MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **8**, Number **2**, April **2011**

doi:10.3934/mbe.2011.8.307

pp. **307–323**

OPTIMAL AND SUBOPTIMAL PROTOCOLS FOR A MATHEMATICAL MODEL FOR TUMOR ANTI-ANGIOGENESIS IN COMBINATION WITH CHEMOTHERAPY

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Abstract. We consider the problem of minimizing the tumor volume with a priori given amounts of anti-angiogenic and cytotoxic agents. For one underlying mathematical model, optimal and suboptimal solutions are given for four versions of this problem: the case when only anti-angiogenic agents are administered, combination treatment with a cytotoxic agent, and when a standard linear pharmacokinetic equation for the anti-angiogenic agent is added to each of these models. It is shown that the solutions to the more complex models naturally build upon the simplified versions. This gives credence to a modeling approach that starts with the analysis of simplified models and then adds increasingly more complex and medically relevant features. Furthermore, for each of the problem formulations considered here, there exist excellent simple piecewise constant controls with a small number of switchings that virtually replicate the optimal values for the objective.

1. **Introduction.** Tumor anti-angiogenesis is an indirect cancer treatment approach with the aim to limit the tumor's growth, possibly even shrink the tumor, by depriving it of the vasculature it needs for a steady supply with nutrients. It had already been proposed by J. Folkman in the seventies [10], but was only enabled with the discovery of inhibitory mechanisms of the tumor in the nineties [11, 15]. This treatment targets the endothelial cells that form the lining of the newly developing blood vessels and capillaries. These are healthy, genetically stable cell lines and consequently no clonal resistance to angiogenic inhibitors has been observed in experimental cancer [1, 16]. Hence this approach has the advantage of not being

2000 *Mathematics Subject Classification.* Primary: 92C50; Secondary: 49K15, 49M99.

Key words and phrases. Combination therapy, tumor anti-angiogenesis, optimal and suboptimal controls.

This material is based upon research supported by the National Science Foundation under collaborative research grants DMS 0707404/0707410 and DMS 1008209/1008221.

susceptible to developing drug resistance [17], all too often the limiting factor in chemotherapy. But anti-angiogenic therapy only limits the tumor's support mechanism and thus it seems clear, and any mathematical model and numerous medical studies confirm this, that the tumor will grow back once treatment is halted. Thus it is not efficient as a stand-alone or monotherapy treatment, but it needs to be combined with other mechanisms like chemotherapy or radiotherapy [9] that kill cancer cells.

Combinations of anti-angiogenic treatment with traditional chemotherapy simultaneously target two compartments, the cancer cells and the vascular cells that support the tumor. Naturally, the question how these treatments should be scheduled arises. For example, chemotherapy needs the vascular system to deliver the cytotoxic agents to the cancer cells while anti-angiogenic treatments precisely target this vasculature. So it might appear reasonable to apply chemotherapy first. On the other hand, tumor angiogenesis is a pathological procedure. With an overexpression of pro-angiogenic factors it creates an intricate, disorganized, and dysfunctional architecture which results in a vascular network with a high fractal dimension. When the tumor is in a stage of uncontrolled growth with the carrying capacity significantly higher than the tumor volume, this vascular network consists of many small capillaries that have a high permeability. As a result, during an all-out attack with cytotoxic agents, much of the drug becomes wasted in this elaborate labyrinth of small and leaky vessels and never reaches the primary tumor. Anti-angiogenic agents naturally are most effective on these small and weak capillaries and these are the first ones to be destroyed. Consequently, anti-angiogenic treatments have the effect of normalizing the tumor vasculature [13, 14] and thus enable a much more efficient drug delivery. In the medical literature the word *"pruning"* has been used in connection with these normalizing capabilities of anti-angiogenic agents. Hence, and there is mounting medical evidence to support this approach, it may be better to start with anti-angiogenic treatment. But these are difficult questions that are far from being answered and the search for an optimal *"therapeutic window"* when chemotherapy is best applied in relation to anti-angiogenic therapy is of great interest and is currently pursued in medical trials.

In this paper, we consider a mathematical model for tumor anti-angiogenesis by Ergun, Camphausen and Wein that has previously been analyzed in combination treatments with radiotherapy [9]. It is a modification of a biologically validated model by Hahnfeldt, Panigrahy, Folkman and Hlatky [12] who derived a minimally parameterized population based model for tumor growth under anti-angiogenic treatment with the primary tumor volume, p, and the carrying capacity of its vasculature, q, as the main variables. The model by Hahnfeldt et al. has been analyzed extensively by d'Onofrio and Gandolfi in [6] and has undergone various modifications and generalizations (e.g., see [5, 7]) including the one considered here. (For modeling related aspects, see the paper [30] in this volume.) For the model by Ergun et al., in earlier research [24, 20], we have given a complete mathematical solution to the monotherapy problem of scheduling an a priori given amount of anti-angiogenic agents in order to maximize the tumor reduction achievable. This is the problem formulation as it was initially posed in [9]; other, related optimal control formulations have been considered by Swierniak (e.g., [31, 32]). In [19] we have shown that the monotherapy solution indeed becomes a basis upon which the optimal solution for a combination with chemotherapy can be built. More specifically, the same structure of optimal combination therapy solutions is valid as it was

verified numerically for a wide range of initial conditions in [8] for the model by Hahnfeldt et al. [12]: *optimal controls for the anti-angiogenic agent follow the optimal angio-monotherapy and then, at a specific time, chemotherapy becomes active and is given in one full dose session.*

