Realizable protocols for optimal administration of drugs in mathematical models for anti-angiogenic treatment

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May 1, 2009

Abstract

Two mathematical models for tumor anti-angiogenesis, one originally formulated by Hahnfeldt, Panigrahy, Folkman and Hlatky (1999) and a modification of this model by Ergun, Camphausen and Wein (2003), are considered as optimal control problem with the aim of maximizing the tumor reduction achievable with an a priori given amount of angiogenic agents. For both models, depending on the initial conditions, optimal controls may contain a segment along which the dosage follows a so-called singular control, a time-varying feedback control. In this paper, for these cases the efficiency of piecewise constant protocols with a small number of switchings is investigated. Through comparison with the theoretically optimal solutions, it will be shown that these protocols provide generally excellent suboptimal strategies that for many initial conditions come within a fraction of 1% of the theoretically optimal values. When the duration of the dosages are a priori

restricted to a daily or semi-daily regimen, still very good approximations of the theoretically optimal solution can be achieved.

keywords: biomathematical modeling, optimal control, tumor anti-angiogenesis, realizable protocols

1 Introduction

Tumor anti-angiogenesis is a novel cancer treatment approach that aims at depriving a growing tumor of the blood vessel network it needs for growth (e.g., Kerbel, 2000). Initially, a growing tumor gets sufficient supply of oxygen and nutrients from the surrounding host blood vessels to allow cell duplication and tumor growth. However, after the avascular growth is over, at the size of about $1-3$ mm in diameter, this is no longer true and most tumor cells enter the dormant stage in the cell cycle. These cells then produce vascular endothelial growth factor (VEGF) to start the process of *angiogenesis* (Folkman, 1972) to recruit surrounding, mature, host blood vessels in order to develop the capillaries the tumor needs for its supply of nutrients. The lining of these newly developing blood vessels consist of endothelial cells that are stimulated by VEGF (Klagsburn and Soker, 1993). Surprisingly, the tumor also produces inhibitors that at times are used to suppress angiogenesis (Folkman, 1995). Anti-angiogenic treatments rely on these mechanisms by bringing in external anti-angiogenic agents (e.g., endostatin) that interfere with the pro-angiogenic actions of growth factors like VEGF. This indirectly effects the tumor which, ideally, deprived of necessary nutrition, regresses. Contrary to traditional chemotherapy, this treatment targets genetically stable normal cells and not the genetically unstable and fast duplicating cancer cells. It has been observed that no resistance to the angiogenic agents has developed in experimental cancer (Boehm et al., 1997). For this reason, tumor anti-angiogenesis has been called a therapy "resistant to resistance" that provides a new hope for the treatment of tumor type cancers (Kerbel, 1997). Naturally, as such it has been an active area of research in the last ten years not only in medicine, but also in related disciplines including mathematical biology.

Models for tumor anti-angiogenesis can broadly be divided into two groups: those that try to accurately reflect the biological processes, (e.g., Chaplain and Anderson, 1997, Anderson and Chaplain, 1998, Anderson et al., 2000, Arakelyan et al., 2003,) and those that aggregate variables into low-dimensional dynamical systems, (e.g., Hahnfeldt et al., 1999, Ergun et al., 2003, d'Onofrio and Gandolfi, 2004, 2006). While the former allow for realistic large scale simulations, the latter enable a theoretical mathematical analysis. A distinctive place among the second group is taken up by the model proposed by Hahnfeldt, Panigrahy, Folkman and Hlatky (1999), a group of researchers then at Harvard Medical School. Modelling the tumor as a sphere and analyzing the underlying consumption-diffusion process theoretically, in this research 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, was developed and biologically validated. The

carrying capacity is the maximum tumor volume sustainable by the vasculature. Since it largely depends on the volume of the endothelial cell population, we also call q the endothelial support of the tumor for short. Several modifications of this model have been introduced and analyzed in the literature since then, the principal ones are those considered by Ergun, Camphausen and Wein from the National Cancer Institute in the U.S., (2003), and by d'Onofrio at the European Institute of Oncology in Milan and Gandolfi at National Research Council in Rome, (2004). The model considered by d'Onofrio and Gandolfi is fully consistent with the modelling implications derived by Hahnfeldt et al., (1999), but both models share the common feature that the dynamics for the endothelial support reaches its steady state very fast. For this reason, Ergun et al., (2003), modified the dynamics for the endothelial support so that the stimulation by the tumor is only proportional to the tumor radius, not its surface area as it is the case for the other two models. Besides these variations in the dynamics for the carrying capacity, also various growth models for the primary tumor volume have been considered. These range from the Gompertzian dynamics originally chosen by Hahnfeldt et al., (1999), to classical and generalized logistic growth (e.g., d'Onofrio and Gandolfi, 2004, Swierniak et al., 2006, Swierniak, 2008, Ledzewicz and Schättler, 2009) to the analysis of growth functions that only satisfy some general convexity properties (Ledzewicz et al., 2009). More general structures of the dynamics with only qualitative growth assumptions have been analyzed by Agur et al., (2004), and Forys et al., (2005).

In various papers (e.g., Ergun et al., 2003, Swierniak et al., 2006, Ledzewicz and Schättler, 2007, 2008a) the problem of scheduling angiogenic agents for these models has been analyzed as an optimal control problem: given an a priori specified amount of angiogenic agents, how should they be scheduled in order to minimize the tumor volume p? Using methods of geometric optimal control we gave complete theoretical solutions to this problem for the original model by Hahnfeldt et al. (Ledzewicz and Schättler, 2007), for the model considered by d'Onofrio and Gandolfi (Ledzewicz and Schättler, 2008a) and for the modification by Ergun et al. (Ledzewicz and Schättler, 2005, 2009). Optimal controls for the model from d'Onofrio and Gandolfi (2004) give all available anti-angiogenic agents in one stretch at maximum dose and thus correspond to a typical medical application scheme. But for the original model formulated by Hahnfeldt et al., (1999) and its modification by Ergun et al., (2003), the optimal solution typically contains a segment along which the control is singular and is given by a time-varying feedback control depending on the actual states $p(t)$ and $q(t)$ of the system. Clearly, with the current state of medical technologies such a control is not realistic. Thus the question arises how close to the optimal solution one can come with some simple, piecewise constant, and hence realizable strategies. The value of knowing the theoretically optimal solution lies in the fact that it provides the benchmark to judge the quality of heuristically chosen simple strategies and protocols. Ledzewicz and Schättler, (2008b), already started looking into this question and, for example, showed that a predetermined maximum dose is not necessarily a good strategy, but that a constant dosage equal to the averaged value of the optimal dosages provides an excellent sub-optimal strategy. Essentially, the simulations by Ledzewicz

and Schättler, (2008b), show that for a constant dosage that is too low no positive effect is achieved while the decrease in the tumor volume that can be achieved with a very high dose becomes marginal. Thus, given a specified amount of agents to be administered, too high a dose unnecessarily wastes inhibitors that can be used more effectively at lower dosages over a larger time-interval. Hence the question arises what are good, simple, and realistic strategies to administer the anti-angiogenic agents.

In this paper, expanding the discussion in the brief communication by Ledzewicz et al., (2008), we optimize treatment protocols over some simple classes of piecewise constant treatment functions and compare their effectiveness for the models by Hahnfeldt et al. (1999), and Ergun et al. (2003). It will be shown that these easily computable strategies which divide the overall amount of anti-angiogenic agents to be given into a small number of constant dose intervals generally come within 1% of the theoretically optimal values for realistic initial conditions. The times of administering a specific dosage are included as variables in this optimization and thus become a part of the solution. We also consider the case when these times are fixed a priori (e.g., there is an 8 hour period when agents are administered followed by a 16 hour rest-period). Naturally, due to the resulting lack of freedom, these strategies do worse, but they still come reasonably close to the theoretically optimal values. While it is not difficult to compute these constant dosages, it is only the knowledge of the theoretically optimal solution that allows to judge their quality. The main conclusion of this paper thus is that *simple, piecewise constant, and hence realistic protocols can be found that come very close to the theoretically optimal solution.* The numerical computations detailed in this paper illustrate this relationship for fixed values of parameters over a certain range of initial conditions for two mathematical models. While the used parameter values are based on the medical literature (Hahnfeldt et al., 1999), clearly this is only intended as a mathematical illustration. However, and inherently this is due to dynamical properties of the system that defines the models under consideration, our main conclusion not only seems to be generally valid for a wide range of initial conditions, but is also fully robust with respect to realistic changes in the parameters.

