constructed by concatenating the singular arcs with trajectories corresponding to the bang controls $u = 0$ and $u = a$ and the corresponding trajectories are optimal in a neighborhood of $\mathcal{S}$ covered by this flow.*

Proof. This essentially is a consequence of the results of Gardner-Moyer about the optimality of singular arcs in $\mathbb{R}^3$ developed in [14]: Let J be an open interval on which a control u_* is singular, takes values in the interior of the control set, and the strengthened Legendre-Clebsch condition is satisfied. Then concatenations of the forms $\mathbf{bs}$ or $\mathbf{sb}$ where $\mathbf{b}$ denotes any one of the two bang controls, $u = 0$ or $u = a$, are extremal. That is, if $(\tau - \varepsilon, \tau + \varepsilon)$ is a small interval with the property that the optimal control is singular on $(\tau - \varepsilon, \tau)$ or $(\tau, \tau + \varepsilon)$ and constant on the complementary interval, $u = 0$ or $u = a$, then the conditions of the Maximum Principle are satisfied. To see this, recall that by Proposition 2 for any control u that is continuous from the left $(-)$ or right $(+)$ the second derivative of the switching function is given by

$$\ddot{\Phi}(t_\pm) = \lambda(t)[f,[f,g]](z(t)) + u(t_\pm)\lambda(t)[g,[f,g]](z(t))$$

and it vanishes identically on J along the singular control. Since the strengthened Legendre-Clebsch condition is satisfied, we have $\lambda(t)[g,[f,g]](z(t)) < 0$. By assumption the singular control takes values in the interior of the control set $[0, a]$ and thus $\lambda(t)[f,[f,g]](z(t)) > 0$. Hence, for $u = 0$ we get $\ddot{\Phi}(t) > 0$ and for $u = a$ we have $\ddot{\Phi}(t) < 0$. These signs are consistent with entry and exit from the singular arc for each control, i.e., for example, if $u = 0$ on an interval $(\tau - \varepsilon, \tau)$, then Φ is positive over this interval consistent with the choice $u = 0$ as minimizing control. This allows to construct a local synthesis around $\mathcal{S}$ by integrating the constant controls $u = 0$ or $u = a$ forward and backward (which ones to use depends on the specific problem and initial data) from the singular arc and it is shown in [14] that these trajectories are locally optimal over a neighborhood covered by the trajectories in this construction. □

Questions about the global optimality are not resolved by this local argument, but it gives a strong indication that the singular arcs will play an important role in the overall solutions to the problem if the strengthened Legendre-Clebsch condition is satisfied. This indeed is the case as will be seen in section 6 for problem [OC]. Methods to verify the optimality of bang-bang controls are developed, for example, in [26], but in this paper our focus in on singular controls.

Using the same notation that was introduced in [21] in the analysis of singular controls for systems with Gompertzian growth function, $F(x) = -\ln x$, $x = \frac{p}{q}$, define Δ as the difference between stimulation and inhibition terms, $\Delta = S - I$. Direct computations verify for a general growth function F that

$$[f,g](z) = G\begin{pmatrix} -\xi p x F'(x) \\ q\frac{\partial \Delta}{\partial q}(p,q) - \Delta(p,q) \\ 0 \end{pmatrix} \tag{33}$$

and

$$[g,[f,g]](z) = G^2 \begin{pmatrix} -\xi p\left[xF'(x) + x^2F''(x)\right] \\ -q^2\frac{\partial^2\Delta}{\partial q^2}(p,q) + q\frac{\partial\Delta}{\partial q}(p,q) - \Delta(p,q) \\ 0 \end{pmatrix}. \tag{34}$$

Because of the special form of the control vector field g, the q-coordinates of Lie brackets with g can be expressed in a succinct form: Let I denote the interval $(0,\infty)$ and for an infinitely often continuously differentiable function $f \in C^\infty(I)$ denote by $\mathcal{L}$ the linear differential operator

$$\mathcal{L} : C^\infty(I) \to C^\infty(I),\ f \mapsto \mathcal{L}f, \tag{35}$$

defined by

$$(\mathcal{L}f)(q) = qf'(q) - f(q). \tag{36}$$

Note that for any $\alpha \in \mathbb{R}$ the powers $f(q) = q^\alpha$ are eigenfunctions of this operator with eigenvalue $\lambda = \alpha - 1$, i.e.,

$$\mathcal{L}(q^\alpha) = (\alpha - 1)q^\alpha. \tag{37}$$

This will allow for very simple and elegant calculations for models (A), (B) and (C) that all have this property. With $\mathcal{L}^n$ defined inductively by $\mathcal{L} \circ \mathcal{L}^{n-1}$, these Lie brackets then take the succinct form

$$[f,g](z) = G \begin{pmatrix} -\xi p x F'(x) \\ \mathcal{L}(\Delta)(p,q) \\ 0 \end{pmatrix}, \tag{38}$$

$$[g,[f,g]](z) = -G^2 \begin{pmatrix} \xi p\left[xF'(x) + x^2F''(x)\right] \\ \mathcal{L}^2(\Delta)(p,q) \\ 0 \end{pmatrix} \tag{39}$$

where the operator $\mathcal{L}$ acts on q with all other variables as parameters. Since the variable y does not appear explicitly in the dynamics of the system, also the bracket $[f,[f,g]]$ has last coordinate 0 and thus for problem $[OC]$ the vector field $[f,[f,g]]$ can be written as

$$[f,[f,g]](z) = \varphi(z)[f,g](z) + \psi(z)[g,[f,g]](z) \tag{40}$$

provided $[f,g]$ and $[g,[f,g]]$ are not parallel. For the same reason the singular set $\mathcal{S}$ in this case is actually a curve in (p,q)-space only and it is the locus where the vector fields f and $[f,g]$ are parallel. Naturally, all these properties depend on F and Δ and we need to specify the models further to obtain more precise results.

