Piecewise Constant Suboptimal Controls for a System Describing Tumor Growth under Angiogenic Treatment

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***Abstract*— A mathematical model for tumor anti-angiogenesis formulated by Ergun et al. [9] is considered as an optimal control problem with the aim of maximizing the tumor reduction achievable with an a priori given amount of anti-angiogenic agents. Optimal controls contain a segment along which the dosage follows a time-varying feedback control. With current medical technologies such a design is not realistic. In this paper the efficiency of piecewise constant, open-loop protocols with a small number of switchings is compared with the theoretically optimal solution derived earlier. It is shown that these protocols generally provide excellent suboptimal strategies, even when the times of applications are restricted to follow daily patterns.**

I. Introduction

Tumor anti-angiogenesis is a relatively new cancer treatment approach that aims at depriving a growing tumor of the blood vessel network it needs for growth. Initially, a growing tumor gets sufficient supply of oxygen and nutrients from the surrounding host blood vessels to allow for cell duplication and tumor growth. However, after this state of avascular growth is over, at the size of about $1-2$ mm in diameter, this no longer is true and most tumor cells enter the dormant stage in the cell cycle. These cells then produce vascular endothelial growth factor (VEGF) initiating the process of *tumor angiogenesis* [11]. During this stage of tumor development, surrounding mature host blood vessels are recruited 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. Surprisingly, the tumor also produces inhibitors that at times are used to suppress this process [12]. Anti-angiogenic treatments rely on these mechanisms by bringing in external inhibitors (e.g., endostatin) that target the endothelial cells and thus block their growth. 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 as a consequence no resistance to angiogenic inhibitors has developed in experimental cancer [5]. 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 [14].

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Mathematical models for tumor angiogenesis can broadly be divided into those that attempt to accurately describe the biological processes and aim at large scale simulations, e.g., [1], [4], and those that aggregate variables into low-dimensional dynamical systems enabling a theoretical analysis, e.g., [7], [8], [9], [13]. Amongst these the most prominent is the one by Hahnfeldt, Panigrahy, Folkman and Hlatky [13] who, modelling the tumor as a sphere, analyzed the underlying consumption diffusion process and formulated and biologically validated a system of ordinary differential equations with the primary tumor volume, p, and the carrying capacity of the vasculature, q, as its principal variables. The carrying capacity is the maximum tumor volume sustainable by the vascular network that supports the tumor with nutrients. Many other models are extensions and modifications based on the theoretical analysis in [13] in the sense that different or more general functions modelling tumor growth are used, and that modifications to the dynamics for the carrying capacity are considered. Here we consider one such modification formulated by Ergun, Camphausen and Wein [9]. The original model proposed in [13] exhibits a strong differential-algebraic character with a fast dynamics for the carrying capacity that reaches its steady-state very quickly. For this reason Ergun et al. modified the original equation so that the stimulation of the vascular support for the tumor becomes proportional to the tumor radius, not its surface area, as it is the case in the original formulation [13].

Although simplified, this model does retain essential qualitative features of the original formulation. In [9] the optimal control problem of how to schedule treatment in order to maximize the tumor reduction achievable with a given amount of angiogenic inhibitors was postulated. (Similar formulations are considered in [22], [21].) Using methods of geometric optimal control (e.g., see [2], [6]), Ledzewicz and Schättler have given a full theoretical solution to this problem in [17] for the original model by Hahnfeldt et al. and in [15] for its modification by Ergun et al. Both solutions are qualitatively identical and consist of two types of controls: bang-bang and singular pieces. These are the typical controls arising in optimal control problems whenever the Hamiltonian is linear in the control and there exists a vast literature devoted to their analysis (e.g., [3], [10], [20]). In the models for tumor anti-angiogenesis considered here,

the control represents the dosage of the drug and bang-bang controls correspond to protocols that give drugs in full dose sessions with rest periods and can easily be implemented. This, however, is not the case for the singular controls that are defined as feedback functions depending on the states $p(t)$ and $q(t)$ of the system. Clearly, given current medical technologies such a control does not give rise to a realizable treatment protocol. Thus the following natural question arises: how good are simple, piecewise constant strategies, the typical way of administering drugs? Knowing the optimal solution allows to evaluate the efficiency of other protocols. In [19] we have shown that excellent approximations can be obtained for the original model by Hahnfeldt et al. if treatment protocols are optimized over some simple classes of piecewise constant treatment functions, both with and without restrictions on their duration. In this paper, we verify that the same is true for the modification by Ergun, Camphausen and Wein. While a minimization with free time intervals obviously does better, even when the duration is restricted to practical schemes (e.g., daily administrations that include rest periods) very good results are obtained.