In all these papers, the simplifying assumption is made to identify the drug dosage with its concentrations. While chemotherapy is administered in the optimal solution in a single maximum dose segment (bang-bang control), the optimal administration of the anti-angiogenic agent follows a time-varying feedback control that depends on the states p and q (singular control). It follows similarly to some of our earlier results for compartmental models for chemotherapy [23], that optimality of bang-bang controls is not affected if a standard linear pharmacokinetic equation is added to the model. But this is different if optimal controls are singular. In this case, the so-called order of the singular arc increases [28] causing qualitative changes. However, as feedback functions that depend on q, singular controls are not really practical for this problem to begin with and the real question is the following one: *what are the effects that the addition of pharmacokinetic equations has on practically realizable and good suboptimal treatment protocols?* In this paper, for a fixed set of initial conditions, we give and compare the optimal solutions for four versions of the underlying optimal control problem. We first present the optimal solutions for both the mono- and combination therapy models when drug dosages and their concentrations are identified and then add a standard linear pharmacokinetic equation to model the concentration of the anti-angiogenic agent. Since chemotherapy is given in one full dose session, in order to keep the model simpler, we did not add a second equation for the cytotoxic agent. In fact, this does not significantly change the structure of solutions and here a simplified model that reasonably well reflects the optimal solution is preferred. It will be shown that while the structure of optimal controls becomes quite a bit more complex with this addition, *there exist simple realizable suboptimal protocols that provide excellent approximations to the optimal values.*

2. **Optimal control for a mathematical model for combination therapy.** We formulate a mathematical model for combination of tumor anti-angiogenesis with chemotherapy that is based on a model by Ergun, Camphausen and Wein in [9]. This model itself is a modification of a biologically validated model by Hahnfeldt et al. from [12] in which the spatial aspects of the underlying consumption-diffusion processes that stimulate and inhibit angiogenesis are incorporated into a non-spatial 2-compartment model with the primary tumor volume p and its carrying capacity q as variables. Tumor growth is modeled by a Gompertzian growth function,

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

where ξ denotes a tumor growth parameter. The dynamics proposed in [9] for the equation modeling the change in the carrying capacity is given by

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

where b (birth) and d (death), respectively, are endogeneous stimulation and inhibition parameters for the endothelial support and the term μq represents natural death terms. The inhibition and stimulation terms, $I(q) = dq^{\frac{4}{3}}$ and $S(q) = bq^{\frac{2}{3}}$, are a modification of the corresponding terms, $I(p,q) = dp^{\frac{2}{3}}q$ and $S(p) = bp$, chosen in [12]. The main reason for this modification lies in a differential-algebraic nature

of the original model with a fast q-dynamics that reaches its steady-state quickly. In (2) this dynamics is slowed down by choosing the inhibitory effect of the tumor proportional to the tumor radius and not its surface area as it is done in [12]. Then still replacing p with q in steady state, this results in a significant mathematical simplification of the q-dynamics since the tumor volume p is eliminated from this equation. (For a more detailed description of the underlying modeling, also see the paper [30] in this volume).

In combination treatments with chemotherapy two controls u and v are introduced that represent anti-angiogenic and cytotoxic agents, respectively. Anti-angiogenic agents typically are biological agents that need to be grown in a lab and still are very expensive and limited. Chemotherapeutic agents, on the other hand, are widely available, but have serious side-effects and thus can only be administered in limited quantities. From a practical point of view it is therefore of importance how given amounts of these agents can be administered to have an "optimal" effect. Mathematically, this can be formulated as an optimal control problem with free terminal time T and isoperimetric constraints that limit the quantities of the agents to be given,

$$\int_0^T u(t)dt \le A \qquad \text{and} \qquad \int_0^T v(t)dt \le B.$$

Adding extra variables y and z that monitor the total amounts of agents that have already been administered, and relabeling the total amounts as $y_{\max}$ and $z_{\max}$ accordingly, mathematically this problem takes the following form:

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

$$\dot p = -\xi p \ln\left(\frac{p}{q}\right) - \varphi p v, \qquad p(0) = p_0, \tag{3}$$

$$\dot q = b q^{\frac{2}{3}} - d q^{\frac{4}{3}} - \mu q - \gamma q u - \eta q v, \qquad q(0) = q_0, \tag{4}$$

$$\dot y = u, \qquad y(0) = 0, \tag{5}$$

$$\dot z = v, \qquad z(0) = 0, \tag{6}$$

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

The coefficients φ, γ and η are non-negative constants that relate the dosages of the respective agents to their effectiveness. The constants $u_{\max}$ and $v_{\max}$ denote the maximum doses of the anti-angiogenic and cytotoxic agents, respectively, with the total available amounts of each agent denoted by $y_{\max}$ and $z_{\max}$. If we formally set $z_{\max} = 0$, i.e., no cytotoxic drugs are available, then we obtain the corresponding anti-angiogenic monotherapy problem and we denote this problem by **[M]**.

Throughout this paper, we shall use the following parameter values in our numerical computations: The variables p and q are volumes measured in mm^3; $\xi = 0.084$ *per day*, $b = 5.85$ *per day*, $d = 0.00873$ *per* mm^2 *per day*, These numerical values are based on the data given in [12]. For illustrative purposes we also chose a small positive value for μ, $\mu = 0.02$ *per day*. In the formulation [C] dosage and concentration of the agents are identified and we give u and v the meaning of dosages with units of *mg of dose per kg per day*; the total amounts $y_{\max}$ and $z_{\max}$ thus are in *mg of dose per kg*. The conversion factor γ in (4) is taken as $\gamma = 0.15$ with units

of *kg per mg of dose*. The maximum dosage for the anti-angiogenic agent is taken to be $u_{\max} = 15$ and we limit the total amount to be $y_{\max} = 45$. These values are chosen for illustrative purposes and are not based on biological data. Regarding the cytotoxic agent we take $\varphi = 0.1$ *kg per mg of dose* and we give results for both $\eta = 0$ and small positive values for η. For biological reasons the relative effects of the cytotoxic agent on the vasculature should be smaller than on the cancer cells, $\eta \leq \varphi$, and in our computations we only observed the expected quantitative changes. Hence we mostly report numerical results for $\eta = 0$. The control limits taken are $v_{\max} = 20$ and $z_{\max} = 100$. We emphasize that our theoretical results about the structure of optimal controls are independent of these parameter values and that they are generally valid. Also, in all our figures we consistently plot p vertically and q horizontally since this better visualizes tumor reductions, the objective in the optimal control problem [C].