5 Optimal Controls for Model (B)

In this section we extend the results from [23] about the structure of optimal controls for model (B) with a Gompertzian growth function to the case of a general growth function satisfying condition (F). For the special case of a classical logistic growth function (3) some of these results are also given by A. Swierniak in [33]. We start with some brief comments about the dynamics. The only equilibrium condition for $\dot{q} = 0$ is given by $\bar{p} = \left(\frac{b-\mu}{d}\right)^{\frac{3}{2}}$ and since $F(1) = 0$ the only equilibrium condition for $\dot{p} = 0$ is for $x = \frac{p}{q} = 1$. Hence the dynamics has a unique equilibrium point at

$$\bar{p} = \left(\frac{b-\mu}{d}\right)^{\frac{3}{2}} = \bar{q}.$$

The Jacobian matrix at the equilibrium point reduces to

$$Df(\bar{p},\bar{q}) = \begin{pmatrix} \xi F'(1) & -\xi F'(1) \\ -\frac{2}{3}d\bar{p}^{\frac{2}{3}} & 0 \end{pmatrix}$$

and the eigenvalues are given by

$$\begin{aligned} \nu_{1,2} &= \frac{\xi F'(1) \pm \sqrt{\xi^2 F'(1)^2 + \frac{8}{3}d\bar{p}^{\frac{2}{3}}\xi F'(1)}}{2} \\ &= \frac{\xi}{2}F'(1)\left(1 \pm \sqrt{1 + \frac{8}{3}\frac{d}{\xi F'(1)}\bar{p}^{\frac{2}{3}}}\right). \end{aligned}$$

Since $F'(1) < 0$ both eigenvalues are either negative or complex conjugate with negative real part. Hence this equilibrium point is locally asymptotically stable. For a Gompertzian or generalized logistic growth function it has been shown in [9] that this equilibrium is globally asymptotically stable and this is the only medically realistic scenario. From a practical point of view it therefore makes sense to restrict the state-space to the region

$$\mathcal{D} = \{(p,q) : 0 < p \leq \bar{p},\ 0 < q \leq \bar{q}\}, \tag{41}$$

restricted in both variables p and q by the equilibrium for the dynamics with $u = 0$. By using a constant control v the equilibrium can be shifted towards the origin along the diagonal and finally be eliminated altogether. As a function of v, the equilibrium is given by

$$\bar{p}(v) = \bar{q}(v) = \left(\frac{b-\mu-Gv}{d}\right)^{\frac{3}{2}} \tag{42}$$

provided $b - \mu > Gv$, and this equilibrium $(\bar{p}(v), \bar{q}(v))$ still is locally asymptotically stable. As $b - \mu \leq Gv$, the system no longer has an equilibrium point and now all trajectories converge to the origin as $t \to \infty$ [9]. Thus, theoretically eradication of the tumor were possible in this case under the unrealistic scenario of constant treatment with unlimited supply of inhibitors.

Proposition 4 *Regardless of the growth function F, for model (B) optimal controls are bang-bang. Optimal controls whose trajectories entirely lie in the square domain $\mathcal{D}$ are bang-bang with at most two switchings of the order* $\mathbf{0a0}$.

Proof. For model (B) by d'Onofrio and Gandolfi [9] the q-dynamics is linear in q and thus both stimulation and inhibition terms lie in the kernel of the operator $\mathcal{L}$, i.e., $\mathcal{L}(\Delta) = \mathcal{L}^2(\Delta) = 0$. Hence

$$[f,g](z) = G\begin{pmatrix} -\xi p x F'(x) \\ 0 \\ 0 \end{pmatrix} \quad \text{and} \quad [g,[f,g]](z) = -G^2\begin{pmatrix} \xi p\left[xF'(x) + x^2F''(x)\right] \\ 0 \\ 0 \end{pmatrix}. \tag{43}$$

Suppose the switching function $\Phi(t) = \lambda(t)g(z(t))$ vanishes at time τ. If $\dot{\Phi}(\tau) \neq 0$,

$$\dot{\Phi}(\tau) = \lambda(\tau)[f,g](z(\tau)) = -\lambda_1(\tau)G\xi p(\tau)x(\tau)F'\left(x(\tau)\right), \tag{44}$$

then the control has a bang-bang switch at time τ. But the term $G\xi p(\tau)x(\tau)F'\left(x(\tau)\right)$ is negative in a neighborhood of τ and so $\dot{\Phi}(\tau)$ can only vanish if $\lambda_1(\tau) = 0$. In this case the adjoint equation (15) implies that

$$\dot{\lambda}_1(\tau) = \lambda_2(\tau)\frac{\partial I}{\partial p}(p(\tau),q(\tau)) = \frac{2}{3}\lambda_2(\tau)d\frac{q(\tau)}{p(\tau)^{\frac{1}{3}}} \neq 0$$

since, by Lemma 2, $\lambda_2(\tau)$ cannot vanish as well. Hence λ_1 changes sign at τ. But then so does the derivative $\dot{\Phi}$ of the switching function Φ. Since $\Phi(\tau) = 0$ this implies that Φ has a strict local minimum or maximum at τ and in either case the corresponding control is constant near τ. Thus overall optimal controls are bang-bang.

We now show that there are at most two switchings if the trajectory lies in $\mathcal{D}$ and that the concatenation structure is of the form $\mathbf{0a0}$. Suppose the optimal control is given by $u_* \equiv 0$ on an interval (α,β) and both α and β are switching times. Then the switching function Φ is positive over this interval and has a maximum at some time $\tau \in (\alpha,\beta)$ where necessarily $\dot{\Phi}(\tau) = 0$ and $\ddot{\Phi}(\tau) \leq 0$. It follows from the argument above that $\lambda_1(\tau) = 0$ and we now show that the condition on the second derivative implies that $\lambda_2(\tau) < 0$. Along the control $u = 0$ we have that

$$\ddot{\Phi}(t) = \lambda(t)[f,[f,g]](z(t))$$

and a direct computation shows that this Lie bracket is of the form

$$[f,[f,g]](z) = \begin{pmatrix} *** \\ -\frac{2}{3}\xi G d p(t)^{\frac{5}{3}}F'(x(t)) \\ 0 \end{pmatrix}. \tag{45}$$

Hence, since $\lambda_1(\tau) = 0$, we have that

$$\ddot{\Phi}(\tau) = -\frac{2}{3}\xi G d p(\tau)^{\frac{5}{3}} F'(x(\tau))\lambda_2(\tau). \tag{46}$$

By assumption F is strictly decreasing and thus $\ddot{\Phi}(\tau) \leq 0$ implies that $\lambda_2(\tau) \leq 0$. But by Lemma 2, $\lambda_2(\tau)$ cannot vanish as well and thus $\lambda_2(\tau)$ actually is negative. Furthermore, along $u \equiv 0$ the Hamiltonian for the problem reduces to

$$H = \lambda_1 \xi p F\left(\frac{p}{q}\right) + \lambda_2 q\left(b - \mu - d p^{\frac{2}{3}}\right) \equiv 0 \tag{47}$$

and therefore at time τ we must have $p(\tau) = \left(\frac{b-\mu}{d}\right)^{\frac{3}{2}} = \bar{p}$. But then the trajectory lies outside $\mathcal{D}$ near τ. $\square$