2 A Mathematical Model for Tumor Anti-Angiogenesis (Hahnfeldt et al., 1999)

This mathematical model was developed and biologically validated by Hahnfeldt, Panigrahy, Folkman and Hlatky (1999) and, as already stated, its principal variables are the primary tumor volume, p, and the carrying capacity of the vasculature, q; that is, the maximum tumor volume sustainable by the vasculature. The dynamics describes the time evolution of these quantities. Tumor growth is modelled by a Gompertzian growth function with variable carrying capacity q, i.e., the rate of change in the volume of primary tumor cells is given by

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

where ξ denotes a tumor growth parameter. The dynamics of the endothelial support consists of a balance between stimulatory and inhibitory effects and is taken of the following form:

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

The term bp represents stimulation which is taken proportional to the tumor volume and the three terms with negative signs represent different types of inhibition. Loss of vascular support through natural causes (death of endothelial cells etc.) is modelled as μq. 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. The second term $dp^{\frac{2}{3}}q$ represents endogenous inhibition due to the fact that the tumor also produces inhibitors that impact its vascular support. These inhibitors are released through the tumor surface (hence the scaling of the tumor volume p to its surface area $p^{\frac{2}{3}}$) and interact with the endothelial cells that form the lining of the newly developing capillaries. The last term Guq models loss of vascular support due to outside anti-angiogenic agents and the variable u represents the control in the system. It corresponds to the angiogenic dose rate with G a constant that represents the anti-angiogenic killing parameter.

The problem which then arises naturally is *how to administer a given amount of angiogenic agents to achieve the "best possible" effect* and this leads to optimal control problems. One possible formulation, considered first by Ergun et al. (2003) and then taken up for this model and two modifications by Ledzewicz and Schättler (2005, 2007, 2008a, 2009) is to minimize the tumor volume or, equivalently, maximize the tumor reduction possible with the given amount of anti-angiogenic agents. We thus consider the following problem:

[H] For a free terminal time T, minimize the value

$$J(u) = p(T) \tag{3}$$

over all piecewise continuous functions u with values in the compact interval $[0, a]$, $u : [0, T] \to [0, a]$, that satisfy a constraint on the total amount of anti-angiogenic agents to be administered,

$$\int_0^T u(t)dt \leq A, \tag{4}$$

subject to the dynamics (1), (2) with initial conditions p_0 and q_0.

The upper limit a in the definition of the control set $U = [0, a]$ is a previously determined maximum dose at which agents can be given. Note that in this formulation the time T does not correspond to a therapy horizon, but instead, it is the time when the maximum tumor reduction is achieved. If all anti-angiogenic agents become exhausted at a time τ and $p(\tau) > q(\tau)$, then even for the control $u \equiv 0$ the tumor volume p will still decrease at times $t > \tau$ until the diagonal $p = q$ is reached. (Regardless of the control, the tumor volume decreases for $p > q$ and

increases for $p < q$.) In this sense the dynamics contains after effects and therefore, if $p(\tau) > q(\tau)$, then the optimal control ends with a segment $(\tau, T]$ where $u \equiv 0$.

Mathematically, it is more convenient to adjoin the constraint as a third variable and define the problem in $\mathbb{R}^3$ which overall leads to the following dynamical equations:

$$\dot{p} = -\xi p \ln\left(\frac{p}{q}\right), \qquad p(0) = p_0, \tag{5}$$

$$\dot{q} = bp - \left(\mu + dp^{\frac{2}{3}}\right) q - Guq, \qquad q(0) = q_0, \tag{6}$$

$$\dot{y} = u, \qquad y(0) = 0. \tag{7}$$

Naturally, from their definitions all state variables need to be positive. It was shown by d'Onofrio and Gandolfi (2004) that this condition is ensured by the dynamics and thus it need not be imposed as an explicit constraint.

Since we consider problem [H] for arbitrary initial conditions, in this formulation degenerate cases are included that we want to exclude for our analysis. These occur if the initial conditions (p_0, q_0) and the overall amount of anti-angiogenic agents A are such that it is not possible to reach the region $\{p > q\}$ where the tumor volume can be reduced. These initial conditions are heavily skewed towards the vascular support and are biologically not realistic. We refer the reader to Ledzewicz and Schättler (2007) for a detailed discussion of these cases, but here we simply assume that the initial data are *well-posed* in the sense that it is possible to lower the tumor volume below its initial condition p_0. In this case the terminal time T along an optimal solution is positive.

3 The Optimal Solution for Model [H]

Ledzewicz and Schättler (2007) gave a complete solution for the optimal control problem [H] in form of a *synthesis* of optimal controls. A synthesis provides a full "road map" to all optimal protocols depending on the initial condition in the problem, both qualitatively and quantitatively. We briefly summarize the general structure of optimal trajectories for this case and then proceed to a precise description of the optimal controls.

Theorem 1 *(Ledzewicz and Schättler, 2007) Given a well-posed initial condition (p_0, q_0), optimal controls are at most concatenations of the form* **0asa0** *where* **0** *denotes an interval along which the optimal control is given by a constant control $u = 0$, that is no anti-angiogenic agents are given,* **a** *denotes an interval along which the optimal control is given by the constant control $u = a$ at full dose, and* **s** *denotes an interval along which the optimal control follows a time-varying singular feedback control. This control is only optimal while the system follows a particular curve $\mathcal{S}$ in the (p, q)-space, the optimal singular arc. Depending on the initial condition (p_0, q_0), not all of these intervals need to be present in a specific solution. For the biologically most relevant initial conditions typically optimal controls have the form* **as0**.

Despite their name, singular controls and the corresponding singular trajectories are to be expected in a synthesis of optimal controls for a problem of the type [H] for nonlinear models (e.g., Bonnard and Chyba, 2003) and we briefly recall how they arise and their significance[1]: For our problem it follows from necessary conditions for optimality that optimal controls u_* minimize an expression H of the form $H = \Psi(t) + \Phi(t)u$ in u over the control set $[0, a]$ where Φ and Ψ are functions that depend on the corresponding trajectory and time-varying multipliers. Since this expression is linear in u, minimizing controls typically lie on the boundary of the control set and are given by the so-called bang controls $u = 0$ if $\Phi > 0$ and $u = a$ if $\Phi < 0$ (the $\mathbf{0}$ and $\mathbf{a}$ in Theorem 1). However, the possibility of an optimal control that takes values in the interior of the control set not only exists, but it even is quite likely. If no upper limit on the control were imposed, then this would indeed be the only option. For a minimizing control that takes values in the interior of the control set, we have $\frac{\partial H}{\partial u} = \Phi(t) \equiv 0$, the first-order necessary condition for a stationary point. For a generic, multi-control, optimal control problem, if the matrix $\frac{\partial^2 H}{\partial u^2}$ is nonsingular, then, by the implicit function theorem the equation $\frac{\partial H}{\partial u}(t, u) = 0$ can locally be solved for u as a function of t and this defines a so-called non-singular interior control. If, however, $\frac{\partial^2 H}{\partial u^2}$ is singular, bifurcations and other degeneracies are possible and there may or may not exist such a control. For problems that are linear in the controls, like the ones considered here, we trivially have $\frac{\partial^2 H}{\partial u^2} = 0$ and thus every interior control necessarily becomes 'singular' and a priori is a candidate for both minimizing as well as maximizing controls. Higher order necessary conditions for optimality, like the Legendre-Clebsch condition (see, e.g., Bryson and Ho, (1975), Bonnard and Chyba, (2003)), allow to distinguish them. In this case, in principle these singular controls (if they exist) can be computed by differentiating the function $\Phi = \frac{\partial H}{\partial u}$ in time until the control u, brought in by the dynamics, explicitly appears and then solving for u. Generally this defines a time-varying control that depends on the states and multipliers from the necessary conditions for optimality. At the same time, since all derivatives of Φ must vanish as well, extra requirements arise that in small dimensions confine the trajectories corresponding to singular controls to thin sets, an optimal singular arc in this example. This arc, however, if minimizing, provides the best possible path and therefore it is sought after by all other optimal trajectories. Hence, if they exist, singular controls and their trajectories lie at the heart of any solution to an optimal control problem. They correspond to the true minimizers, characteristic of the problem, while the bang controls are minimizers that are only brought in because we limit the size of the control. In this sense, the singular control and the geometry of the singular curve $\mathcal{S}$ are the most important part of the analysis of an optimal control problem and in order to construct a full synthesis of optimal solutions, the formulas for singular controls and corresponding

[1]Since knowledge of optimal control theory is not essential for this article, we only give a cursory overview, but refer the interested reader to some classical texts like Bryson and Ho, (1975), Fleming and Rishel, (1975), or some more recent introductory text like Bressan and Piccoli, (2007), for details. Also, the website http://www.scholarpedia.com/ provides a good starting point to explore the subject.

singular trajectories given below are essential. The derivation of these formulas can be found in Ledzewicz and Schättler (2007).