Naturally, in this formulation all states need to be non-negative, but this need not be added as an extra constraint. It is not difficult to show that if p_0 and q_0 are arbitrary positive initial conditions, then for any admissible controls u and v, the solution (p, q, y, z) to the corresponding differential equation exists for all times $t > 0$ and both p and q remain positive (e.g., [20, 19]). It follows from standard results of optimal control (see, e.g., [3]) that optimal controls for problem [C] exist. But *degenerate cases* are possible. The reason lies in the fact that, no matter what control is being used, the cancer volume p increases for $p < q \exp\left(-\frac{\varphi}{\xi} v_{\max}\right)$. Consequently, if the initial condition lies in this region, and if the overall amounts $y_{\max}$ and $z_{\max}$ simply are too small for the system to reach the region $p > q \exp\left(-\frac{\varphi}{\xi} v_{\max}\right)$, then indeed the smallest value for p along any solution is given by the initial condition p_0. Mathematically, in such a case the "optimal" solution simply becomes to do "nothing", i.e., $T = 0$. Other, less degenerate situations are possible as well in which for similar reasons not all available agents are fully used up. It is not too difficult to analyze the dynamics for the system in these cases as well, but their analysis brings the need to distinguish various subcases. Also, from a practical point of view, these initial data (p_0, q_0) and $(y_{\max}, z_{\max})$ are medically not very realistic. For this reason we make the following definition and henceforth consider an initial condition that is well-posed in this sense.

Definition 2.1. We say the initial data (p_0, q_0) and $(y_{\max}, z_{\max})$ are *well-posed* for problem [C] if the optimal final time T is positive and if all anti-angiogenic and cytotoxic agents have been used up, $y(T) = y_{\max}$ and $z(T) = z_{\max}$.

A complete solution to the monotherapy problem [M] (i.e., for $z_{\max} = 0$) was given in [20]. Optimal controls u_* are specific concatenations of the constant controls $u = u_{\max}$ (full dose treatment) and $u = 0$ (no anti-angiogenic agents are being administered) and a specific, time-varying feedback control $u_{\sin}$, a so-called singular control. This control can be calculated explicitly and is given in the Proposition below:

Proposition 1. [20] *If the optimal control u_* is singular on an open interval I, $u_*(t) = u_{sin}(t)$, then*

$$u_{\sin}(t) = \frac{1}{\gamma} \Psi\left(\sqrt[3]{q_*(t)}\right) \tag{7}$$

where with $w = \sqrt[3]{q}$ *we have that*

$$\Psi(w) = \left(\frac{b - dw^2}{w} + 3\xi \frac{b + dw^2}{b - dw^2} - \mu \right). \tag{8}$$

This control is only optimal along one specific curve in (p, q)*-space, the corresponding singular arc* $\mathcal{S}$*, which is the graph of a smooth function* $p_{\sin}$ *of* p *given by*

$$p_{\sin}(q) = q \exp\left(3 \frac{b - dq^{\frac{2}{3}} - \mu q^{\frac{1}{3}}}{b + dq^{\frac{2}{3}}} \right). \tag{9}$$

The singular control $u_{\sin}$ *makes this curve invariant. Admissible controls need to satisfy the control constraint* $0 \le u \le u_{\max}$ *and this restricts the admissible portion of the singular arc to an interval* $[q_\ell^*, q_u^*]$ *with the values* q_ℓ^* *and* q_u^* *the unique solutions to the equation* $\Psi(\sqrt[3]{q}) = \gamma u_{\max}$ *in* $(0, \sqrt{\left(\frac{b}{d}\right)^3})$*. Note that* $u_{\sin}(t)$ *is a smooth feedback control that only depends on* $\sqrt[3]{q_*(t)}$*.* □

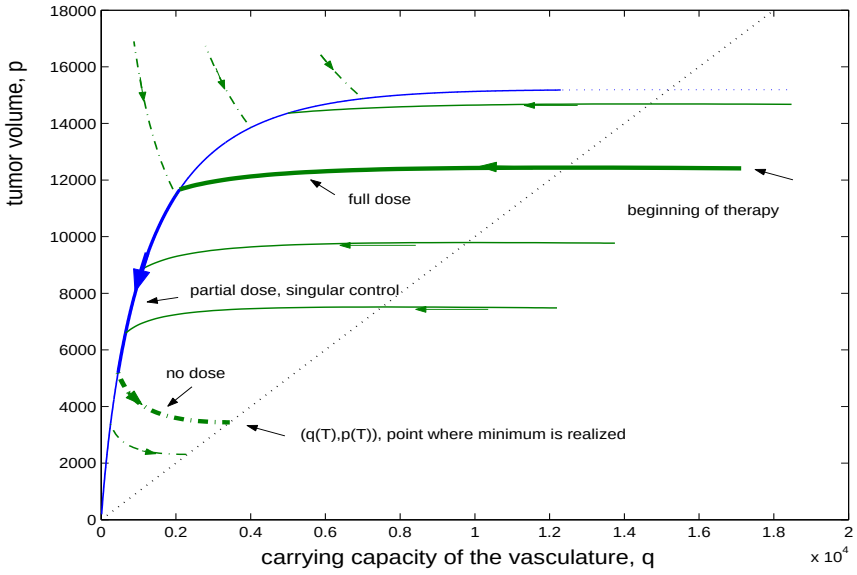

FIGURE 1. Optimal synthesis for the model [M]