Fig. 1 gives an example of an optimal control and its corresponding trajectory for the case of a Gompertzian growth function, $F(x) = -\ln x$. The variables p and q are volumes measured in mm^3 and the parameter values are based on data from [15]. For all the simulations given in this paper we use $\xi = \frac{0.192}{\ln 10} = 0.084$ *per day* (adjusted to the natural logarithm), $b = 5.85$ *per day*, $d = 0.00873$ *per* mm^2 *per day*, $G = 0.15$ *kg per mg of dose per day*, and for illustrative purposes we chose a small positive value for μ, $\mu = 0.02$ *per day*. However, because of differences in the model we use different values for the maximum dosage a and the total amount of inhibitors A given. The qualitative structure of the solutions is unaffected by the specific choices made. For the simulations in Fig. 1 we took $a = 45$ and $A = 25$. Optimal controls are at most of the form **0a0**, but the initial arc with $u = 0$ is only present in the less realistic cases when the endothelial support q_0 is very small relative to the cancer volume p_0 and for a typical scenario optimal controls will simply be of the type **a0** giving all available inhibitors at maximum dose from the beginning. However, as shown in Fig. 1 there is a substantial segment for $u = 0$ when the tumor volume still decreases until its minimum is reached as the diagonal $p = q$ is crossed. In this simulation $p_0 = 9,000\ mm^3$ and $q_0 = 10,000\ mm^3$. The full dosage is given over the interval $t_1 = \frac{A}{a} = .5556$ (days) and the the control is still equal to $u = 0$ for the much longer period of 1.6113 days with the optimal final time T given by $T = 2.1669$. The minimum value for the objective is given by $p_{\min} = 5769.7$. Note that most of the decrease in tumor volume occurs along the $u = 0$ trajectory and is due to after effects. The reason for this behavior lies in the fact that the $\dot{q}$-nullcline is given by $q = 0$ and thus most of the reduction along the full dose will only occur when the q-value is close to zero. In this example the inhibitors bring the system close to this curve, but the benefit in tumor reduction only is achieved after all inhibitors have been used up.

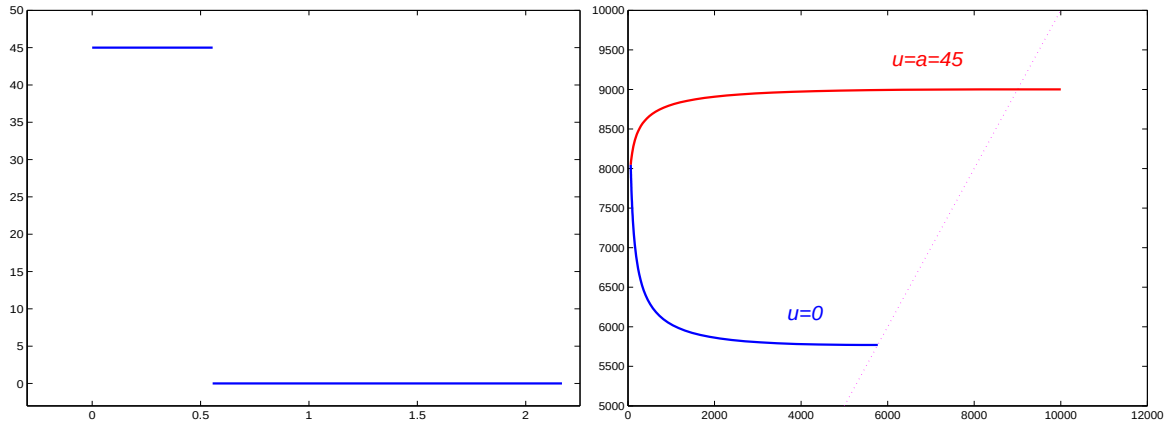

Figure 1: Model (B)- optimal control and corresponding trajectory for initial conditions $p_0 = 9,000$ and $q_0 = 10,000$

6 Optimal Controls for Models with Gompertzian Growth Function

We now focus our attention on models (A) and (C), but with different growth functions F. We first briefly review and also expand on results from [21] where the case of a Gompertzian growth function F, $F(x) = -\ln x$, was analyzed. Here we have

$$xF'(x) = -1, \qquad xF'(x) + x^2F''(x) \equiv 0 \tag{48}$$

and thus the relevant brackets simplify to

$$[f,g](z) = G\begin{pmatrix} \xi p \\ \mathcal{L}(\Delta)(p,q) \\ 0 \end{pmatrix}, \qquad [g,[f,g]](z) = -G^2\begin{pmatrix} 0 \\ \mathcal{L}^2(\Delta)(p,q) \\ 0 \end{pmatrix}. \tag{49}$$

In particular,

$$\lambda(t)[g,[f,g]](z(t)) = -G^2\lambda_2(t)\mathcal{L}^2(\Delta)(p(t),q(t)) \tag{50}$$

and the general calculations above readily apply to yield the following result of [21]:

Theorem 1 *Let the growth of the primary tumor volume be modelled by a Gompertzian growth function, $F(x) = -\ln x$, and suppose a control u_* is singular on some open interval (α,β). Then the strengthened Legendre-Clebsch condition is satisfied on (α,β) if and only if $\mathcal{L}^2(\Delta)(p(t),q(t)) > 0$ and in this case the singular curve $\mathcal{S}$ is locally minimizing for problem [OC]. This curve is the locus of the points (p,q) where the vector fields f and $[f,g]$ are linearly dependent, i.e.*

$$\Delta(p,q) + \mathcal{L}(\Delta)(p,q)\ln\left(\frac{p}{q}\right) - \mu q = 0. \tag{51}$$

The singular curve is admissible at points where the singular control defined by (27) takes values in the control interval $[0, a]$. ■

For models (A) and (C) the stimulation and inhibition terms are all given by powers of q and it is straightforward to evaluate these conditions:

Model (A) [15]. For the model of Hahnfeldt, Panigrahy, Folkman and Hlatky we have $S(p,q) = bp$ and $I(p,q) = dp^{\frac{2}{3}}q$ and thus $\mathcal{L}(S) = -S$ and $\mathcal{L}(I) = 0$. Hence

$$\mathcal{L}(\Delta) = \mathcal{L}(S) - \mathcal{L}(I) = -S \tag{52}$$

and

$$\mathcal{L}^2(\Delta) = \mathcal{L}(-S) = S > 0. \tag{53}$$

Thus by Theorem 1 there exists a locally minimizing singular curve $\mathcal{S}$ for model (A) given by

$$S\left(1 - \ln\left(\frac{p}{q}\right)\right) = \mu q + I, \tag{54}$$

which, upon substituting the expressions for I and S, setting $x = \frac{p}{q}$ and dividing by q, takes the form

$$\mu + dp^{\frac{2}{3}} = bx\left(1 - \ln x\right). \tag{55}$$

Somewhat longer computations that are carried out for this model in [22] verify that the singular control, computed according to (30), is given in feedback form by

$$u_{\sin}(x) = \frac{1}{G}\left[\left(\frac{1}{3}\xi + bx\right)\ln x + \frac{2}{3}\xi\left(1 - \frac{\mu}{bx}\right)\right]. \tag{56}$$