Theorem 2 *Using a blow-up of the form $x = \frac{p}{q}$, the singular curve $\mathcal{S}$ can be parameterized in the form*

$$\mu + dp^{\frac{2}{3}} = bx(1 - \ln x) \tag{8}$$

with $x \in (x_1^*, x_2^*)$ where x_1^* and x_2^* are the unique zeroes of the equation

$$\varphi(x) = \frac{b}{d}x(\ln x - 1) + \frac{\mu}{d} = 0 \tag{9}$$

and satisfy $0 < x_1^* < 1 < x_2^* < e$. The singular control keeps the system on the singular curve and is given as a feedback function of p and q or x in one of the following two equivalent forms,

$$u_{\sin}(t) = u_{\sin}(p(t), q(t)) = \frac{1}{G}\left(\xi \ln\left(\frac{p(t)}{q(t)}\right) + b\frac{p(t)}{q\,(t)} + \frac{2}{3}\xi\frac{d}{b}\frac{q(t)}{p^{\frac{1}{3}}(t)} - \left(\mu + dp^{\frac{2}{3}}(t)\right)\right) \tag{10}$$

or, using (8),

$$u_{\sin}(t) = u_{\sin}(x(t)) = \frac{1}{G}\left[\left(\frac{1}{3}\xi + bx(t)\right)\ln x(t) + \frac{2}{3}\xi\left(1 - \frac{\mu}{bx(t)}\right)\right]. \tag{11}$$

There exists exactly one connected arc on the singular curve $\mathcal{S}$ along which the singular control is admissible, i.e., satisfies the bounds $0 \le u_{\sin}(x) \le a$. This arc is defined over an interval $[x_\ell^*, x_u^*]$ where x_ℓ^* and x_u^* are the unique solutions to the equations $u_{\sin}(x_\ell^*) = 0$ and $u_{\sin}(x_u^*) = a$ and these values satisfy $x_1^* < x_\ell^* < 1 < x_u^* < x_2^*$.

The two graphs given in Fig. 1 illustrate the proposition for the following parameter values taken from Hahnfeldt et al. (1999): The variables p and q are volumes measured in mm^3; $\xi = \frac{0.192}{\ln 10} = 0.084$ *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*. For the control limits we have taken $a = 75$ *mg of dose per day* and $A = 300$ *mg*. Fig. 1(a) shows the plot for the singular control defined by (11) also indicating the values x_ℓ^* and x_u^* where the control saturates at $u_{\sin}(x) = 0$ and $u_{\sin}(x) = a$. Fig. 1(b) shows the graph of the singular curve given by formula (8). In all our figures we plot p vertically and q horizontally since this easier visualizes tumor reductions. Saturation of the singular control at x_ℓ^* and x_u^* restricts the admissible part of this petal-like curve to the portion lying between the lines $p = x_l^* q$ and $p = x_u^* q$. This portion is marked with a solid line in Fig. 1(b). The qualitative structures shown in these figures are generally valid for arbitrary parameter values, both for the control and the singular curve. Naturally, with decreasing values for the upper control limit a the admissible portion shrinks.

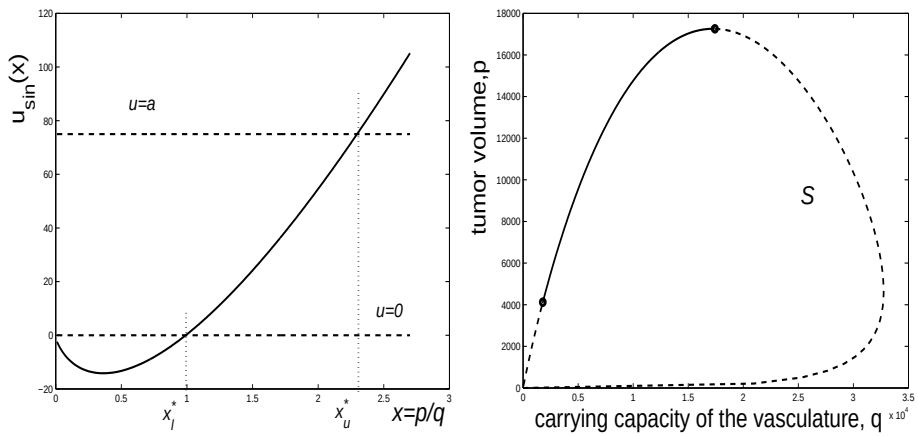

Figure 1: Singular control (a, left) and singular curve $\mathcal{S}$ with the admissible portion marked as a solid curve (b, right) for model [H]

The admissible singular arc becomes the center piece for the synthesis of optimal solutions that is depicted in Fig. 2. The important curves 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. This diagram represents 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 curves 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 anti-angiogenic agents 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. During this period the anti-angiogenic agents drive down the vascular support and in this way prevent a further growth of the tumor that otherwise, enabled by ample vascular support, would occur. Once the trajectory corresponding to the full dose hits the singular arc $\mathcal{S}$, it is no longer optimal to give full dose and the optimal controls here switch to the singular control. The optimal trajectory then follows the singular arc until all agents are exhausted. At this time therapy is over. But due to after effects the maximum tumor reduction is only realized as the trajectory for the control $u = 0$ crosses the diagonal $p = q$. The corresponding time then is the optimal free end-time T considered in the problem formulation $[H]$. We only remark that the scenario described here assumes that no saturation occurs along the singular arc. If that were the case, then optimal controls no longer follow the singular regimen until saturation, but in fact optimal trajectories leave the singular arc with the control $u = a$ prior to the saturation

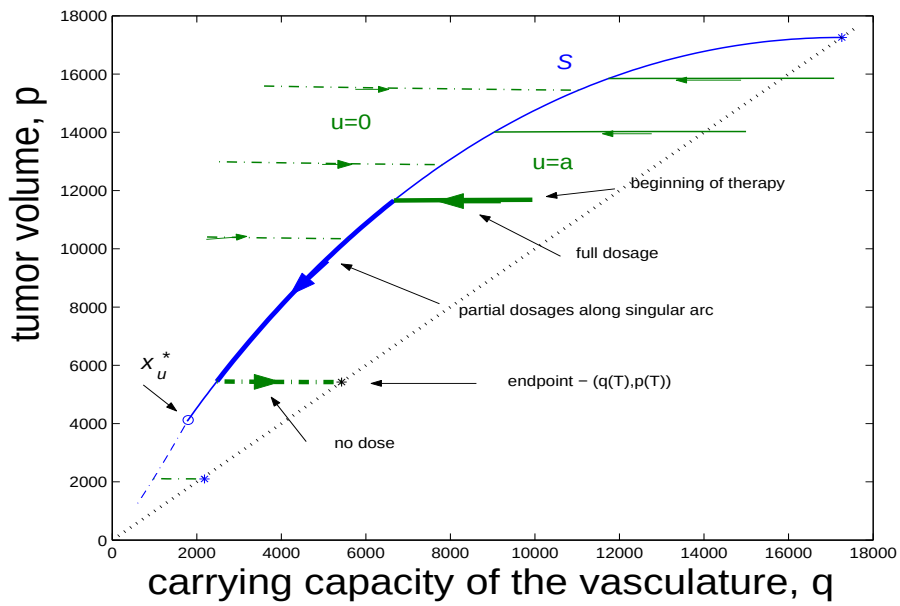

Figure 2: Synthesis of optimal trajectories for problem [H]: The thick curves mark one typical optimal trajectory of the form "as0". After following the maximum dose control $u = a$ until the singular arc $\mathcal{S}$ is reached, at that point the optimal control becomes singular and the trajectory follows the singular arc until all anti-angiogenic agents are exhausted. Due to after effects, the minimum tumor volume is only realized along a trajectory for $u = 0$ as the diagonal $p = q$ is crossed. The thin curves represent initial segments of optimal trajectories for other initial conditions.

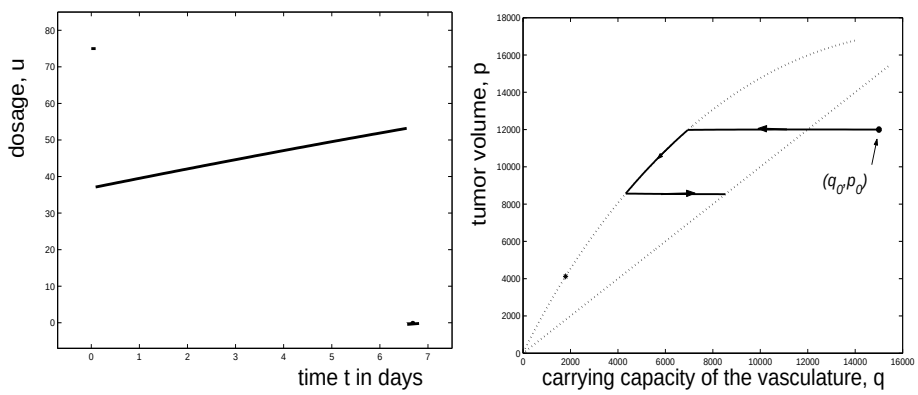

Figure 3: Optimal control (a, left) and corresponding trajectory (b, right) for problem [H] and initial conditions $(p_0, q_0) = (12,000\, mm^3; 15,000\, mm^3)$

point. Simply continuing the control with $u = a$ is not optimal (Ledzewicz and Schättler, 2007). Also, for initial conditions (p_0, q_0) with a small tumor volume (more precisely, initial conditions that lie below the backward orbit for the control $u = a$ through the saturation point (p_u^*, q_u^*) on the singular arc, labelled x_u^* in Fig. 2) the values for the singular control lie above the upper limit a and are no longer admissible. For these initial conditions the optimal controls do not contain a singular segment and are at most of the form **0a0**, i.e., give all available anti-angiogenic agents at maximum dose until they are exhausted. Clearly, in this case the optimal protocol is realizable and no additional considerations are needed. In this paper we therefore consider only initial conditions (p_0, q_0) for which the optimal control contains a singular portion.