For a typical well-posed initial condition (p_0, q_0) with $p_0 \le q_0$ (i.e., the tumor is growing), optimal monotherapy controls start with an initial segment along which anti-angiogenic agents are given at the maximum dose $u_{\max}$ until the singular arc $\mathcal{S}$ is reached. At this point optimal controls switch to the singular control $u_{\sin}$ and the corresponding optimal trajectory now descends along the singular arc until all anti-angiogenic agents are exhausted. It is here where most of the tumor shrinkage occurs. When the inhibitors have been exhausted, active therapy is over. However, even as no more agents are given, i.e., along a trajectory for the control $u = 0$, there still is an additional tumor reduction. The reason for this lies in the fact that inhibitors run out in the region $p > q$ where the tumor volume still shrinks, even for $u = 0$. Hence, because of after effects, the minimum tumor volume is only realized when the trajectory corresponding to $u = 0$ crosses the diagonal $p = q$. The

corresponding time T then is the limit of the horizon considered in the problem formulation [M]. Depending on the actual initial condition (p_0, q_0) and the available amount $y_{\max}$ of anti-angiogenic agents, there exist changes in this structure, most notably if the singular control saturates (i.e., reaches its upper limit $u_{\max}$) before all inhibitors have been used up. But here we concentrate on this most common scenario and refer the reader to [25] for a detailed discussion of other aspects of the structure of optimal controls.

Fig. 1 shows the synthesis of optimal controlled trajectories for the monotherapy problem [M]. Such a synthesis provides a road map of *all* optimal trajectories depending on their initial conditions. The center piece is the singular arc $\mathcal{S}$ shown as a solid blue curve in the figure. The trajectories corresponding to the constant controls $u = 0$ (dash-dotted green curves) and $u = u_{\max}$ (solid green curves) give the response of the system to these controls and the dotted line marks the diagonal $p = q$ where the maximum tumor reduction is realized. In the diagram several optimal trajectories are indicated and the thick curves in the graph mark one particular such trajectory that follows the concatenation structure $\mathbf{u}_{\max}/\mathbf{u}_{\sin}/\mathbf{0}$ described above.

Fig. 2 gives the optimal control and its corresponding trajectory for the initial conditions $p_0 = 8,000$ $[mm^3]$ and $q_0 = 10,000$ $[mm^3]$. In this case, the optimal concatenation sequence is $\mathbf{u}_{\max}/\mathbf{u}_{\sin}/\mathbf{0}$: the optimal control is given at full dosage $u = u_{\max} = 15$ 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 5.063 days. Due to after effects the maximum tumor reduction is realized along a trajectory for control $u = 0$ at the optimal terminal time $T = 9.378$ days when the trajectory reaches the diagonal $p = q$,

$$u_*(t) = \begin{cases} u_{\max} & \text{for} \quad 0 \le t < 1.341 \\ u_{\sin} & \text{for} \quad 1.341 \le t < 5.063 \\ 0 & \text{for} \quad 5.063 \le t < 9.378 \end{cases} . \tag{10}$$

The theoretically optimal minimum value for these data is given by $p_{[M]} = 2242.65$.

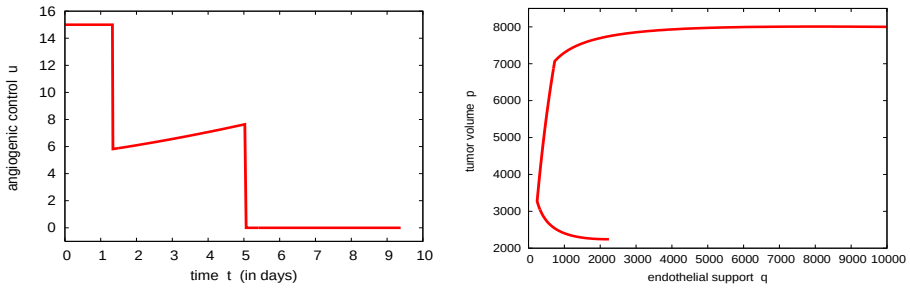

FIGURE 2. Optimal control (a, left) and corresponding trajectory (b, right) for the monotherapy problem [M] with initial data $(p_0, q_0) = (8,000\, mm^3; 10,000\, mm^3)$

Once chemotherapy is added to the model, this solution to the monotherapy problem actually becomes the basis on which the optimal combination therapy controls are built. Such a property is *not generally valid* for multi-control problems, but it holds here because of certain relations between higher-order Lie brackets of

the drift and control vector fields defining the dynamics (3) and (4). We have the following characterization of the singular control for the anti-angiogenic agent in the presence of chemotherapy.

Proposition 2. [19] *If the optimal anti-angiogenic agent u_* is singular on an open interval I, $u_*(t) = u_{sin}(t)$, and the optimal cytotoxic agent is given by $v_*(t)$ on I, then*

$$\gamma u_{sin}(t) + \eta v_*(t) = \Psi\left(\sqrt[3]{q_*(t)}\right) \tag{11}$$

with Ψ the same function as given above, (8). Furthermore, on the interval I the control v_* is bang-bang with at most one switching from $v = 0$ to $v = v_{\max}$. For $v_* \equiv 0$ the corresponding trajectory must follow the singular arc $\mathcal{S}$ of the monotherapy solution; the trajectory is not constrained for $v_* \equiv v_{\max}$. □

For combination treatments, however, the theoretical analysis of optimal concatenations is more complex and it has not been completed so far. For example, it has not yet been excluded theoretically that the chemotherapeutic agent v could follow a singular regimen. From a biological perspective such a protocol is not welcome since low dosages are known to foster developing drug resistance. In fact, for various mathematical models for cell-cycle specific chemotherapy [21, 22, 33], we have proven that optimal controls are bang-bang. Also, for the model [C] considered here this structure has been supported in many numerical computations. In fact, we have always seen as optimal the following structure: *optimal controls for the anti-angiogenic agent u follow the optimal angio-monotherapy and at a specific time τ chemotherapy becomes active and all available cytotoxic agents u are given in one full dose session.* For the same initial conditions given above, $p_0 = 8,000$ $[mm^3]$ and $q_0 = 10,000$ $[mm^3]$, and small values of η the optimal controls are of the following form

$$(u_*(t), v_*(t)) = \begin{cases} (u_{max}, 0) & \text{for} \quad 0 \le t < t_1 \\ (u_{sin}(t), 0) & \text{for} \quad t_1 \le t < t_2 \\ (u_{sin}(t), v_{max}) & \text{for} \quad t_2 \le t < t_3 \\ (0, v_{max}) & \text{for} \quad t_3 \le t < T \end{cases} . \tag{12}$$