Thus the singular control only depends on the quotient $x(t) = p(t)/q(t)$. An equivalent expression in terms of p and q that uses (55) is given by

$$u_{\sin}(p,q) = \frac{1}{G}\left(\xi \ln\left(\frac{p}{q}\right) + b\frac{p}{q} + \frac{2}{3}\xi\frac{d}{b}\frac{q}{p^{\frac{1}{3}}} - \left(\mu + dp^{\frac{2}{3}}\right)\right). \tag{57}$$

While the second formula offers some computational advantages, the first one is easier to use to analyze where the singular control is admissible. In fact, it shown in [22] that for $\mu < b$ there exists exactly one connected arc on the singular curve $\mathcal{S}$ along which the control is admissible, i.e., satisfies the bounds $0 \leq u_{\sin} \leq a$. All these results are strongly *robust* in the sense that the same qualitative structure is valid regardless of the specific numerical values of the parameters, only making the realistic assumption (B).

Fig. 2 depicts the singular curve for the same parameter values taken from [15] given earlier. The solid curve in Fig. 2 represents the admissible portion of the petal like singular curve $\mathcal{S}$ for $a = 75$; the full singular curve is shown dashed. The qualitative structure shown is generally valid with the admissible portion shrinking for smaller values a.

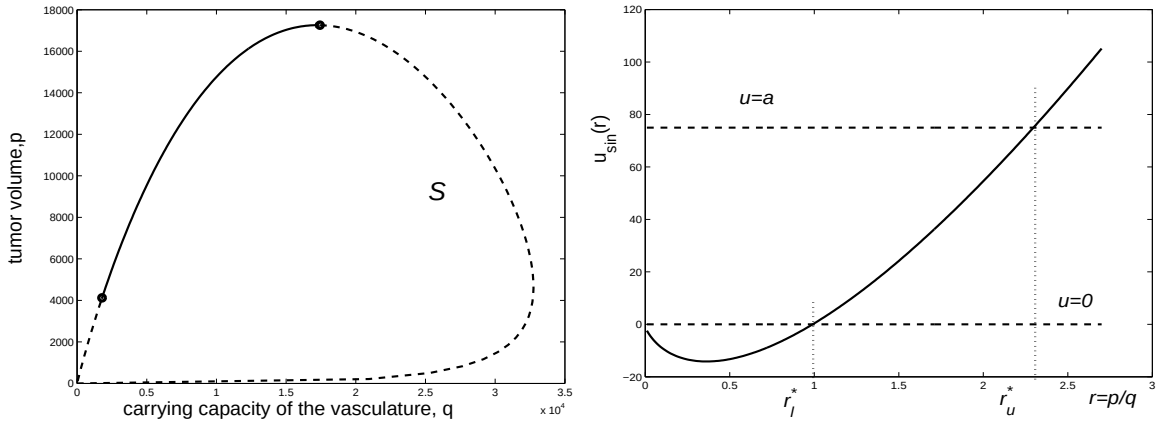

Figure 2: Model (A)- the singular curve, its admissible portion and the singular control

The admissible singular arc is the corner piece to a complete solution for problem $[OC]$ for this model in terms of a full synthesis of all optimal trajectories that was derived in [22] and is visualized in Fig. 3. The important curves for the synthesis are the admissible portions of the singular curve (solid blue curve), portions of trajectories corresponding to the constant controls $u = 0$ (dash-dotted green curves) and $u = a$ (solid green curves), and the line $p = q$ (dotted black line) where the trajectories achieve the maximum tumor reduction. These diagrams represent the optimal trajectories as a whole and each of the different curves gives a different optimal trajectory depending on the actual initial condition. The thick lines in the graph mark one specific such trajectory. In this case the initial value p_0 for the tumor volume and q_0 for the endothelial support are high and require to immediately start with the treatment. The optimal trajectory therefore initially follows the curve corresponding to the control $u = a$. Note that, although inhibitors are given at full dose along this curve, this shows very little effect on the number of the cancer cells in a sense of decrease. Once the trajectory corresponding to the full dose hits the singular arc $\mathcal{S}$, according to our analysis it is no longer optimal to give full dose and the optimal controls here switch to the singular control and the optimal trajectory follows the singular arc. Ignoring some special cases that are due to saturation of the singular control along this arc and are described in [22], the optimal control will now follow the singular arc until all inhibitors are exhausted according to the condition that $y(T) = A$. It is clear that this is the part where most of the shrinkage of the tumor occurs. When the inhibitors have been exhausted, therapy is over, but there still is an additional tumor reduction as the optimal trajectory follows a trajectory for the control $u = 0$. The reason for this lies in the fact that inhibitors become exhausted in the region $p > q$ where the tumor volume still shrinks even for $u = 0$ and thus due to these aftereffects the minimum tumor volume is only realized when this trajectory crosses the diagonal $p = q$. The corresponding time T then is the limit of the horizon considered in the problem

formulation $[OC]$. Fig. 4 shows the graph of the optimal control for initial conditions $p_0 = 9,000\ mm^3$ and $q_0 = 10,000\ mm^3$. The control is of type **as0** and the switchings times are $t_1 = .1178$ (days), $t_2 = 5.2246$ and the final time is given by $T = 5.3740$ with minimum value $p_{\min} = 6586.9$.

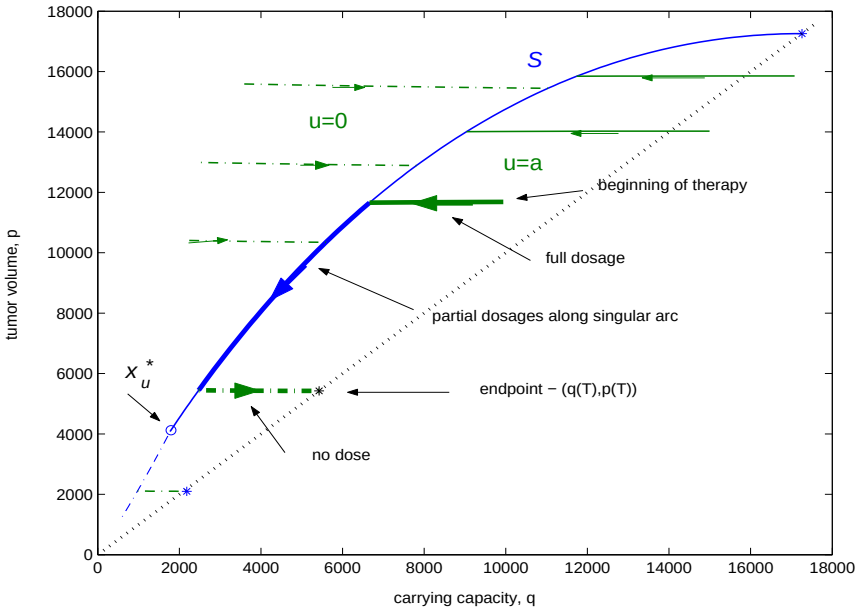

Figure 3: A synthesis of optimal controlled trajectories for model (A)