II. A Mathematical Model for Tumor Anti-Angiogenesis

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

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

with ξ a growth parameter. The dynamics for the carrying capacity q consists of a balance between stimulatory and inhibitory effects. In this modification of the model from [13] by Ergun et al. [9], the stimulation of the vascular support by the tumor is taken proportional to the tumor radius. Furthermore, replacing p with q in steady state allows to simplify the dynamics to become independent of p,

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

The terms $bq^{\frac{2}{3}}$ and $dq^{\frac{4}{3}}$ represent endogenous stimulation and inhibition terms, respectively, while loss of vascular support through natural causes 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 last term Guq models loss of vascular support due to outside inhibition 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 obvious question *how to administer a given amount of angiogenic inhibitors to achieve the "best possible" effect* then arises and this leads to an optimal control problem. One natural formulation, first posed in [9] and then taken up by us in [15]-[17], is to maximize the tumor reduction achievable with a given amount of inhibitors. It follows from the p-dynamics that, regardless of the control, the tumor volume always decreases in the region $p > q$. Thus, if p is greater than q when all inhibitors have been exhausted, the minimum of the tumor volume will only be realized along a subsequent trajectory corresponding to the control $u = 0$ when this trajectory crosses the diagonal $p = q$. We thus consider the following problem:

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

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

subject to the dynamics (1), (2) with initial conditions p_0 and q_0 over all Lebesgue measurable 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,

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

The upper limit a in the definition of the control set $U = [0, a]$ is a previously determined maximum dose at which inhibitors can be given. In the formulation T is not a therapy horizon, but is the time when the maximum tumor reduction is achieved.

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

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

$$\dot{q} = bq^{\frac{2}{3}} - \mu q - dq^{\frac{4}{3}} - Guq, \qquad q(0) = q_0, \tag{6}$$

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

Naturally, by their definition all the state variables need to be positive. It is easily seen [16] that this condition is ensured by the dynamics and thus it need not be imposed as an explicit constraint. The problem formulation $[OC]$ also includes initial conditions that are ill-posed in the sense that available inhibitors are too small to achieve a tumor reduction at all and in this case the mathematically optimal solution is given by $T = 0$ (see, [17]). In this paper, we only consider *well-posed* data for which T is positive.

III. The Optimal Solution for Problem [OC] [15]

We summarize the complete solution for the optimal control problem $[OC]$ presented in the form of a *synthesis* of optimal controls in [15]. A synthesis provides a full "road map" to all optimal protocols depending on the initial condition in the problem, both qualitatively and quantitatively.

Theorem 3.1: [15] 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 no inhibitors are given, $u \equiv 0$, **a** denotes an interval along which the optimal control is constant at full dose, $u \equiv a$, and **s** denotes an interval along which the optimal control follows a time-varying feedback control. This so-called singular 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 with **as0** the biologically most relevant scenario. ■

Despite their name, for an optimal control problem of the type $[OC]$ with nonlinear dynamics singular controls and the corresponding singular curves are to be expected in a synthesis of optimal controls [6]. In fact, the singular control and the geometry of the singular curve $\mathcal{S}$ are the most important piece in the design of optimal protocols and below we give their analytic formulas that were derived in [15], [16].

Theorem 3.2: There exists a locally minimizing singular arc $\mathcal{S}$ defined in (p,q)-space as a function of q by

$$p_{\sin}(q) = q \exp\left(3\frac{b - dq^{\frac{2}{3}} - \mu q^{\frac{1}{3}}}{b + dq^{\frac{2}{3}}}\right) \tag{8}$$

over an interval $q_\ell^* \leq q \leq q_u^*$; the corresponding singular control is given in feedback form as

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

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

Fig. 1 illustrates the singular curve $\mathcal{S}$ and its admissible portion is shown as the solid segment on the curve. The parameter values that were used are taken from [13]: 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 $a = 15$ *mg of dose per day* and $A = 45$ *mg*. In all our figures we plot p vertically and q horizontally since this more easily visualizes tumor reductions. We would like to emphasize that all our theoretical results (Theorems 3.1 and 3.2, and also the structure of the synthesis of optimal controlled trajectories described below), are fully robust with respect to *all* parameters and that these values are only used for numerical illustration.