Table 1 summarizes some of our numerical results for various values of η. For $\eta = 0$ the switching times for the optimal control u_* are the same as in the monotherapy case: the control switches from full dose to singular at time $t_1 = 1.341$ as the singular arc is reached and all anti-angiogenic inhibitors are exhausted at time $t_3 = 5.063$. Chemotherapy commences earlier at time $t_2 = 4.378$, but since $\eta = 0$ this does not effect the time when anti-angiogenic agents will be exhausted. However, different from the monotherapy case, the minimum tumor reduction no longer is achieved as the trajectory crosses the diagonal. Now we have $q(T) = 2242.65$ and the minimum tumor volume is given by $p_{[C,\eta=0]} = 991.14$. The reason for this change lies in the fact that the cytotoxic agent gives tumor reductions also in the region $p < q$ which is not possible for monotherapy only. The final value for $q(T)$ is identical with the final value for the monotherapy problem if $\eta = 0$. For positive values of η this naturally no longer is true and the quantitative changes in the optimal values depend on the effectiveness. But overall the structure of the controls does not change. Figs. 3 and 4 show the optimal controls and their corresponding trajectories for $\eta = 0.01$ and $\eta = 0.02$. Note the drop in the dosage of the anti-angiogenic agent u that occurs as the chemotherapy becomes active. It is caused by the presence of the positive η-term in (11) which adjusts the overall effectiveness of the combined anti-angiogenic

η	t_1	t_2	t_3	T	$p(T)$
0	1.341	4.378	5.063	9.378	991.14
0.01	1.341	4.604	5.159	9.605	875.15
0.02	1.341	4.830	5.186	9.830	774.78

TABLE 1. Optimal switching times for problem [C] for various values of η

and cytotoxic effects on the vasculature (see (4)) to follow the optimal relation Ψ as described in Proposition 2.

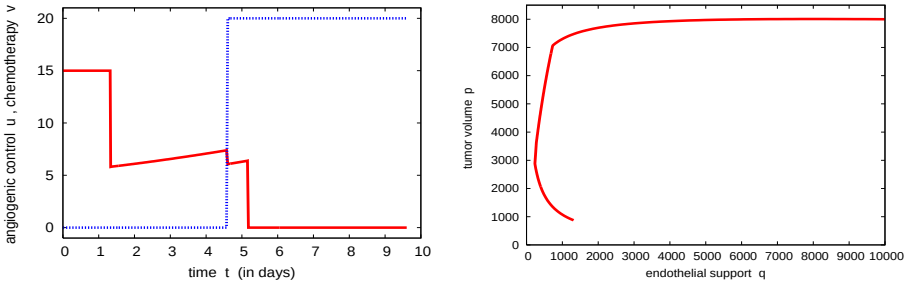

FIGURE 3. Optimal controls (left) and corresponding trajectory (right) for the combination therapy model [C] with initial data $(p_0, q_0) = (8,000\,mm^3; 10,000\,mm^3)$ and $\eta = 0.01$. The dosages of the anti-angiogenic and cytotoxic agents are shown on the left in red and blue, respectively.

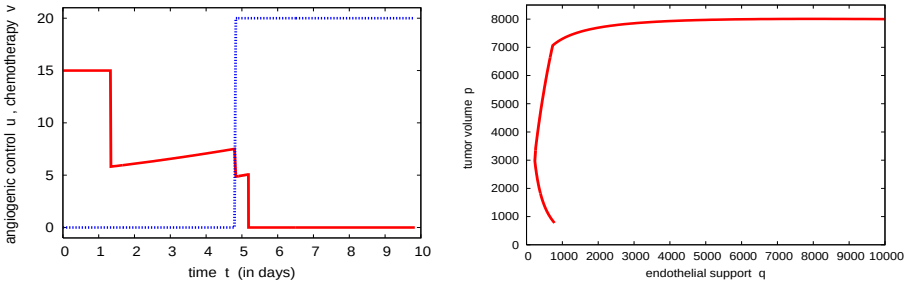

FIGURE 4. Optimal controls (left) and corresponding trajectory (right) for the combination therapy model [C] with initial data $(p_0, q_0) = (8,000\,mm^3; 10,000\,mm^3)$ and $\eta = 0.02$. The dosages of the anti-angiogenic and cytotoxic agents are shown on the left in red and blue, respectively.

3. **Mono- and combination therapies with a linear pharmacokinetic model.** A commonly made simplification in mathematical models for cancer treatments identifies the agents' dosage with their concentrations and effects. In reality

these clearly are different and their relations are studied under the names of *pharmacokinetics (PK)* and *pharmacodynamics (PD)*. Pharmacokinetic equations model the drugs' concentrations and pharmacodynamics models their effectiveness. The full process is known as *drug delivery* in the medical literature. The standard and most commonly used model for PK in the pharmaceutical industry is a simple model of exponential growth and decay given by

$$\dot{c} = -kc + u, \qquad c(0) = 0, \tag{13}$$

where u denotes the dosage of the agent and c its concentration. The coefficient k is the clearance rate and is related to the half-life of the agents. In this section we show how the optimal controls given above change when this linear pharmacokinetic equation is added to the model. For our numerical computations we take $\eta = 0$ in this section.