Model (C) [11]. For the model by Ergun, Camphausen and Wein we have $S(p,q) = bq^{\frac{2}{3}}$ and $I(p,q) = dq^{\frac{4}{3}}$ and thus $\mathcal{L}(S) = -\frac{1}{3}S$ and $\mathcal{L}(I) = \frac{1}{3}I$. In this case we therefore get $\mathcal{L}(\Delta) = -\frac{1}{3}(S+I)$ and hence

$$\mathcal{L}^2(\Delta) = \frac{1}{9}\Delta = \frac{1}{9}q^{\frac{2}{3}}\left(b - dq^{\frac{2}{3}}\right). \tag{58}$$

This quantity is positive for $q < \left(\frac{b}{d}\right)^{\frac{3}{2}}$ which includes the medically relevant region that contains the equilibrium point $\bar{q} = \left(\frac{b-\mu}{d}\right)^{\frac{3}{2}}$. Analogous as for model (A), by Theorem 1 there exists a locally minimizing singular curve $\mathcal{S}$ which now is given by

$$bq^{\frac{2}{3}} - dq^{\frac{4}{3}} - \frac{1}{3}\left(bq^{\frac{2}{3}} + dq^{\frac{4}{3}}\right)\ln\left(\frac{p}{q}\right) - \mu q = 0. \tag{59}$$

Dividing by $q^{\frac{2}{3}}$ this equation can explicitly be solved for p as

$$p = q\exp\left(3\frac{b - \mu q^{\frac{1}{3}} - dq^{\frac{2}{3}}}{b + dq^{\frac{2}{3}}}\right). \tag{60}$$

Fig. 5 depicts the singular curve for this model with the same values as above and again the admissible portion is marked by the solid line, but this time $a = 15$ is taken as the upper limit. Again the singular

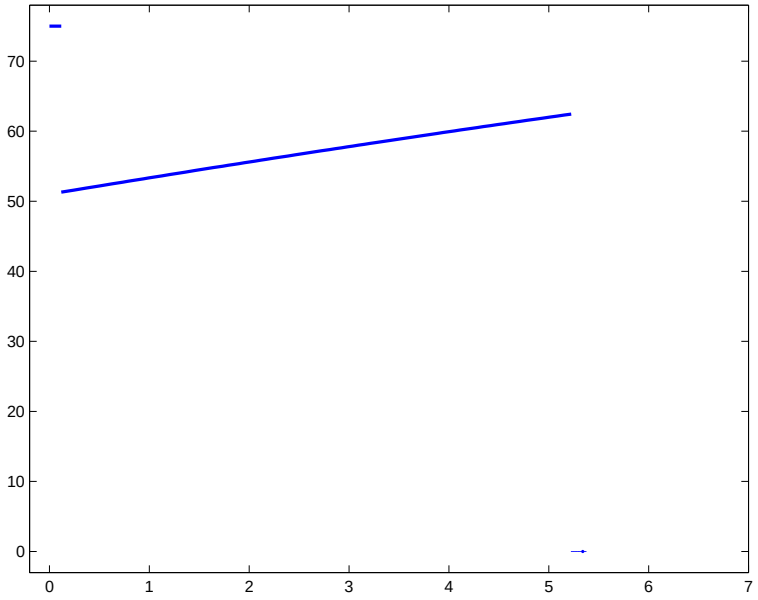

Figure 4: Optimal control for model (A) for $p_0 = 9,000\ mm^3$ and $q_0 = 10,000\ mm^3$

arc is the key to a full synthesis of optimal trajectories [20] and this synthesis, which qualitatively is identical with the one of model (A), is shown in Fig. 6. Fig. 7 gives the optimal control for initial conditions $p_0 = 9,000\ mm^3$ and $q_0 = 6,000\ mm^3$. The control is of type **as0** and the switchings times are $t_1 = .9663$ (days), $t_2 = 5.6061$ and the final time is given by $T = 9.8590$ with minimum value $p_{\min} = 1519.1$. Contrary to model (A) here the q-dynamics is slower, the main reason behind this modification, and thus the times along the constant controls $u = a$ and $u = 0$ are much more pronounced. The optimal singular control is quite similar in shape to the one for model (A).

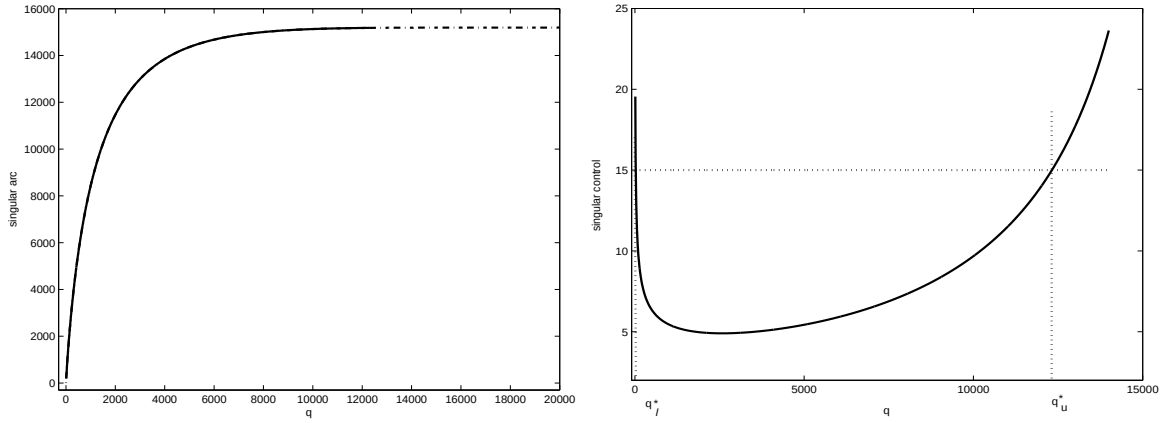

Figure 5: Model (C)-the singular curve, its admissible portion and the singular control