Fig. 3 gives the optimal control (a, left) and its corresponding trajectory (b, right) for the initial conditions $(p_0, q_0) = (12,000\, mm^3; 15,000\, mm^3)$. For this initial condition the optimal concatenation sequence is **as0**: first the optimal control is given at full dosage $u = a = 75$ until the singular curve $\mathcal{S}$ is reached at time $t_1 = 0.091$ days. Then administration follows the time-varying singular control until the anti-angiogenic agents are exhausted at time $t_2 = 6.558$ days. Due to after effects the maximum tumor reduction is realized along a trajectory for control $u = 0$ at the optimal terminal time $T = 6.722$ days when the trajectory reaches the diagonal $p = q$. In the next section we will use these initial conditions to construct realizable protocols and compare their minimum values. The theoretically optimal minimum value for these data is given by $p_* = p(T) = 8533.38$. The numerical results for the various optimal and suboptimal protocols were obtained using the optimization toolbox of Matlab and the arc-parametrization method developed by Maurer et al. (2005).

4 Realizable Suboptimal Protocols for Problem [H]

In this section we now construct several suboptimal, piecewise constant controls - hence realizable protocols - for the same initial condition $(p_0, q_0) = (12,000, mm^3; 15,000\, mm^3)$ and compare the minimum values for these classes with the optimal one. We start with controls that give all available agents in one constant dosage. One way to approach the problem is to simply give the available amount A of anti-angiogenic agents at a constant dose u over time $t_u = \frac{A}{u}$ and to take as the dosage the value $\hat{u}$ that minimizes the values of the solutions $\hat{p}_u$ at the times t_u,

$$\hat{u} = \arg\min \hat{p}_u\left(t_u\right). \tag{12}$$

This is a straightforward one-dimensional numerical minimization problem and for the parameter values specified earlier the optimal dosage and the final time are given by

$$\hat{u} = 45.27 \quad t_u = A/\hat{u} = 6.626 \text{ days}. \tag{13}$$

However, this formulation is not fully consistent with the optimal control problem $[H]$ formulated above since the terminal values of the trajectories, $(\hat{p}_u\left(t_u\right), \hat{q}_u\left(t_u\right))$,

do not lie on the diagonal. For example, we have for the optimal value $\hat{u} = 45.27$ that $(\hat{p}_{\hat{u}}(t_{\hat{u}}), \hat{q}_{\hat{u}}(t_{\hat{u}})) = (8570.0, 4807.1)$. Since the carrying capacity is smaller than the tumor volume, there will still be an additional tumor reduction after the agents have all been exhausted. The amount of this reduction also depends on the value of the carrying capacity $\hat{q}_u(t_u)$ at the endpoint and this indeed slightly changes the value of the optimal dosage.

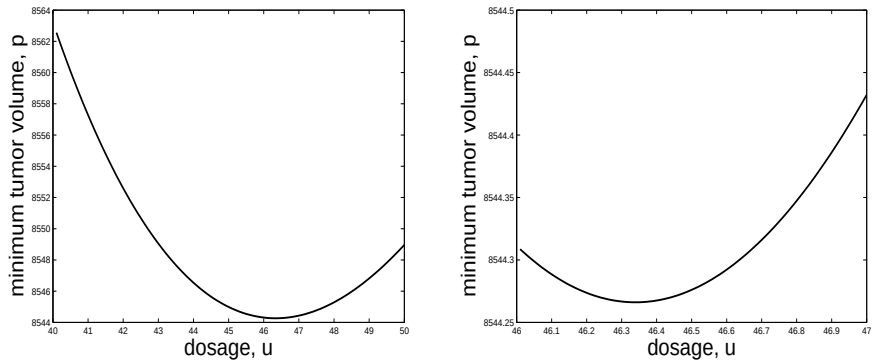

Figure 4: Graph of $\pi_u(T_u)$ over $[40, 50]$ (a, left) and a blow-up over $[46, 47]$ (b, right)

A formulation that is consistent with problem $[H]$ is to give all available anti-angiogenic agents at rate u over the interval $[0, \frac{A}{u}]$ and then still concatenate the trajectory at the point $(\hat{p}_u(t_u), \hat{q}_u(t_u))$ when all agents have been exhausted with a trajectory corresponding to the control $u = 0$. The minimum tumor volume then is realized as this trajectory crosses the diagonal at some time T_u and we denote this minimum tumor volume by $\pi_u(T_u)$. Minimizing over u gives the following optimal constant dosage,

$$u_* = \arg\min \pi_u(T_u) = 46.34, \tag{14}$$

and the minimal tumor volume is $p_* = 8544.15$. Fig. 4 gives the graph of the function $\pi_u(T_u)$ with a small interval around the optimal value blown up on the right. For comparison, if one still adds the $u = 0$ segment to the trajectory for $\hat{u} = 45.27$, then the corresponding value on the diagonal is slightly larger given by $\pi_{\hat{u}}(T_{\hat{u}}) = 8544.62$ with final time $T = 6.777$ days. Clearly, from a practical point of view there is no significant difference between these values and both are extraordinarily close to the theoretically optimal value 8533.38.

As another comparison, Ledzewicz and Schättler (2008b) also considered the constant dosage $\bar{u} = 45.75$ that was computed by averaging the theoretically optimal dosages over the time span of 6.558 days when drugs are administered (not including the final segment with $u = 0$). Such a dose can always be obtained as an immediate byproduct of the calculation of the optimal control. This gave the value

control	minimal value (mm^3)	terminal time (days)	switching time to $u = 0$ (days)
optimal	8533.38	6.722	6.558
$\bar{u} = 45.75$	8570.09	6.558	no switching
$\bar{u} = 45.75$	8544.30	6.709	6.558
$\hat{u} = 45.27$	8570.00	6.626	no switching
$\hat{u} = 45.27$	8544.62	6.777	6.626
$u_* = 46.34$	8544.15	6.626	6.474

Table 1: Comparison of minimal values for various constant dosage protocols for problem [H]. The control $\bar{u}$ is the averaged value of the optimal control for the given initial condition; $\hat{u}$ and u_*, respectively, denote the dosages that minimize the tumor volume over constant dose protocols, measured when all anti-angiogenic agents are exhausted and when the minimal tumor volume is realized.

$p_{\bar{u}} = 8570.09$. Adding the final segment $u = 0$ we get the minimum value 8544.30 with final time $T = 6.709$ days. Table 1 summarizes the numerical results.

Clearly, these constant dose protocols already provide excellent approximations to the theoretically optimal control. The value can still be improved upon by increasing the number of switchings in the control. Since the constant approximations already do so well, we only consider controls that have one switching, i.e., give a constant dose u_1 for time t_1 and then give a second constant dose u_2 for time t_2 where the second time is calculated so that all anti-angiogenic agents become exhausted, i.e.,

$$u_1 t_1 + u_2 t_2 = A. \tag{15}$$

Thus this is a 3-dimensional minimization problem with variables u_1, t_1, and u_2, and we denote this 3-tuple by v, $v = (u_1, t_1; u_2)$. As above, if we denote the point when the agents are exhausted by $(\hat{p}_v(t_v), \hat{q}_v(t_v))$ and the associated point on the diagonal by $\pi_v(T_v)$, then we can define controls $\hat{v}$ and v_* as the corresponding minimizers,

$$\hat{v} = \arg\min \hat{p}_v(t_v) \qquad \text{and} \qquad v_* = \arg\min \pi_v(T_v). \tag{16}$$

The optimal values for the same data and initial conditions specified earlier are summarized in Table 2. The dosages are close to each other, but their durations differ by quite a bit. However, this does not effect the minimum tumor volume much, although overall of course there is improvement in the sense that the difference to the optimal value is cut in half. But on an absolute scale the improvement is not important.

Figs. 5 and 6 give two graphs of the values $\pi_v(T_v)$ when the first and second dosages, respectively, are fixed at their optimal values, $u_1 = 42.47$ and $u_2 = 49.73$. Fig. 7 gives the graphs of the trajectories corresponding to the controls $\hat{v}$ and v_* while Fig. 8 compares the single-dose control u_* (in red) with the 2-stage control v_* (in blue). Consistent with dose intensification along the optimal singular control, these dosages increase: $u_2 > u_1$.

