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THE SCHEDULING OF ANGIOGENIC INHIBITORS MINIMIZING TUMOR VOLUME

The efficiency of piecewise constant protocols with a small number of switchings is investigated for a mathematical model of tumor anti-angiogenesis formulated originally by Hahnfeldt et al. in [8]. By comparing with the theoretically optimal solution derived earlier [12] it will be seen that for the problem of minimizing the primary cancer volume with a given amount of angiogenic inhibitors to be administered constant protocols already provide very good suboptimal strategies.

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. 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, at the size of about 2 mm in diameter, this no longer is true and many of the tumor cells enter the dormant stage G_0 in the cell cycle. These cells then produce vascular endothelial growth factor (VEGF) to start the process of *angiogenesis* [6] to recruit surrounding, mature, host blood vessels in order to develop the tumor's own blood vessel capillaries needed for supply of nutrients [10]. 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 [7]. Overall angiogenesis is based on a complex balance of tightly regulated stimulatory and inhibitory mechanisms. Anti-angiogenic treatments rely on these mechanisms by bringing in external angiogenic 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. Since 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 inhibitors has developed in experimental cancer [3]. 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 [9] and as such in the last ten years it has been an active area of research not only in medicine, but also in related disciplines including mathematical biology.

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Following these advances in medical research, several mathematical models describing the dynamics of angiogenesis have been proposed that try to accurately reflect the biological processes, e.g., [1, 2]. However, due to the inherent complexity of these processes naturally such models are more suitable for large scale simulations than mathematical analysis. A notable distinction is the model proposed in [8] by Hahnfeldt, Panigrahy, Folkman and Hlatky, a group of researchers then at Harvard Medical School, who developed and biologically validated a two-dimensional model of ordinary differential equations for the interactions between the primary tumor volume, p, and the carrying capacity of the vasculature, q. Since the carrying capacity largely depends on the volume of endothelial cells, we also call q the endothelial support for short. Several modifications of this model have been introduced and analyzed in the literature since then, e.g., [4, 5], and in various papers like [12, 15] the problem of scheduling angiogenic inhibitors has been analyzed for these models as an optimal control problem: given an a priori specified amount of angiogenic inhibitors, how should they be scheduled in order to minimize the tumor volume p? Using methods of geometric optimal control in [12] we gave a complete theoretical solution to this problem for all possible initial conditions for the model formulated in [8]. This optimal solution typically has a segment along which the control is singular and is given by a feedback control depending on the current states $p(t)$ and $q(t)$ of the system. However, with the current state of medical technologies such a control is not a realizable treatment protocol. Hence the question as to what are good, but simple and realistic strategies arises. Knowing the optimal solution to the problem allows us to judge the quality of heuristically chosen strategies or protocols that are optimized over a simple class of treatment functions and thus make a well informed assessment of the quality of these strategies. In this paper we consider some of these simple strategies and evaluate their effectiveness for the model by Hahnfeldt et al. [8].

2. A MATHEMATICAL MODEL FOR TUMOR ANTI-ANGIOGENESIS, [8]

This mathematical model was developed and biologically validated by Hahnfeldt, Panigrahy, Folkman and Hlatky in [8] 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 modeled 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 in [8]

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

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 modeled as μq. 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. It is argued in [8] that this term grows like volume of cancer

cells to the power $\frac{2}{3}$ with the exponent $\frac{2}{3}$ arising through the interplay of the surface of the tumor through which the inhibitor needs to be released with the volume of endothelial cells that form the lining of the newly developing capillaries. 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 problem which then arises naturally is *how to administer a given amount of angiogenic inhibitors to achieve the "best possible" effect* and this leads to optimal control problems. One possible formulation, considered first in [5] and then taken up by us in [12] for this model and also in [11, **?**] for two of its variations, is to minimize the tumor volume or, what is the same, maximize the tumor reduction possible with the given amount of inhibitors. Since the dynamics includes after effects of the treatment - even for the control $u = 0$ we have that $\dot{p} < 0$ whenever $p > q$ - in a mathematical formulation this is taken into account by leaving the terminal time T free or, equivalently, minimize over trajectories defined on the full semi-infinite interval $[0, \infty)$. We thus consider the following problem:

[OC] For a free terminal time T, minimize the value $J(u) = p(T)$ 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 inhibitors to be administered,

$$\int_0^T u(t)dt \leq A, \tag{3}$$

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 inhibitors 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 p is greater than q when all inhibitors have been exhausted, this minimum for the tumor volume will only be realized along a subsequent trajectory corresponding to the control $u = 0$ when this trajectory reaches the diagonal $p = q$.