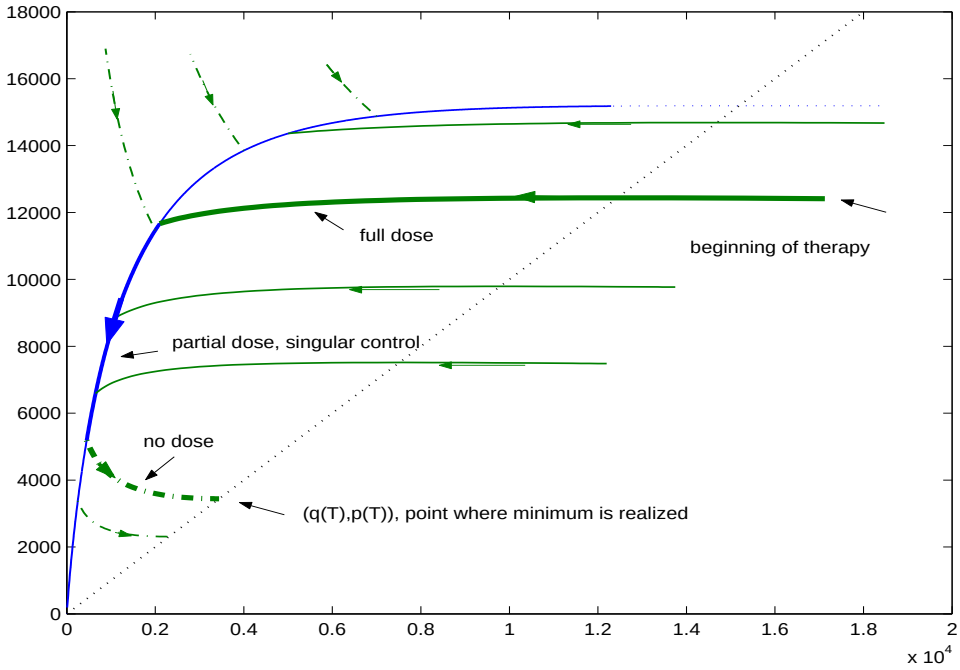

Figure 6: A synthesis of optimal controlled trajectories for model (C)

7 Optimal Controls for Models with Generalized Logistic Growth Function

We now consider the case of a generalized logistic growth function F given by $F(x) = 1 - x^\theta$ with θ a positive constant. In this case we have

$$xF'(x) = -\theta x^\theta, \qquad xF'(x) + x^2F''(x) \equiv -\theta^2 x^\theta \tag{61}$$

and thus

$$[f,g](z) = G\begin{pmatrix} \xi\theta p x^\theta \\ \mathcal{L}(\Delta)(p,q) \\ 0 \end{pmatrix}, \qquad [g,[f,g]](z) = -G^2\begin{pmatrix} -\xi\theta^2 p x^\theta \\ \mathcal{L}^2(\Delta)(p,q) \\ 0 \end{pmatrix}. \tag{62}$$

Hence

$$\lambda(t)[g,[f,g]](z(t)) = G^2\left[\lambda_1(t)\xi\theta^2 p x^\theta - \lambda_2(t)\mathcal{L}^2(\Delta)(p(t),q(t))\right].$$

Along the singular arc we have that

$$0 = \lambda(t)[f,g](z(t)) = G\left[\lambda_1(t)\xi\theta p x^\theta + \lambda_2(t)\mathcal{L}(\Delta)(p(t),q(t))\right]$$

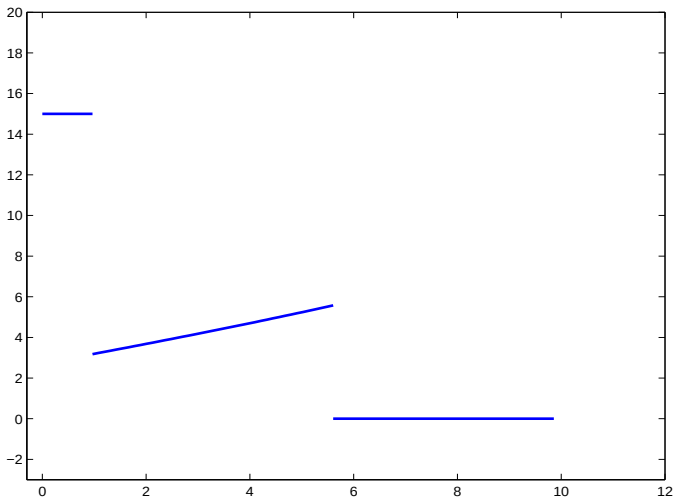

Figure 7: Optimal control for model (C) for $p_0 = 9,000\ mm^3$ and $q_0 = 6,000\ mm^3$

and thus the strengthened Legendre-Clebsch condition simplifies to

$$\begin{aligned}\lambda(t)[g,[f,g]](z(t)) &= G^2\left[-\theta\lambda_2(t)\mathcal{L}(\Delta)(p(t),q(t)) - \lambda_2(t)\mathcal{L}^2(\Delta)(p(t),q(t))\right] \\ &= -\lambda_2(t)G^2\left\{\theta\mathcal{L}(\Delta) + \mathcal{L}^2(\Delta)\right\}(p(t),q(t)). \end{aligned} \tag{63}$$

We thus have the following result:

Theorem 2 *Let the growth of the primary tumor volume be modelled by a generalized logistic growth function, $F(x) = 1 - x^\theta$, $\theta > 0$, and suppose a control u_* is singular on some open interval (α, β). Then the strengthened Legendre-Clebsch condition is satisfied on (α, β) if and only if the operator $\theta\mathcal{L}(\Delta) + \mathcal{L}^2(\Delta)$ is positive along the singular arc,*

$$\theta\mathcal{L}(\Delta)(p(t),q(t)) + \mathcal{L}^2(\Delta)(p(t),q(t)) > 0. \tag{64}$$

In this case the singular curve $\mathcal{S}$ is locally minimizing for problem [OC]. ■

Model (A) [15]. It follows from our earlier computations that

$$\theta\mathcal{L}(\Delta) + \mathcal{L}^2(\Delta) = \theta\,(-S) + S = (1-\theta)\,S$$

and thus the strengthened Legendre condition is satisfied for $\theta < 1$ and violated if $\theta > 1$. The limiting behavior $\theta = 1$ is when the convexity properties of the growth function change from strictly convex ($\theta < 1$) to strictly concave ($\theta > 1$) and thus *singular arcs are locally minimizing when the growth function is strictly convex and locally maximizing when the growth function is strictly concave*. We shall

see a repetition of this behavior in section 8 below where we investigate the optimality of singular arcs for model (A) with an arbitrary growth function. It will also be shown there that no singular arcs exist for the bifurcation value $\theta = 1$, the case of classical logistic growth.

Model (C) [11]. For this model we have that

$$\theta\mathcal{L}(\Delta) + \mathcal{L}^2(\Delta) = -\frac{\theta}{3}(S+I) + \frac{1}{9}(S-I) \tag{65}$$

$$= \frac{1}{9}S(1-3\theta) - \frac{1}{9}I(1+3\theta) \tag{66}$$

and for a general value of θ this condition is not conclusive. However, if $\theta > \frac{1}{3}$, then this quantity is negative and thus the strengthened Legendre-Clebsch condition is violated, i.e., singular arcs are not optimal in these cases. In particular, they are not optimal for classical logistic growth.