Clearly, there will be quantitative differences. Equation (13) slows down the clearance of the drug and consequently the anti-angiogenic agent will remain effective over a longer time period and thus give lower minimum tumor volumes. But does this change effect the structure of optimal protocols qualitatively? If it doesn't, then simple extensions of our previous results will accommodate this change. If it does, the analysis needs to be modified and possibly done anew. In mathematical models for chemotherapy that we had considered earlier this was not the case [23, 26]. The reason was that optimal controls were bang-bang and this structure is preserved when a linear pharmacokinetic equation (13) is added to the model. But optimal solutions for the anti-angiogenic agent are given by singular controls and here this is no longer true. In [28] we have shown that while optimality properties of singular arcs are preserved, its so-called intrinsic order increases from 1 to 2. It is well-known in the control literature [2, 34] that an optimal smooth singular control with values in the interior of the control set cannot be concatenated optimally with either of the constant bang controls $u = 0$ or $u = u_{\max}$. These concatenations are now accomplished by means of *chattering arcs*, trajectories that correspond to controls that switch infinitely many times between their upper and lower values on a finite interval. This fact is known as the Fuller phenomenon in the optimal control literature. While such a structure may appear odd, it actually is not (the simplest example is a bouncing ball without friction) and it is generic in high dimension [18]. Thus it needs to be expected and be dealt with. We therefore add the standard linear pharmacokinetic model (13) for the anti-angiogenic agent to the mathematical model and, as a simple model for PD, replace the control u in (4) by its concentration c, but otherwise preserve the same formulation. We do not incorporate a second equation for the cytotoxic agent here since we want to demonstrate the effects on one control and it is the anti-angiogenic agent that leads to more interesting phenomena. We thus now consider the following modification of problem [C]:

[CwPK]: for a free final time T, minimize $p(T)$ subject to

$$\dot{p} = -\xi p \ln\left(\frac{p}{q}\right) - \varphi p v, \qquad p(0) = p_0, \tag{14}$$

$$\dot{q} = b q^{\frac{2}{3}} - d q^{\frac{4}{3}} - \mu q - \gamma q c - \eta q v, \qquad q(0) = q_0, \tag{15}$$

$$\dot{c} = -kc + u, \qquad c(0) = 0, \tag{16}$$

$$\dot{y} = u, \qquad y(0) = 0, \tag{17}$$

$$\dot{z} = v, \qquad z(0) = 0, \tag{18}$$

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

In this formulation, as before, u and v are dosages measured in *mg of dose per kg per day*, but now the conversion factor γ in (15) relates the concentration c to the carrying capacity and thus is in units of *kg per mg of dose per day*.

It is shown in [28] that the optimality status of the singular arc is preserved under the addition of such a linear pharmacokinetic model. In fact, the equations that define the singular control and arc in the monotherapy model [M] remain valid, only with a different interpretation. The singular curve $\mathcal{S}$ defined by (9) is preserved as a vertical surface $\hat{\mathcal{S}}$ in (p, q, c)-space and the singular arc for the monotherapy problem [MwPK] (i.e., $z_{\max} = 0$) is now given by the intersection of this cylindrical surface $\hat{\mathcal{S}}$ with the graph of the function $c = \frac{1}{\gamma}\Psi\left(\sqrt[3]{q}\right)$ defined by (8), see Fig. 5.

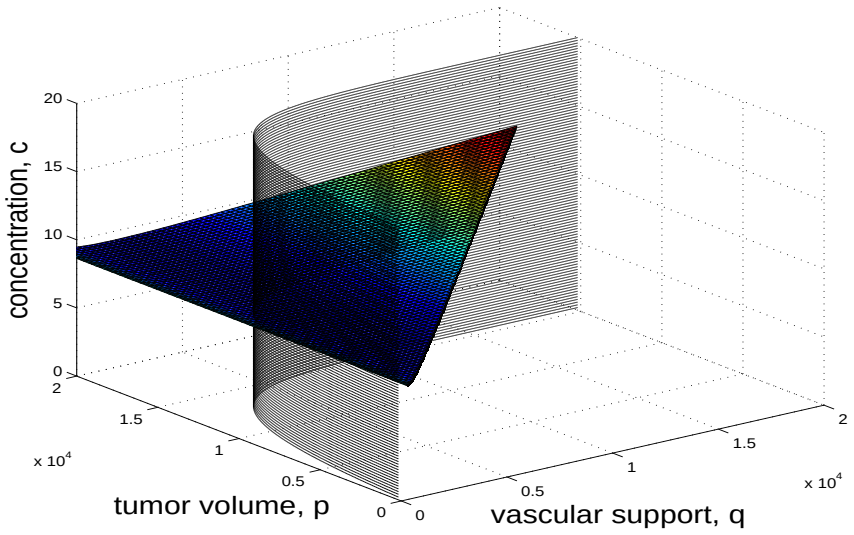

FIGURE 5. Vertical singular surface $\hat{\mathcal{S}}$ in (p, q, c)-space and graph of the concentration $c = \frac{1}{\gamma}\Psi(\sqrt[3]{q})$

But concatenations with the singular arc are now no longer accomplished by means of the constant controls $u = 0$ or $u = u_{\max}$, but through *chattering controls* that switch infinitely often between these values. Fig. 6 gives the graphs of a numerically computed optimal control u for this model and the corresponding concentration c. Again, the same initial conditions $p_0 = 8,000$ $[mm^3]$ and $q_0 = 10,000$ $[mm^3]$ were used and in the numerical computations we have taken a value for the half-life k that is supported by experiments with angiostatin, $k = 0.39$ *per day*, [12]. The optimal control package NUDOCCCS due to Büskens [4] was used to compute

a solution of the discretized control problem using nonlinear programming methods with 400 grid points and a seventh order Runge-Kutta integration method. Fig. 6 shows the resulting control and the corresponding concentration. The irregular structure of the numerically computed control on the left is caused by the fact that the theoretically optimal control chatters and has a singular middle segment. As the intervals between the switchings shrink to 0, the numerical values for the controls no longer alternate between their upper and lower values, but already try to connect with the singular control values that lie in the interior of the control interval. The corresponding value of the objective is within the desired stopping criterion for the algorithm. Now the final time is $T = 15.548$ [*days*] and the minimum tumor volume is given by $p_{[M,pk]} = 564.762$ [mm^3]. An interesting observation is that this value is significantly smaller than for the model without a pharmacokinetic equation. The reason is that with a clearance rate k the concentration remains high for a much longer time than in the original modeling - we now have $T = 15.548$ [*days*] versus $T = 9.378$ [*days*] in the model [M] - and the cumulative effects on the carrying capacity q are significant. In some sense, the original modeling is that of a fast acting agent that quickly gets cleared. This model clearly favors slow acting agents that have a low clearance rate.