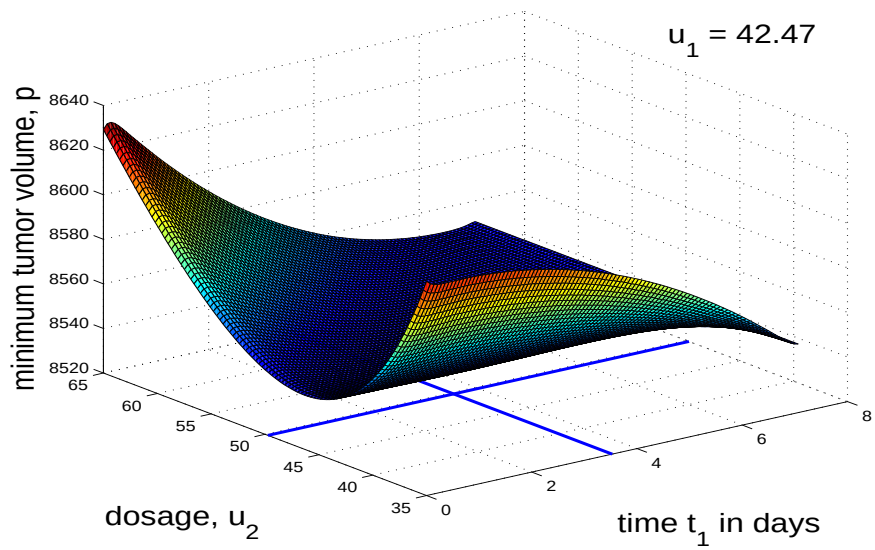

Figure 5: A cross section through the graph of $\pi_v(T_v)$ at $u_1 = 42.47$ for problem [H]

control	u_1	t_1 (days)	u_2	t_2 (days)	minimal value (mm^3)	terminal time (days)
optimal					8533.38	6.722
$\hat{v}$	41.83	2.931	47.20	3.758	8540.20	6.843
v_*	42.47	3.525	49.73	3.022	8539.21	6.736

Table 2: Comparison of minimal values for various 2-stage constant dosages protocols for problem [H]. The controls $\hat{v}$ and v_*, respectively, denote the dosages that minimize the tumor volume measured when all anti-angiogenic agents are exhausted and when the minimal tumor volume is realized.

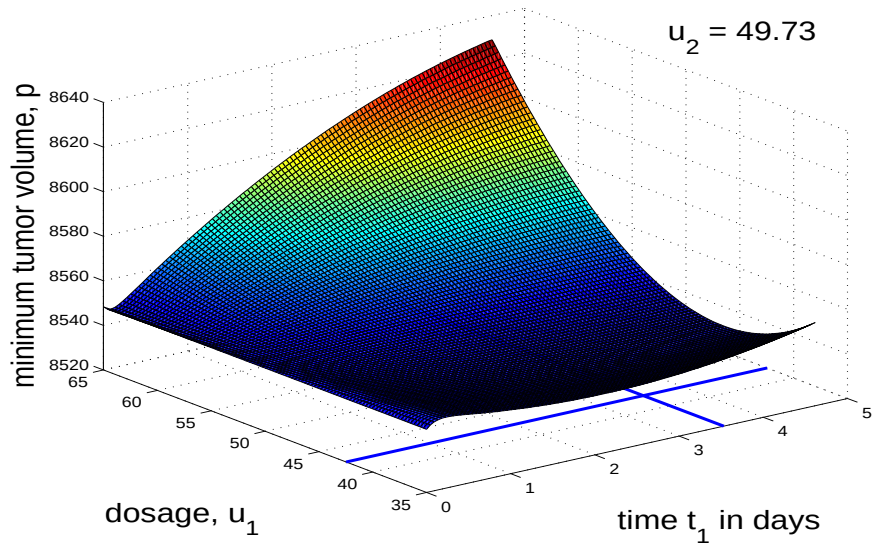

Figure 6: A cross section through the graph of $\pi_v(T_v)$ at $u_2 = 49.73$ for problem [H]

5 The Optimal Solution for Model [E]

Ergun, Camphausen and Wein (2003) modified the q-dynamics from Hahnfeldt et al. (1999) to

$$\dot{q} = bq^{\frac{2}{3}} - dq^{\frac{4}{3}} - Guq - \mu q, \tag{17}$$

with the same interpretation for the parameters. These endogenous inhibition and stimulation terms, $I(q) = dq^{\frac{4}{3}}$ and $S(q) = bq^{\frac{2}{3}}$, result in a significant mathematical simplification of the q-dynamics since they eliminate the tumor volume p from this equation. The argument for this change put forth by Ergun et al., (2003), is the differential-algebraic nature of the original model with a q-dynamics that reaches its steady-state extremely fast. With the proposed modification this no longer is the case and overall there is a better balance in the substitution of stimulation and inhibition. Since p and q tend to move together in steady state, and the steady state is what the model intends to capture, there is some justification to replace p with q in the q-dynamics and arrive at an equation of the form

$$\dot{q} = bq^{\gamma} - bq^{\gamma+\frac{2}{3}}$$

for the endogeneous inhibition and stimulation terms. A choice of $\gamma = 1$ in this sense would be consistent with the spatial analysis carried out by Hahnfeldt et al., (1999), while the choice $\gamma = \frac{2}{3}$ made by Ergun et al., (2003), is consistent with

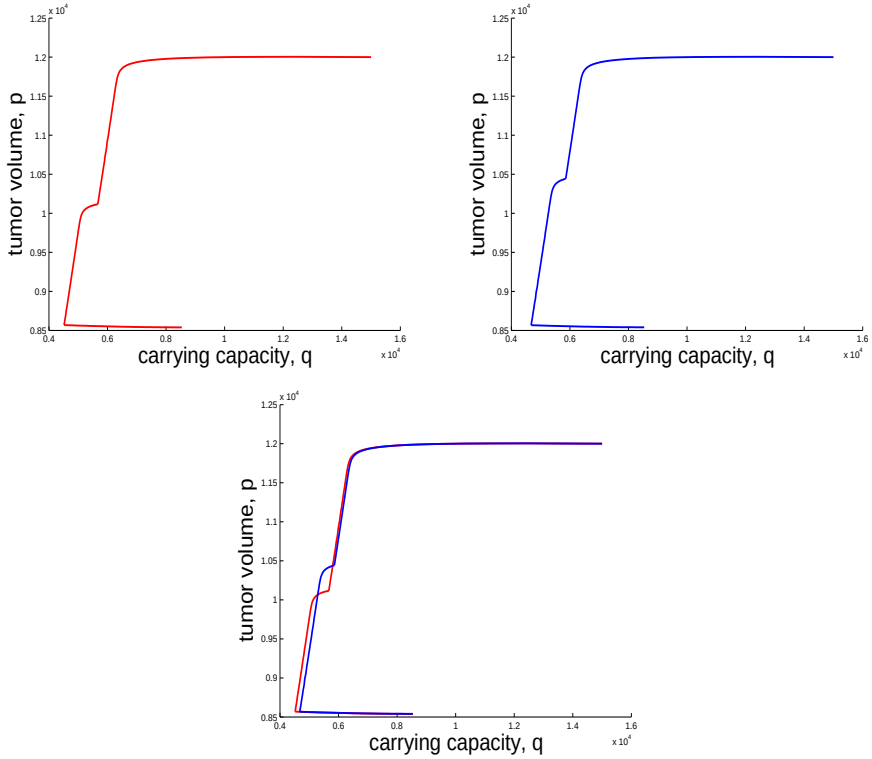

Figure 7: Trajectories for the control v_*, (a, top left), and $\hat{v}$ (b, top right) with comparison (c, bottom)

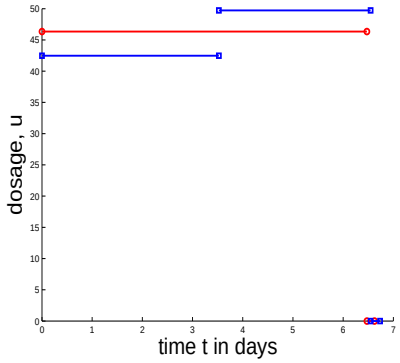

Figure 8: Sub-optimal controls u_* and v_* for problem [H]

the inhibition term being proportional to the tumor radius, not its surface area. If we replace the q-dynamics (2) with (17) to obtain problem formulation [**E**], then it turns out that the structure of optimal solutions indeed is qualitatively identical (Ledzewicz and Schättler, 2005, 2009). In fact, for this model Theorem 1 remains true verbatim. Thus, while clearly simplifying the dynamics, this modification does retain essential qualitative features of the original model. Of course, the quantitative formulas for the singular control and arc change and these are given below in Theorem 3.

Theorem 3 *There exists a locally minimizing singular arc $\mathcal{S}$ in (p,q)-space defined as a function of q over an interval $q_\ell^* \leq q \leq q_u^*$ by*

$$p_{\sin}(q) = q \exp\left(3\frac{b - dq^{\frac{2}{3}} - \mu q^{\frac{1}{3}}}{b + dq^{\frac{2}{3}}}\right). \tag{18}$$

The corresponding singular control is given in feedback form as

$$u_{\sin}(q) = \frac{1}{G}\left(\frac{b - dq^{\frac{2}{3}}}{q^{\frac{1}{3}}} + 3\xi\frac{b + dq^{\frac{2}{3}}}{b - dq^{\frac{2}{3}}} - \mu\right) \tag{19}$$

and the values q_ℓ^* and q_u^* are the unique solutions to the equation $u_{\sin}(q) = a$ in $(0, \sqrt{\left(\frac{b}{d}\right)^3})$. ■

The two graphs given in Fig. 9 illustrate the singular control and the geometry of the singular curve for this model and the same system parameter values considered before. Due to the changes in the dynamics, however, we now have taken $a = 15$ *mg of dose per day* and $A = 45$ *mg* for the control limits. In this case saturation of the singular control only occurs at the upper limit $u = a$ and restricts the admissible part to the interval $[q_\ell^*, q_u^*]$. This portion is marked as the solid curve in Fig. 9(b). The lower limit q_ℓ^* is so small that for all practical purposes this saturation can be ignored. Again, the qualitative structure shown in these figures is generally valid for arbitrary parameter values, both for the control and the singular curve. But in this case the admissible portion on the singular arc shrinks with decreasing values for the upper control limit a until it disappears for some low control limit a^* when the singular control no longer is admissible.