8 General Tumor Growth Models with Dynamics (A)

As the examples in section 6 show the existence of a locally optimal singular arc is the determining factor in a synthesis of optimal controlled trajectories. In this section we investigate the status of singular controls for the dynamics originally chosen in [15] for the endothelial support with a general growth function F modeling the tumor growth. Recall that for model (A) we have $\mathcal{L}(\Delta) = -S$ and $\mathcal{L}^2(\Delta) = S$ and thus the Lie brackets simplify to

$$[f,g](z) = -Gp\begin{pmatrix} \xi x F'(x) \\ b \\ 0 \end{pmatrix} \quad \text{and} \quad [g,[f,g]](z) = -G^2p\begin{pmatrix} \xi\left[xF'(x) + x^2F''(x)\right] \\ b \\ 0 \end{pmatrix}. \tag{67}$$

If u_* is a singular control on an open interval (α,β), then $\dot{\Phi}(t) = \lambda(t)[f,g](z(t)) = 0$ implies that

$$\lambda_1(t)\xi x(t)F'(x(t)) + \lambda_2(t)b \equiv 0. \tag{68}$$

It follows from Lemma 3 that λ_2 is positive and F' is negative since F is strictly decreasing. Hence λ_1 is positive on J. Furthermore,

$$\lambda(t)[g,[f,g]](z(t)) = -G^2p(t)\left[\lambda_1(t)\xi x(t)F'(x(t)) + \lambda_2(t)b\right] - G^2p(t)\lambda_1(t)\xi x^2(t)F''(x(t))$$

$$= -G^2\xi\lambda_1(t)p(t)x^2(t)F''(x(t)) \tag{69}$$

and thus $\lambda(t)[g,[f,g]](z(t))$ has the opposite sign as $F''(x(t))$. Therefore the strengthened Legendre Clebsch condition for minimization is satisfied over the interval (α,β) if and only if F is strictly convex on (α,β) and it is violated if and only if F is strictly concave. Since singular arcs that satisfy the strengthened Legendre conditions are locally minimizing, respectively maximizing if this quantity is positive, we have the following result:

Theorem 3 *Consider model (A) for the q-dynamics,*

$$\dot{q} = bp - \left(\mu + dp^{\frac{2}{3}}\right) q - Guq,$$

with a general growth function $F : (0, \infty) \to \mathbb{R}$, $x \mapsto F(x)$, for the primary tumor volume, Suppose F satisfies the conditions (F), that is F is twice continuously differentiable, strictly decreasing and satisfies $F(1) = 0$. Then a singular control is locally minimizing in regions where F is strictly convex, locally maximizing where F is strictly concave. □

Examples of functions F that are always strictly convex are the Gompertzian growth, $F(x) = -\ln x$, considered above, but also generalized logistic growth, $F(x) = 1 - x^\theta$, for $\theta < 1$. However, as already shown for $\theta > 1$ this function is concave and now singular arcs are maximizing. Thus $\theta = 1$ is the bifurcation value at which singular arcs change from locally minimizing to maximizing and we still show that no singular arcs exist for this value. For this purpose, more generally we compute the singular curve $\mathcal{S}$ for model (A). As before, this is the locus where f and the Lie-bracket $[f, g]$ are parallel, i.e.,

$$\begin{aligned} 0 &= \begin{vmatrix} \xi p F(x) & \xi x F'(x) \\ bp - \left(\mu + dp^{\frac{2}{3}}\right) q & b \end{vmatrix} \\ &= \xi p \begin{vmatrix} F(x) & F'(x) \\ bx - \left(\mu + dp^{\frac{2}{3}}\right) & b \end{vmatrix} \\ &= \xi p \left[b\left(F(x) - xF'(x)\right) + \left(\mu + dp^{\frac{2}{3}}\right) F'(x) \right]. \end{aligned}$$

Thus the singular curve $\mathcal{S}$ is given by the solutions to (also see (55)),

$$\mu + dp^{\frac{2}{3}} = b\left(x - \frac{F(x)}{F'(x)}\right). \tag{70}$$

For classical logistic growth, $F(x) = 1 - x$, we have

$$x - \frac{F(x)}{F'(x)} \equiv 1$$

and therefore the only solution to this equation is the equilibrium point $(\bar{p}, \bar{q})$ of the uncontrolled system, $\bar{p} = \left(\frac{b-\mu}{d}\right)^{\frac{3}{2}}$. Hence no singular curve exists for this case. This is also shown by A. Swierniak in [33].

9 Conclusion

In this paper we formulated a meta-system representing a class of mathematical models for tumor anti-angiogenesis with a general general growth function F on the tumor volume and arbitrary models for stimulation and inhibition terms. We considered the problem to administer a given amount of angiogenic

inhibitors in order to maximize the possible tumor reduction achievable as an optimal control problem. Both general properties of the optimal solution were established and more specific results for special cases of the models were given. A simple, but general formalism was developed that allows for quick determinations of the local optimality of singular arcs. This is of interest since it is precisely the local optimality status of these singular arcs that determines the structure of an optimal synthesis of controls and trajectories. We gave two examples of such syntheses with analytically calculated formulas for singular controls and corresponding singular arcs. More generally, we showed that the optimality of singular arcs for some models (for example, the original model by Hahnfeldt et al.) and their absence in the synthesis for others (the model by Hahnfeldt et al., but with logistic growth) depends on convexity properties of the function describing the tumor growth. Overall, the analysis presented here provides a theoretical background that explains various phenomena observed in particular models considered before and, for other models that share the same general characteristics, it provides information about the qualitative structure of their solutions without a need for a detailed separate analysis.

It is particularly of interest if these solutions contain feedback type controls, like the singular controls under investigation here. These controls represent protocols that would administer time varying partial doses and for obvious reasons are not yet implementable in practice. On the other hand, the calculated theoretically optimal controls provide benchmarks for construction of excellent suboptimal protocols of constant doses which are easily implemented. For models (A) and (C) with a Gompertzian growth function this aspect has been investigated in [24] and, for example, it has been shown that the controls that administer the available inhibitors at a constant dosage given by the averaged values of the optimal controls are excellent suboptimal protocols, better than simple ad-hoc full dose strategies. Singular controls, although they require complicated mathematical considerations, give optimal protocols which could never be found on a trial and error basis, neither clinically or as an outcome of numerical simulations, and provide valuable information in the design of realizable therapy scheduling.