3. THE OPTIMAL SOLUTION FOR PROBLEM [OC], [12]

In [12] we gave a complete solution for the optimal control problem $[OC]$ 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. For this model an interval along which the optimal control follows a time-varying singular feedback control is central to the synthesis. This control is only optimal while the system follows a specific curve $\mathcal{S}$ in the (p, q)-space, the optimal singular arc. Despite their name, singular controls are to be expected in a synthesis of optimal controls for a problem of the type $[OC]$ for nonlinear models and are an essential part of the design of the optimal protocol. The derivation of the formulas for singular controls and the corresponding singular curve below are given in [12].

Using $x = \frac{p}{q}$ the singular curve $\mathcal{S}$ can be parameterized in the form

$$\mu + dp^{\frac{2}{3}} = bx(1 - \ln x) \tag{4}$$

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

$$\varphi(x) = \frac{b}{d}x(\ln x - 1) + \frac{\mu}{d} = 0 \tag{5}$$

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 x by

$$u_{\sin}(t) = u_{\sin}(x(t)) = \frac{1}{G}\left[\left(\frac{1}{3}\xi + bx(t)\right)\ln x(t) + \frac{2}{3}\xi\left(1 - \frac{\mu}{bx(t)}\right)\right]. \tag{6}$$

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 $x_1^* < x_\ell^* < 1 < x_u^* < x_2^*$.

Fig. 1 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 the numerical computations the following parameter values taken from [8] were used: 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*. For this initial condition the concatenation sequence for the optimal control is **as0**: first the optimal control is given at full dosage $u = a = 75$ until the singular curve $\mathcal{S}$ is reached at time $t_1 = 0.0905$ days. Then administration follows the time-varying singular control until inhibitors are exhausted at time $t_2 = 6.5578$ days. Due to after effects the maximum tumor reduction is realized along a trajectory for control $u = 0$ at the optimal terminal time $T = 6.7220$ days when the trajectory reaches the diagonal $p = q$. In the remainder of this paper 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 $p_* = p(T) = 8533.38$.

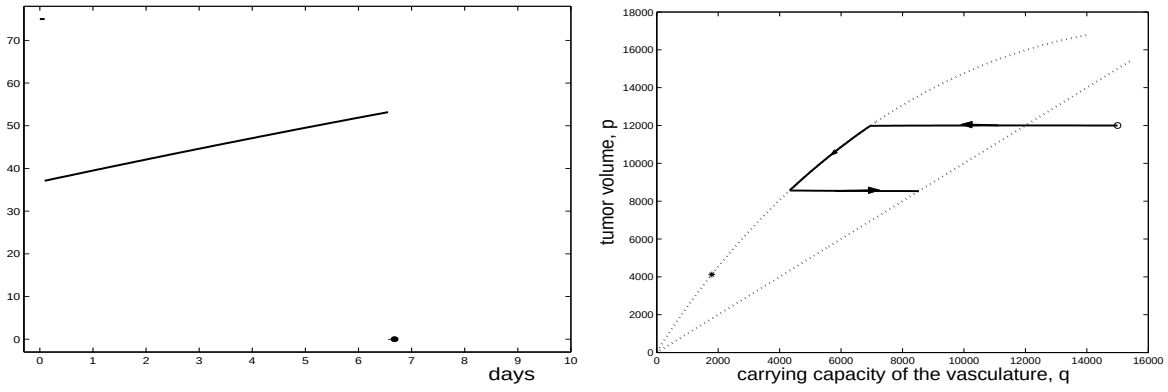

Figure 1: (a, left) Optimal control and (b, right) corresponding trajectory for $(p_0, q_0) = (12,000\,mm^3; 15,000\,mm^3)$

4. REALIZABLE SUBOPTIMAL PROTOCOLS

We now calculate several suboptimal, piecewise continuous controls for the same initial condition $(p_0, q_0) = (12,000\, mm^3; 15,000\, mm^3)$ starting with controls that give all available inhibitors in one constant dosage. The following numerical results for the different suboptimal protocols were obtained using the optimization toolbox of Matlab and the arc-parametrization method developed in Maurer, Büskens, Kim and Kaya [14].