Like in the model by Hahnfeldt et al., (1999), the singular curve becomes the center piece of a synthesis of optimal controlled trajectories and this synthesis, shown in Fig. 10, is qualitatively identical with the previous one. Fig. 11 gives the optimal control and its corresponding trajectory for the initial conditions $(p_0, q_0) = (8,000\, mm^3; 10,000\, mm^3)$. For this initial condition the optimal concatenation sequence also is **as0**: the optimal control is given at full dosage $u = a = 15$ until the singular curve $\mathcal{S}$ is reached at time $t_1 = 1.341$ days. The administration then follows the time-varying singular control for $t_2 = 3.722$ days until all anti-angiogenic agents are exhausted after 5.062 days. Due to after effects the maximum tumor reduction is realized along a trajectory for control $u = 0$ at the optimal terminal time $T =$

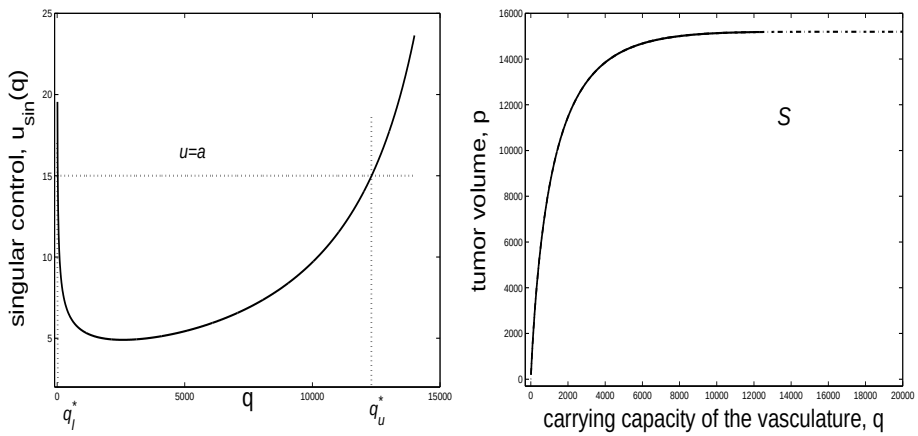

Figure 9: Singular control (a, left) and admissible portion of the singular arc (b, right) for problem [E]

9.378 days when the trajectory reaches the diagonal $p = q$. The theoretically optimal minimum value for these data is given by $p_* = p(T) = 2242.65$. Note the significantly longer pieces along the constant controls $u = a$ and $u = 0$ for this model, the effect desired in this modification of the original model.

6 Realizable Suboptimal Protocols for Problem [E]

We again consider piecewise constant controls for this initial condition $(p_0, q_0) = (8,000\, mm^3; 10,000\, mm^3)$ and compare the minimum values for these classes with the theoretically optimal value. Although the simulation is done for a different initial condition and the parameter values are not directly comparable because of the different q-dynamics, we shall see that the quality of approximations is equally excellent for this model. We again start with strategies that give the full amount A of anti-angiogenic agents at a constant rate and minimize the tumor volume achievable in this way. Here, since the deviations are minimal, we now only consider the optimal constant dose where a trajectory with the control $u = 0$ has been added to reach the diagonal, i.e., the control u_*. The best constant dosage is $u_* = 9.246$ and is given over $t_1 = 4.867$ days; then the control is still given by $u_* = 0$ for $t_2 = 4.735$ days until the minimum tumor volume is realized as the trajectory crosses the diagonal at the time $T = 9.602$ days. Fig. 12(a) shows the graph of the associated value function $\pi_u(T_u)$ for dosages lying between $u = 8$ and $u = 11$ around the optimal value u_* and Fig. 12(b) shows the best constant dose trajectory. The minimal tumor volume realized this way is $p_* = 2264.22$ and only has a relative error of 0.97% compared with the optimal value.

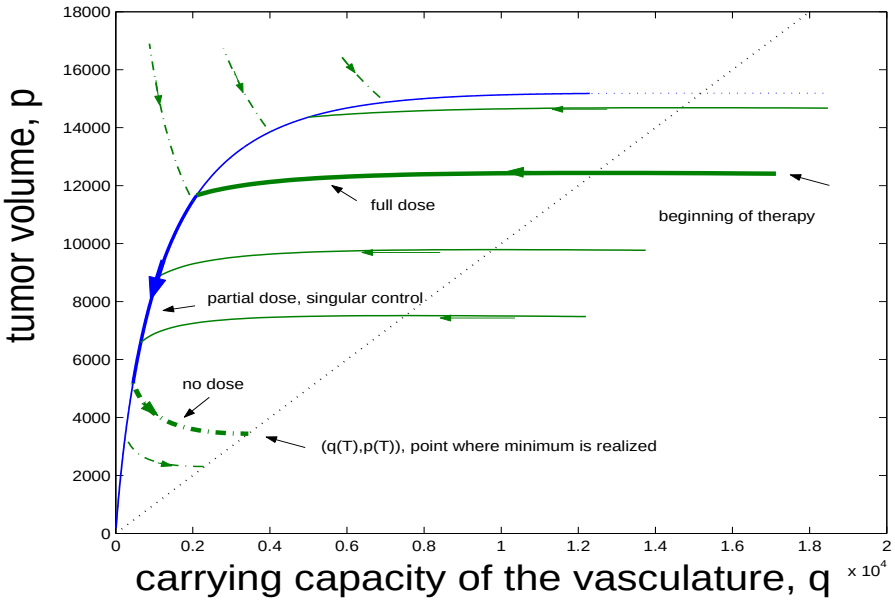

Figure 10: Synthesis of optimal trajectories for problem [E]: The thick curves mark one typical optimal trajectory of the form "as0". After following the maximum dose control $u = a$ until the singular arc $\mathcal{S}$ is reached, at that point the optimal control becomes singular and the trajectory follows the singular arc until all anti-angiogenic agents are exhausted. Due to after effects, the minimum tumor volume is only realized along a trajectory for $u = 0$ as the diagonal $p = q$ is crossed. The thin curves represent initial or final segments of optimal trajectories for other initial conditions.

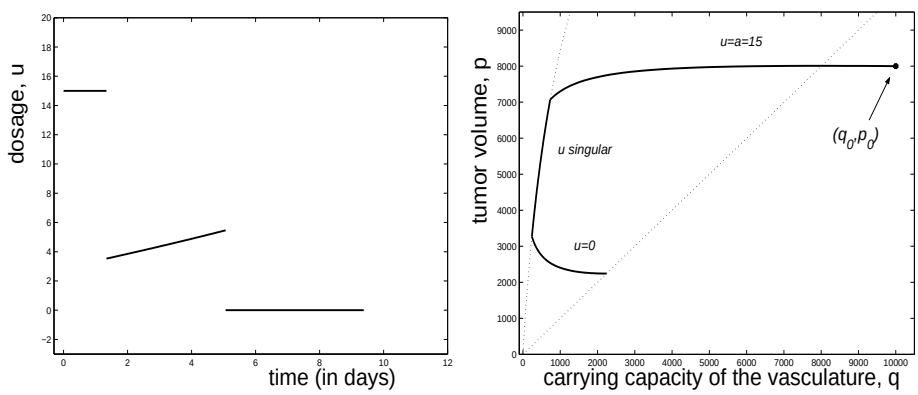

Figure 11: Optimal control (a, left) and corresponding trajectory (b, right) for problem [E] initial data $(p_0, q_0) = (8,000\, mm^3; 10,000\, mm^3)$

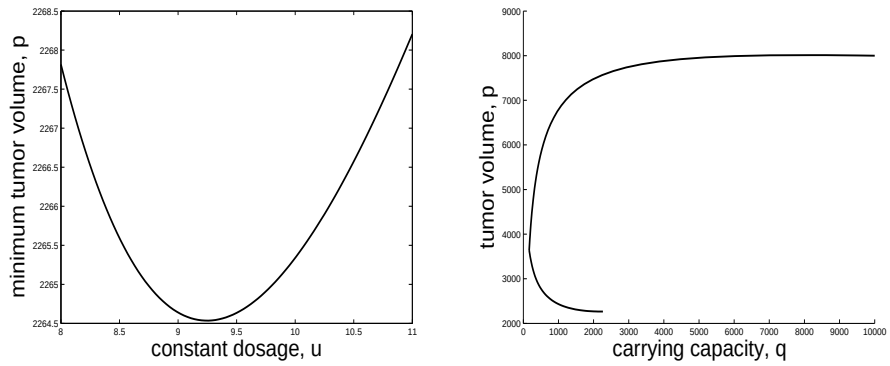

Figure 12: Graph of $\pi_u(T_u)$ for problem [E] over $[8, 11]$ (a, left) and optimal constant dose trajectory (b, right)

For comparison, in Ledzewicz and Schättler, (2008b), we considered the constant dosage $\bar{u} = 8.888$ that was computed by averaging the theoretically optimal dosages over the time span of 5.063 days when drugs are administered along the optimal solution (not including the final segment with $u = 0$). For this strategy virtually the identical value $p_{\bar{u}} = 2264.44$ is obtained at $T = 9.732$ days. In fact the value $\pi_u(T_u)$ is rather flat around its minimum value and any control between $u = 8$ and $u = 11$ gives excellent approximations.