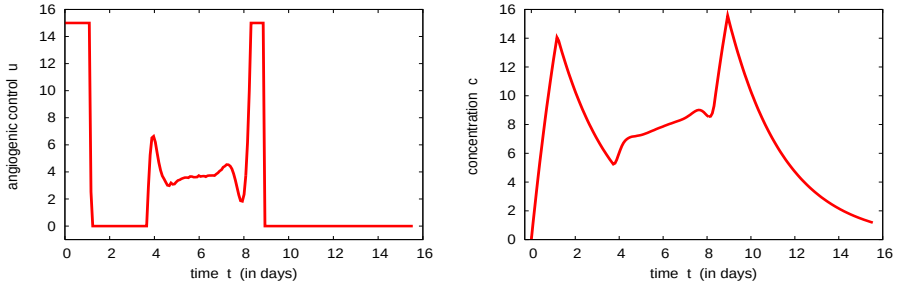

FIGURE 6. A numerically computed 'optimal' chattering control u (left) with corresponding concentration c (right) for problem [MwPK]

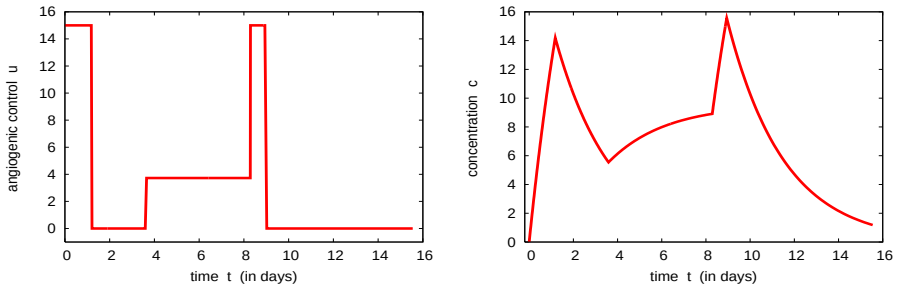

FIGURE 7. A suboptimal bang-bang control with five arcs (left) and corresponding concentration c (right) for problem [MwPK]

Obviously, chattering controls are not of practical interest and the relevant question is what are the effects on the value of the objective. Do there exist good

and simple, practically realizable suboptimal protocols? As for the original model [M], this is indeed the case. Fig. 7 gives an example of a suboptimal control that was computed taking the following simple piecewise constant approximation for the optimal control:

$$\tilde{u}(t) = \begin{cases} u_{\max} & \text{for } 0 \le t < t_1 \\ 0 & \text{for } t_1 \le t < t_2 \\ \bar{u} & \text{for } t_2 \le t < t_3 \\ u_{\max} & \text{for } t_3 \le t < t_4 \\ 0 & \text{for } t_4 \le t \le T \end{cases} . \tag{19}$$

Here both chattering arcs at the beginning and end of the singular arc are approximated by the trajectory of a simple bang-bang control that switches once from $u_{\max}$ to 0 and the singular control is approximated by a constant control $\bar{u}$. This particular choice is probably the simplest reasonable approximation to the control structure that the theory predicts as optimal: a chattering control followed by a singular control and one more chattering control. The switching times t_i, $i = 1, \dots, 4$, the final time T, and the value $\bar{u}$ of the control are free optimization variables. Using the arc-parametrization method developed in [29] and the code NUDOCCCS [4], we obtain the optimal switching times $t_1 = 1.210$, $t_2 = 3.649$, $t_3 = 8.294$, $t_4 = 9.022$, the final time $T = 15.544$ and the constant control $\bar{u}$ is given by $\bar{u} = 3.725$. This gives a minimal tumor volume of $\tilde{p}_{[M,pk]} = 564.763$ that is virtually identical with the optimal minimal tumor volume $p_{[M,pk]} = 564.762$ for the "chattering control" in Fig. 6. The numerical computations also show that second order sufficient conditions for the underlying optimization problem are satisfied and hence this control is a strict (local) minimum. Fig. 7 shows the best suboptimal control on the left and the corresponding concentration on the right. Overall, the behavior is very similar as in case of the chattering control, but the system has a much smoother and thus for many aspects preferable response. Since the final time T is much longer, even better approximations are realized in this case than in the monotherapy model [M]. The trajectories for the optimal and sub-optimal controls are indistinguishable.

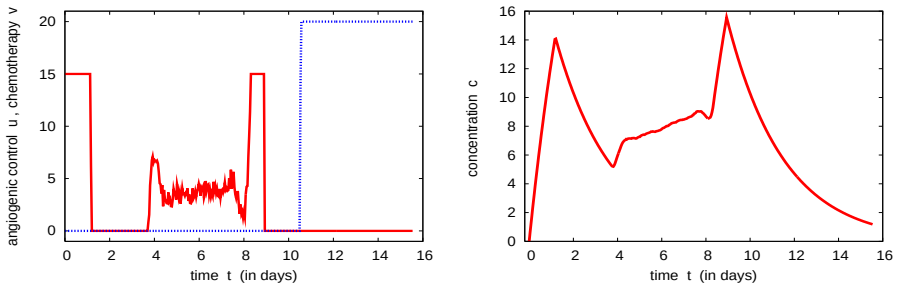

FIGURE 8. A numerically computed 'optimal' chattering control u (dosages of the anti-angiogenic agent, shown in red on the left) and its corresponding concentration c (on the right) for problem [CwPK]; the control v, the dosage of the cytotoxic agent, is included in blue on the left.