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 corresponds to a different optimal trajectory depending on the actual initial condition. The thicker 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 carrying capacity are high and require to start the treatment immediately. This is the most characteristic scenario and corresponds to a phase when the tumor is growing aggressively. The optimal controlled trajectory therefore initially follows the curve corresponding to the control $u = a$. Note that, although

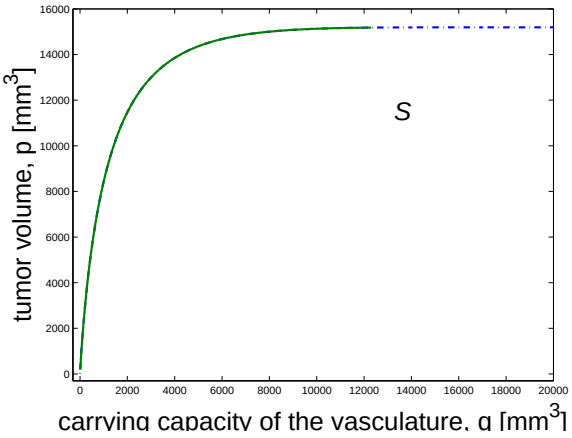

Fig. 1. The singular arc $\mathcal{S}$ with its admissible portion identified as a solid curve

inhibitors are given at full dose along this curve, only when the trajectory gets near the singular curve the cancer volume starts to decrease. The reason is that during the beginning phase of treatment the inhibitors drive down the carrying capacity and in this way prevent a further growth of the tumor that otherwise, enabled by its 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. In the absence of saturation of the singular control at its upper limit a, the optimal trajectory then follows the singular arc until all inhibitors become 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 $p = q$.

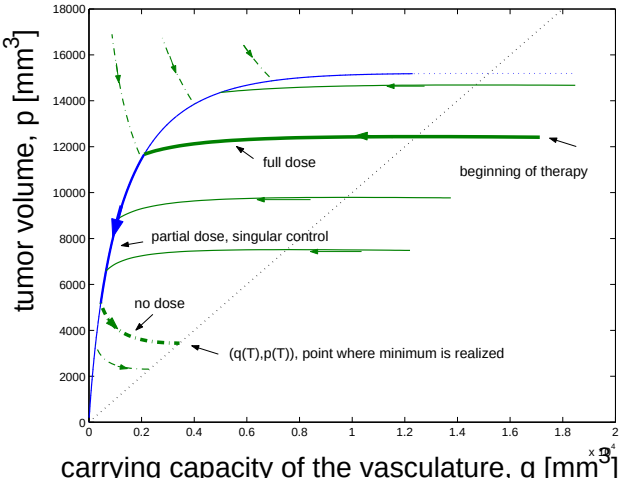

Fig. 2. Synthesis of optimal controlled trajectories

Fig. 3 gives an example of the optimal control for the initial conditions $(p_0, q_0) = (8,000\,mm^3; 10,000\,mm^3)$, a typical initial condition in the region $p_0 < q_0$. The optimal concatenation sequence is **as0**: first 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. Then administration follows the time-varying singular control for $t_2 = 3.722$ days until inhibitors are exhausted at time 5.062 days. Due to after effects, the maximum tumor reduction is realized along a trajectory for the control $u = 0$ at the terminal time $T = 9.379$ days when the trajectory reaches the diagonal $p = q$. The theoretically optimal minimum value for these data is given by $p_* = p(T) = 2242.65$.