Going to a 2-stage protocol, the approximation of the optimal value can still be improved upon. Following the same scheme and using the same notation as in section 4, the minimizing controls $v_* = \arg\min \pi_v(T_v)$ are given by $u_1 = 15.00$ for time $t_1 = 1.273$ days, $u_2 = 6.710$ for $t_2 = 3.861$ days, and $t_3 = 4.240$ the time along the final $u = 0$ segment until the diagonal is reached at time $T = 9.374$ when the minimum value is realized. The optimal value decreases to 2242.75 compared with the optimal value of 2242.65 and thus for any practical standard such a protocol duplicates the optimal solution. In this case the optimal two-stage regimen starts out at maximum dose (like the theoretically optimal control) and then lowers the value to reflect the lower dosages along the singular control. Fig. 13 gives a cross section of the value $\pi_v(T_v)$ when the first dosage is kept fixed at its optimal (and maximum) value $u_1 = 15.00$. Fig. 14 gives the graph of the corresponding optimal trajectory. We summarize the results for the constant and 2-stage protocols in Table 3.

7 Daily and Semi-Daily Regimes

In the two approaches above the durations of the various dosages are included as optimization variables; in other words, the times for how long dosages are given are unrestricted. It is sometimes of practical interest to specify these durations

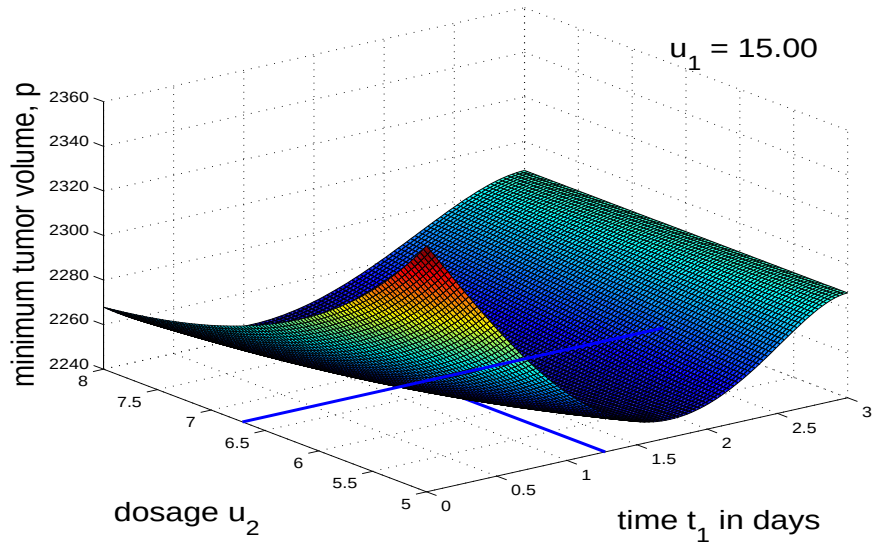

Figure 13: A cross section through the graph of $\pi_v(T_v)$ for problem [E] at $u_1 = 15.00$

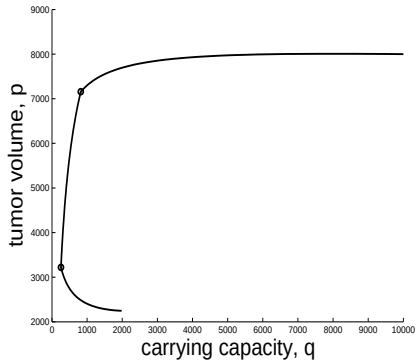

Figure 14: Trajectory corresponding to the optimal two-dosage protocol v_* for problem [E]

control	u_1	t_1	u_2	t_2	t_3	T	min. value
optimal	15.00	1.341	singular	3.722	4.315	9.378	2242.65
one stage, u_*	9.246	4.867	–	–	4.735	9.602	2264.22
avg. optimal, $\bar{u}$	8.888	5.063	–	–	4.669	9.732	2264.44
two stage, v_*	15.00	1.273	6.710	3.861	4.240	9.374	2242.75

Table 3: Comparison of the minimal value for piecewise constant dosage protocols for problem [E]; t_1, t_2 and t_3 denote the times of administration (in days)

a priori and consider daily or even semi-daily dosages (e.g., give the dosage for 8 or 12 hour periods and then include a rest period during the night). Clearly any such strategy reduces the flexibility and thus the number of segments needs to be increased to obtain a similar degree of approximation. It appears reasonable to give the full amount A of anti-angiogenic agents over the same time period as the optimal control does, and in this section we still consider these optimization problems for the two models (and the same data as before).

For the model by Hahnfeldt et al., (1999), the full amount of anti-angiogenic agents is given over 6.56 days and if we specify to give the same total amount in 6 constant daily doses, then the optimal dosages are given by

$$u_1 = 46.61,\ u_2 = 45.31,\ u_3 = 48.15,\ u_4 = 50.71,\ u_5 = 53.20,\ \text{and}\ u_6 = 56.02 \quad (20)$$

and the tumor volume still decreases along the trajectory for $u = 0$ for time $t_7 = 0.169$ days until the diagonal $p = q$ is reached with minimal value $p(T) = 8544.4$. Note that there is a small dip in the dosage from the first to the second day and then the dosages gradually increase over the remaining days. This is in agreement with the structure of the theoretically optimal control that initially applies maximum dose and then switches to the singular control. Since the piece along which the optimal control is at maximum is small, the first daily value is significantly lower than $a = 75$, but it still is higher than the second daily dose. Along the optimal singular arc the dose intensifies and this is reflected in the increasing values of the daily doses over the remaining days. Still, specifying the time structure by restricting to daily dosages reduces the quality of the approximation. The minimal value of 8544.30 for the 6 piece strategy is virtually identical with the optimal constant dose value, but having a larger number of pieces does not yet make up for the loss of freedom by choosing the times in a 2-piece control when the minimal value is 8539.2. Fig. 15 shows the daily dosages and corresponding trajectory in the (p, q)-space with p shown horizontally and q vertically.

Similarly, for the model consider in Ergun et al., (2003), the anti-angiogenic agents are being used up in 5.062 days along the optimal solution. In fact, if we run the minimization over 6 constant daily doses, then it turns out that the optimal dose for the sixth day is equal to $u = 0$. Minimizing a daily regimen therefore leads to the following optimal dosages,

$$u_1 = 15.00,\ u_2 = 9.73,\ u_3 = 5.45,\ u_4 = 6.88,\ \text{and}\ u_5 = 7.94 \quad (21)$$

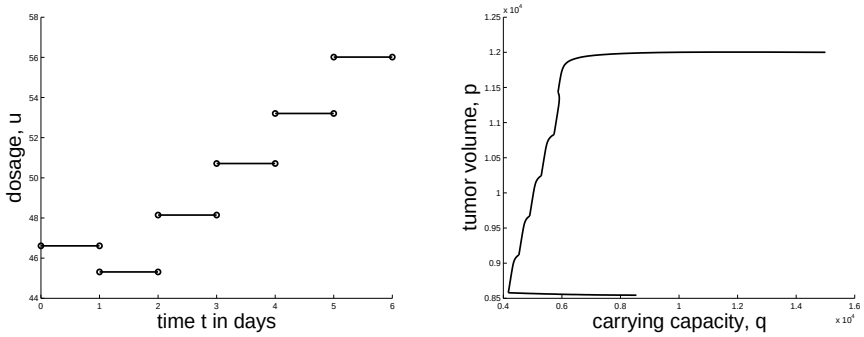

Figure 15: Optimal daily doses (a, left) and corresponding trajectory (b, right) for problem [H] and initial conditions $(p_0, q_0) = (12,000\, mm^3; 15,000\, mm^3)$

with the minimum value realized given by 2243.15. Again, this is the value that the trajectory corresponding to the control $u = 0$ has as the diagonal $p = q$ is crossed, in this case at time at 9.373 days. Here, and the reason being the slower q-dynamics of this modification, the optimal daily strategy is comparable to the optimal 2-stage regimen v_*. Fig. 16 shows these dosages and the corresponding trajectory.