One way to approach the problem is to simply give the available amount A of inhibitors 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,

$$\hat{u} = \arg\min \hat{p}_u(t_u). \tag{7}$$

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

$$\hat{u} = 45.27 \quad t_u = A/\hat{u} = 6.626. \tag{8}$$

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

A formulation that is consistent with problem $[OC]$ is to give all available inhibitors 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 inhibitors have been exhausted 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 were the minimum tumor value for this strategy is realized. Minimizing the p-value on the diagonal gives the following optimal control

$$u_* = \arg\min \pi_u(T_u) = 46.34 \tag{9}$$

and the corresponding minimal tumor volume is $p_* = 8544.15$. 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 $T = 6.777$. 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, in [13] we also considered the constant dosage,

$$\bar{u} = 45.75, \tag{10}$$

that was computed by averaging the theoretically optimal dosages over the time span $t_2 = 6.558$ 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 $p_{\bar{u}} = 8570.09$. Adding the final segment $u = 0$ we get the minimum value 8544.30 with final time $T = 6.709$.

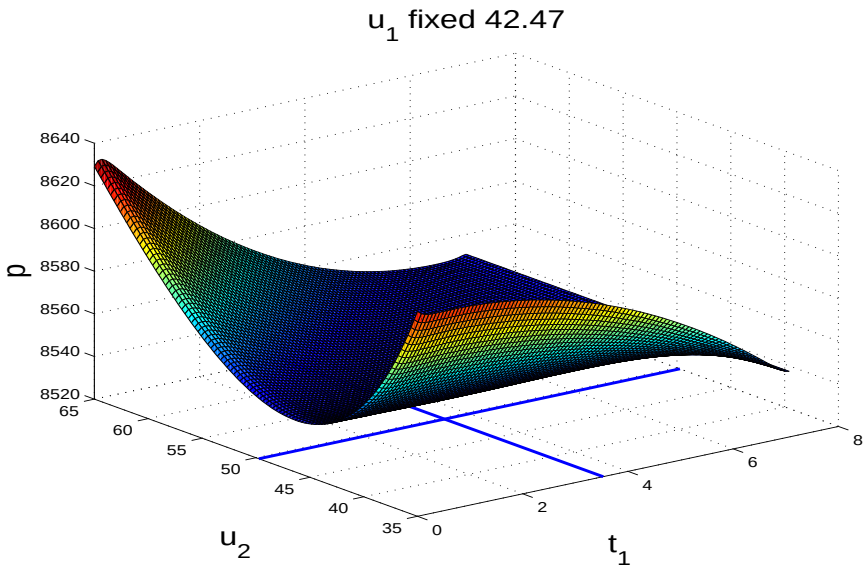

Figure 2: A cross section through the graph of $\pi_v(T_v)$ for $u_1 = 42.47$

Clearly these constant dose protocols already provide excellent approximations to the theoretically optimal control. Since this one contains a singular piece and it is a common understanding that an optimal singular arc can be approximated by a sequence of bang-bang trajectories with improving accuracy with an increasing number of switchings, it is expected that the 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 inhibitors become exhausted, i.e.,

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

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 inhibitors 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,

$$\hat{v} = \arg\min \hat{p}_v(t_v) \qquad \text{and} \qquad v_* = \arg\min \pi_v(T_v). \tag{12}$$

The optimal values for the same data and initial conditions specified earlier are summarized in Table 1. Consistent with the dose intensification along the optimal singular control these dosages increase: $u_2 > u_1$. Note that $\hat{v}$ and v_* are close to each other, but their durations differ by quite a bit. However, this does not much effect the minimum tumor volume and overall 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. Fig. 2 gives the graph of the values $\pi_v(T_v)$ when the first dosage is kept fixed at its optimal value $u_1 = 42.47$

In these approaches so far we left the durations of the various dosages free, i.e., included the times along these dosages as an optimization variable. It may be of practical interest to specify these durations a priori, for instance, give daily dosages. However, any such strategy reduces the flexibility and leads to weaker approximations, even if the number of pieces is increased.

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

Table 1: Comparison of minimal values for various 2-stage constant dosages protocols

For example, for the same data, if we specify to give all available inhibitors in 6 daily doses, then the optimal dosages are given by

$$u_1 = 46.61,\ u_2 = 45.31,\ u_3 = 48.15,\ u_4 = 50.71,\ u_5 = 53.20,\ \text{and}\ u_6 = 56.02. \qquad (13)$$

We then still follow the trajectory for $u = 0$ for time $t_7 = 0.1690$ until the diagonal $p = q$ is reached with minimal value $p(T) = 8544.40$. 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 optimal control that initially gives the control at maximum dose and then switches to the singular control. Since the piece along which the optimal control is at maximum dose is small, the first daily value is significantly lower, but it still is higher than the second daily dose. Along the optimal singular arc the doses intensify 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. In this case, having 6 pieces gives a minimal tumor value of 8544.40. Thus this is comparable to the constant dosages, but it does not yet make up for the loss of freedom by choosing the times in a 2-piece control. Fig. 3 shows the corresponding trajectory in the (p, q)-space with p shown horizontally and q vertically.