References

[1] Z. Agur, L. Arakelyan, P. Daugulis and Y. Ginosar, Hopf point analysis for angiogenesis models, *Discrete and Continuous Dynamical Systems, Series B*, **4**, no. 1, (2004), pp. 29-38

[2] A. Anderson and M. Chaplain, Continuous and discrete mathematical models of tumor-induced angiogenesis, *Bull. Math. Biol.*, **60**, (1998), pp. 857ff

[3] B. Bonnard and M. Chyba, *Singular Trajectories and their Role in Control Theory*, Springer Verlag, Series: Mathematics and Applications, Vol. 40, 2003

[4] A. Bressan and B. Piccoli, *Introduction to the Mathematical Theory of Control*, American Institute of Mathematical Sciences, 2007

[5] A.E. Bryson and Y.C. Ho, *Applied Optimal Control*, Hemisphere Publishing, 1975

[6] F. Castiglione and B. Piccoli, Optimal control in a model of dendritic cell transfection cancer immunotherapy, *Bulletin of Mathematical Biology*, **68**, (2006), pp. 255-274

[7] L.G. de Pillis and A. Radunskaya, A mathematical tumor model with immune resistance and drug therapy: an optimal control approach, *J. of Theoretical Medicine*, **3**, (2001), pp. 79-100

[8] A. d'Onofrio, A general framework for modeling tumor-immune system competition and immunotherapy: mathematical analysis and biomedical inferences, *Physica D*, **208**, 2005, pp. 220-235

[9] A. d'Onofrio and A. Gandolfi, Tumour eradication by antiangiogenic therapy: analysis and extensions of the model by Hahnfeldt et al. (1999), *Math. Biosci.*, **191**, (2004), pp. 159-184

[10] M. Eisen, *Mathematical Models in Cell Biology and Cancer Chemotherapy*, Lecture Notes in Biomathematics, Vol. 30, Springer Verlag, (1979)

[11] A. Ergun, K. Camphausen and L.M. Wein, Optimal scheduling of radiotherapy and angiogenic inhibitors, *Bull. of Math. Biology*, **65**, (2003), pp. 407-424

[12] K. R. Fister and J.C. Panetta, Optimal control applied to cell-cycle-specific cancer chemotherapy, *SIAM J. Appl. Math.*, **60**, (2000), pp. 1059-1072

[13] U. Forys, Y. Keifetz and Y. Kogan, Critical-point analysis for three-variable cancer angiogenesis models, *Mathematical Biosciences and Engineering*, **2**, no. 3, (2005), pp. 511-525

[14] H. Gardner-Moyer, Sufficient conditions for a strong minimum in singular control problems, *SIAM J. Control*, **11**, (1973), pp. 620-636

[15] P. Hahnfeldt, D. Panigrahy, J. Folkman and L. Hlatky, Tumor development under angiogenic signaling: a dynamical theory of tumor growth, treatment response, and postvascular dormancy, *Cancer Research*, **59**, (1999), pp. 4770-4775

[16] R.S. Kerbel, A cancer therapy resistant to resistance, *Nature*, **390**, (1997), pp. 335-336

[17] A. Krener, The high-order maximal principle and its application to singular controls, *SIAM J. Control and Optimization*, **15**, (1977), pp. 256-293

[18] U. Ledzewicz and H. Schättler, Optimal bang-bang controls for a 2-compartment model in cancer chemotherapy, *Journal of Optimization Theory and Applications - JOTA*, **114**, (2002), pp. 609-637

[19] U. Ledzewicz and H. Schättler, Optimal control for a bilinear model with recruiting agent in cancer chemotherapy, Proceedings of the 42nd IEEE Conference on Decision and Control (CDC), Maui, Hawaii, December 2003, pp. 2762-2767

[20] U. Ledzewicz and H. Schättler, A synthesis of optimal controls for a model of tumor growth under angiogenic inhibitors, Proceedings of the *44th IEEE Conference on Decision and Control (CDC)* and *European Control Conference ECC'05*, Sevilla, Spain, December 2005, pp. 934-939

[21] U. Ledzewicz and H. Schättler, On a class of systems describing tumor anti-angiogenesis under Gompertzian growth, *WSEAS Transactions on Systems*, **4**, No.6, (2007), pp. 758-766

[22] U. Ledzewicz and H. Schättler, Anti-angiogenic therapy in cancer treatment as an optimal control problem, *SIAM J. on Control and Optimization*, **46**, (2007), pp. 1052-1079.

[23] U. Ledzewicz and H. Schättler, Analysis of a mathematical model for tumor anti-angiogenesis, *Optimal Control Appl. and Methods*, **29**, (1), (2008), pp. 41-57

[24] U. Ledzewicz and H. Schättler, Optimal and suboptimal protocols for a class of mathematical models of tumor anti-angiogenesis, *J. of Theoretical Biology*, **252**, (2008), pg. 295-312

[25] U. Ledzewicz and H. Schättler, Effect of the objective on optimal controls for a system describing tumor anti-angiogenesis, *Proceedings of the WSEAS Conference on Systems*, July 2008, Heraklion, Greece, to appear

[26] H. Maurer, C. Büskens, J.-H. Kim and Y. Kaja, Optimization techniques for the verification of second-order sufficient conditions for bang-bang controls, *Optimal Control, Applications and Methods*, **26**, (2005), pp. 129-156

[27] L.S. Pontryagin, V.G. Boltyanskii, R.V. Gamkrelidze and E.F. Mishchenko, *The Mathematical Theory of Optimal Processes*, MacMillan, New York, (1964)

[28] R.K. Sachs, L.R. Hlatky and P. Hahnfeldt, Simple ODE models of tumor growth and anti-angiogenic or radiation treatment, *Math. Comput. Mod.*, **33**, (2001), pp. 1297ff

[29] G. Stefani, On sufficient optimality conditions for singular extremals, Proceedings of the *42nd IEEE Conference on Decision and Control (CDC)*, Maui, Hi, USA, December 2003, pp. 2746-2749

[30] G.W. Swan, Role of optimal control in cancer chemotherapy, *Math. Biosci.*, **101**, (1990), pp. 237-284

[31] A. Swierniak, A. Polanski and M. Kimmel, Optimal control problems arising in cell-cycle-specific cancer chemotherapy, *Cell prolif.*, **29**, (1996), pp. 117-139

[32] A. Swierniak, G. Gala, A. Gandolfi and A. d'Onofrio, Optimization of angiogenic therapy as optimal control problem, Proceedings of the 4th IASTED Conference on Biomechanics, Acta Press, (Ed. M. Doblare), (2006), pp. 56-60

[33] A. Swierniak, Comparison of control theoretic properties of models of antiangiogenic therapy, Proceedings of the 6th International IASTED Conference on Biomedical Engineering, Acta Press, (2008), pp. 156-160