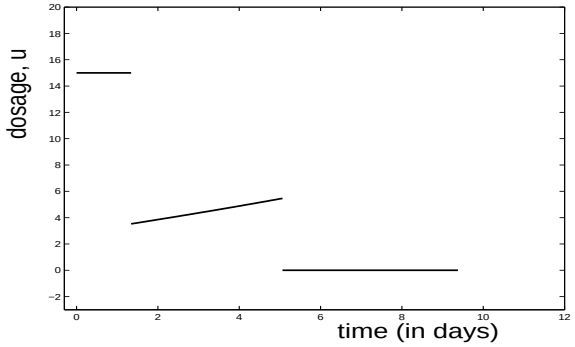

Fig. 3. Optimal control for $(p_0, q_0) = (8,000\, mm^3; 10,000\, mm^3)$

IV. Realizable Suboptimal Protocols

We now use the same initial condition $(p_0, q_0) = (8,000\, mm^3; 10,000\, mm^3)$ to construct several suboptimal, piecewise constant controls - hence realizable protocols - and compare their minimum values with the optimal one.

A. Optimal constant dosage protocols

We start with strategies that give the full amount A of inhibitors at a constant rate and minimize the tumor volume achievable in this way. Given $u \in [0, a]$, let $t_u = \frac{A}{u}$ and denote the endpoint by $(p_u(t_u), q_u(t_u))$. If this point lies above the diagonal, $p_u(t_u) > q_u(t_u)$, then, since the carrying capacity is smaller than the tumor volume, there will still be an additional tumor reduction. Hence, and in order to be consistent with the problem formulation $[OC]$, we still concatenate the trajectory at the point $(p_u(t_u), q_u(t_u))$ with a trajectory corresponding to the control $u = 0$ that steers the system to its unique associated point $(\pi_u(T_u), \pi_u(T_u))$ on the diagonal. Minimizing the values $\pi_u(T_u)$ gives the optimal constant dosage,

$$u_* = \arg\min \pi_u(T_u) = 9.246, \tag{10}$$

with corresponding minimal tumor volume $p_* = 2264.22$. Inhibitors are given for $t_1 = 4.867$ days and then the control is $u_* = 0$ 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. 4 shows the optimal constant dosage trajectory.

For comparison, in [18] we considered the constant dosage $\bar{u} = 8.888$ that was computed by averaging the theoretically optimal dosages over the time span of 5.062 days when drugs are administered (not including the final segment with $u = 0$). Such a dose can always be obtained as an immediate

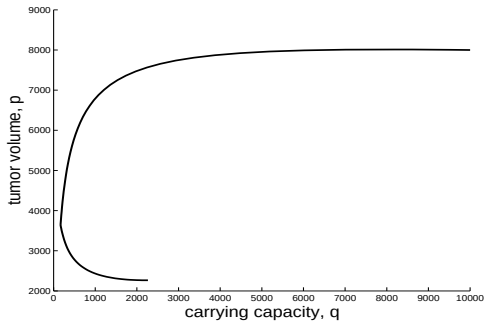

Fig. 4. Optimal constant dosage trajectory

byproduct of the calculation of the optimal control. For this strategy the virtually identical value $p_{\bar{u}} = 2264.44$ is obtained at $T = 9.732$ days. Both numerical results are within about 1% of the theoretically optimal value and thus provide an excellent approximation. Furthermore, the value function $\pi_u(T_u)$ is rather flat around its minimum value and thus any dosage that will be reasonably close to the minimum dosage u_* gives excellent values.

B. Optimal 2-stage protocols

The optimal control contains a singular piece that can be approximated with better accuracy by bang-bang controls with an increasing number of switchings [6], [20]. It is therefore expected that the value $p_* = 2264.22$ can be improved upon by increasing the number of switchings in the control. We thus also 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 inhibitors become exhausted, i.e.,

$$u_1 t_1 + u_2 t_2 = A. \tag{11}$$

This becomes 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, we denote the point when the inhibitors are exhausted by $(p_v(t_v), q_v(t_v))$ and by $\pi_v(T_v)$ the associated point on the diagonal that is obtained by still following a trajectory for $u = 0$ until the diagonal $p = q$ is reached at time T. The minimizing controls v_*,

$$v_* = \arg\min \pi_v(T_v), \tag{12}$$

are then given by $u_1 = 15$ for time $t_1 = 1.273$ days and $u_2 = 6.710$ for $t_2 = 3.861$ days with $t_3 = 4.240$ the time along the final $u = 0$ segment and $T = 9.374$. In this case, since the optimal control for problem $[OC]$ is at maximum dose for a significant time interval, 1.341 days, the optimal two-stage regimen starts out at maximum dose and even the times are close. The second dosage u_2 gives the remaining inhibitors at a slightly higher value than the averaged singular control would do, but shorter in time. The optimal value decreases to 2242.75, practically identical with the optimal value 2242.65.