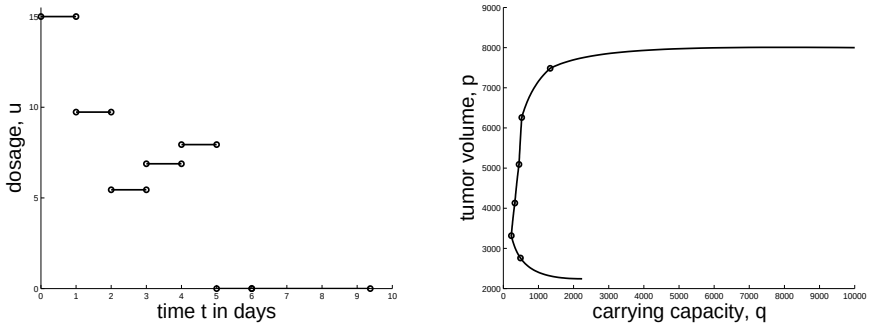

Figure 16: Optimal daily doses (a, left) and corresponding trajectory (b, left) for problem [E] and initial conditions $(p_0, q_0) = (8,000\, mm^3; 10,000\, mm^3)$

Again the pattern resembles the structure of the optimal control. During the first day the control is at maximum level and then drops down. The value for the second day is an average of the maximum dose with the much lower singular control. In the optimal solution the dosage is still at maximum for about 8 hours while it then is lowered to the value $u = 3.53$ at the onset of the singular arc. In the dose for the second day this averages out to a value that still is higher than

the third dose when the optimal control is singular for the entire period, and hence much smaller than the maximum. But the dosage intensifies along the singular arc (see Fig. 11) and thus the values increase. The last daily dosage on the fifth day is determined by the fact that all agents are being used up, but still increases because of dose intensification along the singular arc and the fact that the optimal time exceeds 6 hours, so an average over slightly more than one day is being taken.

If one were to include rest periods into each daily regimen, say anti-angiogenic agents are given at a constant rate for 8, respectively 12, hours, then the 12 hour scheme would use up the amount $A = 45$ in exactly 6 daily dosages at the maximum $u = 15$ and, due to the requirement that all agents should be exhausted, no optimization becomes feasible. Similarly, if we only give anti-angiogenic agents for 8 hours, then, in order to use up all agents, 9 days need to be considered at maximum dosage. The trajectories corresponding to these strategies are shown in Fig. 17 and naturally the quality of approximation decreases further. As a reference, in this and the subsequent figures the black curve is the optimal trajectory. For the 12 hour scheme the realized value is given by $p_{12\text{hr}} = 2262.29$ and for the 8 hour scheme by $p_{8\text{hr}} = 2335.99$. While the 12 hour value still realizes a value in the range of the optimal constant dosage, degradation starts to occur if the rest-periods become too large. Longer rest periods allow the vascular support to recover and with the 8 hour scheme the relative error now is 4.16%, quite large compared to other values.

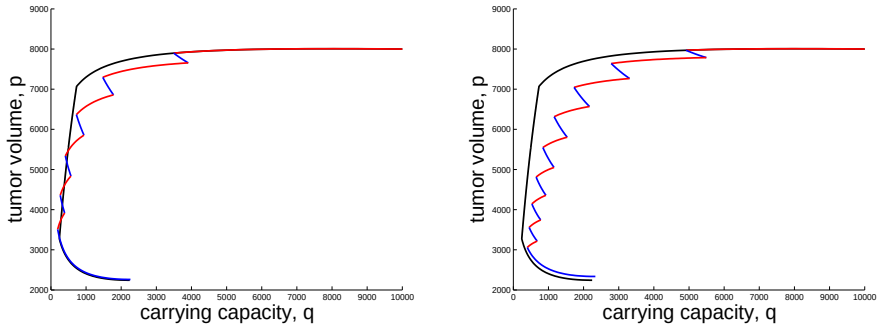

Figure 17: Trajectories corresponding to 12 (a, left), respectively, 8 (b, right) hour daily doses for problem [E]

Fig. 18 (a) compares the corresponding optimal strategies when the upper limit a in the control set has been doubled to $a = 30$. The solid red lines correspond to the optimal 12 hour doses while the solid blue lines give the optimal daily doses when $a = 15$. For comparison, the dashed lines are the average values of the 12 hour doses for the full day and these are close to these optimal daily values. The optimal trajectory for the semi-daily doses is shown in Fig. 18 (b). In this figure we also kept the optimal trajectory for $a = 15$ as the black curve and it is seen how closely now the semi-daily doses approximate this particular trajectory. But

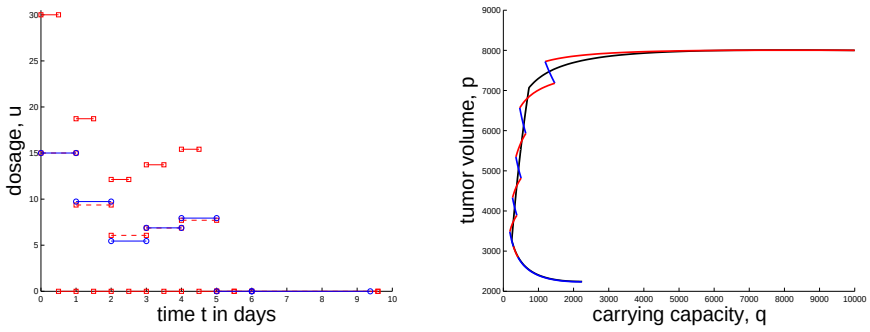

Figure 18: Comparison of the optimal daily doses for $a = 15$ with the optimal 12 hour dosages for $a = 30$ (a, left) and trajectory of the optimal 12 hour regimen for $a = 30$ (b, right)

of course the optimal control for problem $[E]$ with $a = 30$ is different and in this case the maximum tumor reduction possible is given by $p_{**} = 2231.98$ compared with $p_* = 2242.65$ when $a = 15$. It is interesting to note that a higher initial boost which drives the system to the singular arc faster leads to a small decrease in the optimal value. Thus the optimal overall strategy seems to be to get to the singular arc as fast as possible by a high dose bolus injection (mathematically, an impulse) and then follow the singular arc with much smaller dosages.

8 Conclusion

Optimal solutions for mathematical models for tumor anti-angiogenesis formulated by Hahnfeldt et al., (1999), and its modification by Ergun et al., (2003), contain a segment where the optimal control is given by a time-varying feedback function of the state variables p and q, the primary tumor volume and its carrying capacity, and thus is not realizable. In this paper we have shown for both models that easily computable, piecewise constant controls give excellent suboptimal protocols. For the model by Hahnfeldt et al., (1999), and the initial condition $(p_0, q_0) = (12,000\, mm^3; 15,000\, mm^3)$ they come within 0.25% of the optimal tumor values for the specified data. Similarly, for the model by Ergun et al., (2003), and the initial condition $(p_0, q_0) = (8,000\, mm^3; 10,000\, mm^3)$ these values lie within 1% of the optimal value. In fact, in each case the corresponding value functions are relatively flat around the optimal solution and thus any dosage that is reasonably close to the optimal values does not show any degradation in the approximation. Similar conclusions can be drawn over a wide range of initial conditions (c.f., also Ledzewicz and Schättler, 2008). From a practical point of view the conclusion can be drawn that while constant dosage protocols indeed provide very good approximations to the optimal solutions, the choice of the actual dosage, however, does make a

difference. Dosages that are too small simply may not show any effect at all and dosages that are too high unnecessarily waste anti-angiogenic agents. In this sense, for these models for tumor anti-angiogenesis, the calculation of *optimal, piecewise constant dosages* with a small number of switchings, a simple and easy numerical procedure, always is worthwhile.

This main conclusion reported here remains valid if the models are made more realistic by including a standard linear pharmacokinetic model for the anti-angiogenic agents. In this paper, as a first approximation, the dosage of the anti-angiogenic agents was identified with their concentrations in the plasma. If a linear pharmacokinetic equation is added to the model that relates the dosage u to the concentration c of the agents in the plasma, $\dot{c} = -kc + hu$, then the concatenation structure of the optimal controls is effected. The singular arc is preserved (and the same equations are valid) and remains optimal, but what was the singular control in this paper then becomes the optimal concentration (again, exactly the same formula is retained) and the optimal singular control, now the dosage, is calculated from the pharmacokinetic model through differentiation of this relation (see, Ledzewicz et al., 2009a,b). However, mathematically, the order of the singular arc increases from 1 to 2 and this generates a more complicated optimal transition scheme to and off the singular arc which now involves rapid switchings, so-called chattering arcs. Like for the model considered here, practically these are unrealistic and, like in many engineering applications as well, will need to be approximated by bang-bang controls with a small number of switchings, exactly as it was done in this paper for the simplified model. This research currently is in progress.

Acknowledgement. This material is partially based upon research supported by the National Science Foundation under collaborative research grants DMS 0707404/ 0707410. We also would like to thank three anonymous referees for their valuable comments.

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