Similar results are valid for the problem [CwPK] with chemotherapy. The structure for the anti-angiogenic inhibitor is the same as for the monotherapy problem

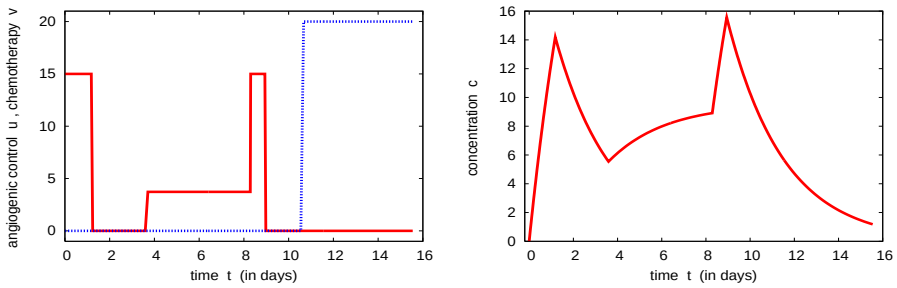

FIGURE 9. A suboptimal bang-bang control u (dosages of the anti-angiogenic agent, shown in red on the left) and its corresponding concentration c (on the right) for problem [CwPK]; the control v, the dosage of the cytotoxic agent, is included in blue on the left.

with the irregular pattern in the numerically computed control much more pronounced. For these data, chemotherapy only becomes active after all inhibitors have been used up. The reason for this is that the PK slows down the clearance of the anti-angiogenic agent to such an extent that the final time T is more than 5 days after all anti-angiogenic inhibitors have been given. Since no PK was included for the chemotherapeutic agent, the time period when it is given at maximum dose, 5 days in this case, is unchanged. Optimization clearly favors to put the chemotherapy last. The final time $T = 15.540$ is almost identical with the one for the monotherapy problem and the minimum tumor volume is given by $p_{[C,pk]} = 249.598$. As before, the value of the carrying capacity at the final time, $q(T) = 564.528$, is almost identical with the optimal value in the monotherapy problem. In the suboptimal approximation there obviously is no need to approximate the control v that is already bang-bang. Choosing the same structure (19) as before, we now obtain the optimal switching times for the anti-angiogenic agent u as $t_1 = 1.180$, $t_2 = 3.590$, $t_3 = 8.286$ and $t_4 = 8.940$. The cytotoxic agent becomes activated at time $\tau = 10.545$ and the final time is given by $T = 15.545$. The constant approximation for the singular control is, as in the monotherapy problem, $\bar{u} = 3.725$, and the minimum tumor volume is $\tilde{p}_{[C,sub]} = 249.598$, once again identical with the optimal value.

4. **Conclusion.** In this paper, for four related mathematical models, we have given optimal solutions for the problem of minimizing the tumor volume with a priori given amounts of anti-angiogenic and cytotoxic agents. For the monotherapy problem [M] this solution is based on a complete analytical solution given earlier [20], for the other versions we presented numerically optimal solutions whose structures are in agreement with existing partial theoretical results. Clearly, the results that we presented are for one set of parameters and initial conditions. But we have seen the same structures of the optimal controls when parameters and initial conditions were varied (extreme variations, however, were not considered). For example, in accordance with existing cost limitations the numerical values used here somewhat make the anti-angiogenic agent the limiting quantity, but the structure of the solutions does not change if the total amount $y_{\max}$ is increased. Also based on theoretical analysis, there are three important conclusions that come out of our research:

(1) Optimal protocols for the combination therapy models can be built upon the structure of the optimal monotherapy solutions when only anti-angiogenic agents

are given. This is not generally true, in fact, quite rare, for arbitrary multi-input nonlinear control systems. It significantly aids in the solution of the combination therapy problem since it allows for an inductive solution procedure.

(2) The addition of a linear pharmacokinetic model changes the qualitative structure of the optimal control u for the anti-angiogenic agent, but only as far as the concatenations with the optimal singular control are concerned. These are now accomplished by means of chattering arcs. As our numerical results show, however, quantitative differences can be substantial.

(3) Although the mathematically optimal solutions are not practical, they provide guidelines on how to find simple, piecewise constant, sub-optimal controls with a very small number of segments that approximate the optimal values arbitrarily closely. These sub-optimal protocols generally can easily be computed as solution to some low-dimensional optimization problem. But it is only the fact that the optimal solution is known that allows to judge their effectiveness.

All our conclusions support a mathematical modeling approach that starts with the analysis of simplified models and then adds increasingly more complex and medically relevant features. If it is possible to build up the solutions step by step - this is the case with the model considered here, but also holds for other mathematical models for tumor anti-angiogenesis - then this approach has the advantage that it clearly brings out the importance of the individual portions (e.g., chemotherapy versus anti-angiogenic treatments). This also is one of the advantages of low-dimensional, minimally parameterized models. Large and complex models that try to fully and accurately reflect the underlying biology necessarily need to rely on simulations and thus only have a limited or local scope. Low-dimensional aggregate models make mathematical analysis possible that can give give more global insights into the underlying mechanisms. For example, the proposed suboptimal protocols are simple and thus realizable. They suggest that *few properly timed and chosen constant dosages are an effective means of administering the agents*. Naturally, any clinical implementation would be strongly dependent on the accuracy or correctness of the underlying model, but nevertheless our results provide a clear guidance as to what to look for.

Acknowledgments. We would like to thank the referees of this paper for their helpful comments.

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Received March 4, 2010; Accepted September 15, 2010.

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