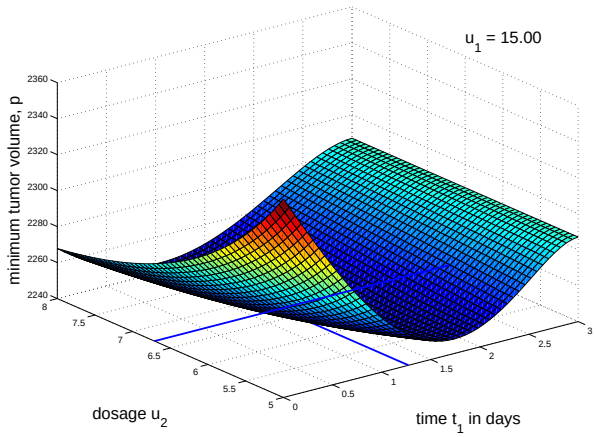

Fig. 5. A cross section through the graph of $\pi_v(T_v)$ for $u_1 = 15.00$

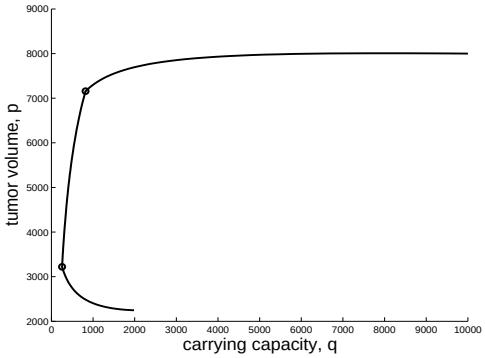

Fig. 6. Trajectory for the optimal two-dosage protocol v_*

Fig. 5 shows a cross section of the value $\pi_v(T_v)$ when the first dosage is kept fixed at its optimal (and maximum) value $u_1 = 15.00$. It is interesting to note how much worse a higher second dose u_2 does in this case. Essentially, the carrying capacity has been lowered enough so that too high a dose just wastes inhibitors. Fig. 6 gives the graph of the corresponding optimal trajectory.

We summarize the results for the optimal constant and 2-stage protocols in Table I.

C. Daily regimes

In the two optimization schemes considered above, we left the time durations for the dosages free, i.e., these times were optimization variables. It is of practical interest to also consider treatment schedules that specify these durations a priori. Of course, doing this reduces the flexibility and leads to weaker approximations. But this effect can be offset by increasing the number of segments. It appears reasonable, to give all available inhibitors over the same time period as the optimal control does, but not counting the final segment along which $u = 0$. For the initial condition $(p_0, q_0) = (8,000\,mm^3; 10,000\,mm^3)$ all inhibitors are being exhausted in 5.063 days along the optimal solution.

control	*optimal*	u_*	v_*
u_1	15.00	9.246	15.00
t_1	1.341	4.867	1.273
u_2	*singular*	–	6.710
t_2	3.722	–	3.861
t_3	4.315	4.735	4.240
T	9.378	9.602	9.374
minimal value	2242.65	2264.22	2242.75

TABLE I

COMPARISON OF THE MINIMAL VALUES FOR PIECEWISE CONSTANT DOSAGE PROTOCOLS FOR THE MODEL BY ERGUN ET AL. [9]: u_* IS THE BEST CONSTANT DOSE, v_* GIVES THE BEST 2-STAGE VALUES.

Minimizing daily doses over 6 periods, it turns out that the optimal dosage for the sixth day is equal to $u = 0$ and we obtain the following optimal daily dosages,

$$u_1 = 15, \quad u_2 = 9.73, \quad u_3 = 5.45,$$
$$u_4 = 6.88, \quad u_5 = 7.94 \quad u_6 = 0. \tag{13}$$

The minimum value realized is given by $p(T) = 2243.15$, slightly worse than the optimal 2-stage protocol with free times. Allowing for 6 dosages thus makes up for the loss of freedom by choosing the times in a 2-stage control.

Note the dips in the dosages on the second and third day while the dosage increases for the fourth and fifth day. This pattern follows the structure of the optimal control. At the junction with the singular arc after 1.341 days, the optimal control drops to the value $u = 3.53$ at the onset of the singular portion. In the daily doses for the second day this still averages out to a value that is higher than the third dose when the optimal control is singular for the entire period. Then the dosage intensifies along the singular arc (see Fig. 3) and this is reflected in the optimal daily dosages.

If one includes rest periods into each daily regimen, say inhibitors are given at a constant rate only for 8 or 12 hours, then the 12-hours scheme would use up the amount $A = 45$ in exactly 6 daily dosages at the maximum $u = 15$. Because of the requirement that all inhibitors should be exhausted, in this case no optimization problem arises. Similarly, if we only give inhibitors for 8 hours, then 9 days need to be considered at maximum dosage. Fig. 7 shows this 8-hours on, 16-hours off trajectory and for comparison we also include the optimal trajectory as the black curve. Naturally, the quality of the approximation decreases with these schemes. The minimal tumor volume realized with the 12-hours scheme is $p_{12\text{hr}} = 2262.29$ and for the 8-hours scheme it is $p_{8\text{hr}} = 2335.99$. While the value for 12-hour periods is still in the same range as the optimal constant dosage, degradation occurs if the rest-periods become too large. Longer rest periods allow the carrying capacity to recover and for the 8 hour scheme the relative error now is 4.16%, quite large compared to other values.

Fig. 8 compares the optimal daily controls when the upper limit a in the control set has been doubled to $a = 30$. The solid red lines correspond to the optimal 12-hours dosages while the solid blue lines give the optimal daily doses. For

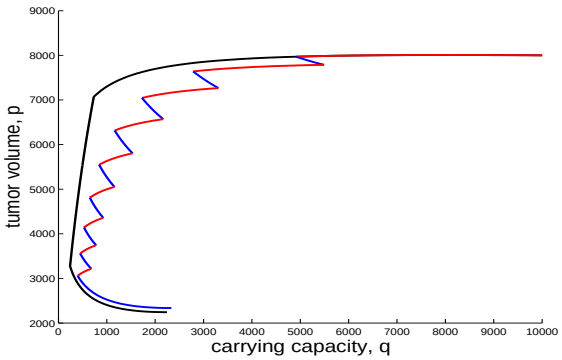

Fig. 7. Trajectory corresponding to 8-hours daily doses

comparison, the dashed lines are the average values of the 12-hours doses for the full day and these are very close to the optimal daily values.

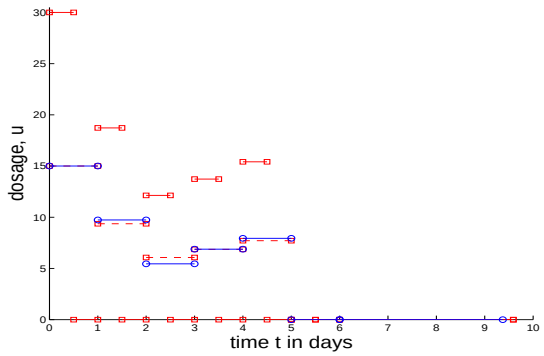

Fig. 8. Comparison of the optimal 8- and 12-hours dosages for $a = 30$.

V. Conclusion

The solutions to an optimal control problem for a mathematical model for tumor anti-angiogenesis formulated by Hahnfeldt et al. [13] and also its modification by Ergun et al. [9] considered in this paper contain segments where the optimal control is given by a feedback function of the state variables. While such a strategy does not give rise to a realistic therapy protocol, knowing the optimal solutions allows to judge how close to optimal other simple and realizable strategies come. In this paper, we have shown for the model by Ergun et al. [9] that easily computable, piecewise constant controls provide very good suboptimal practical protocols. Both the structure of the optimal controls and its suboptimal approximations clearly point to the importance of selecting a good level for the dosages. If the dosage is too small, or if rest periods are inserted that are too long, then the overall effects are diminished and treatment may simply become ineffective. On the other hand, too high a dosage becomes wasteful use of inhibitors. Typically results improved when, rather than giving inhibitors at full rate, their dosages were lowered and the administration of the overall amount of inhibitors was spread out in time. Thus there seems to exist "optimal" dosages to give over time and their determination should also be of practical interest.

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