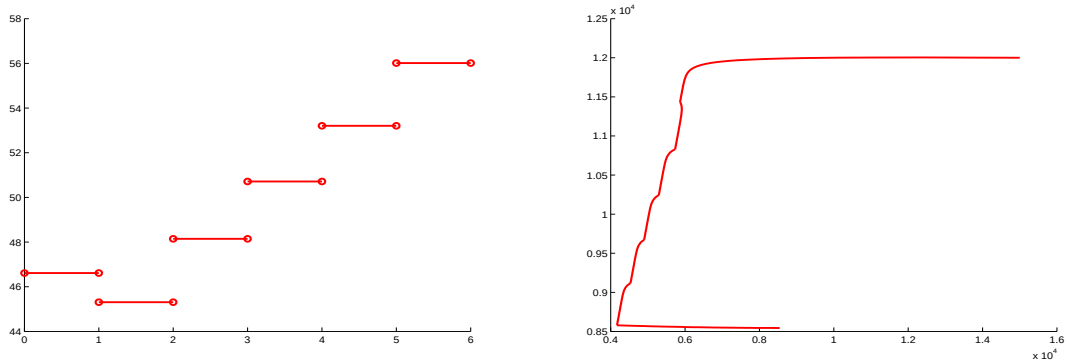

Figure 3: (a, left) Optimal daily doses and (b, right) corresponding trajectory

5. CONCLUSION

In this paper, based on knowledge of the theoretically optimal solution, we have shown that easily computable piecewise constant controls give excellent suboptimal protocols that come within 0.25% of the optimal tumor values for the initial condition $(p_0, q_0) = (12,000\, mm^3; 15,000\, mm^3)$ and the data specified. More generally, for realistic initial conditions strategies

that divide the overall amount of inhibitors into a small number of constant dose intervals come within 1% of the theoretically optimal values (see [13]). We also considered strategies that rather than allowing to optimize the time periods a priori fixed this structure in time to giving daily doses. Summarizing, simple piecewise constant approximations to the optimal singular control provide excellent suboptimal realizable protocols. 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.

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References

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

[2] ARAKELYAN L., VAINSTAIN V., and AGUR Z., A computer algorithm describing the process of vessel formation and maturation, and its use for predicting the effects of anti-angiogenic and anti-maturation therapy on vascular tumour growth, *Angiogenesis*, **5**, (2003), 203ff

[3] BOEHM T., Folkman J., BROWDER T., and O'REILLY M.S., Antiangiogenic therapy of experimental cancer does not induce acquired drug resistance, *Nature*, 390, (1997), pp. 404ff

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

[5] ERGUN A., CAMPHAUSEN K., and WEIN L.M., Optimal scheduling of radiotherapy and angiogenic inhibitors, *Bull. of Math. Biology*, **65**, (2003), pp. 407-424

[6] FOLKMAN J., Antiangiogenesis: new concept for therapy of solid tumors, *Ann. Surg.*, 175, (1972), pp. 409-416

[7] FOLKMAN J., Angiogenesis inhibitors generated by tumors, *Mol. Med.*, **1**, (1995), pp. 120-122

[8] HAHNFELDT P., PANIGRAHY D., FOLKMAN J. and HLATKY L., Tumor development under angiogenic signaling: a dynamical theory of tumor growth, treatment response, and postvascular dormancy, *Cancer Research*, **59**, (1999), pp. 4770-4775

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

[10] KLAGSBURN M. and SOKER S., VEGF/VPF: the angiogenesis factor found?, *Curr. Biol.*, **3**, (1993), pp. 699-702

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

[12] LEDZEWICZ U. and SCHÄTTLER H., Anti-Angiogenic Therapy in Cancer treatment as an Optimal Control Problem, *SIAM J. on Control and Optimization*, **46** (3), (2007), pp. 1052-1079

[13] LEDZEWICZ U. and SCHÄTTLER H., Optimal and Suboptimal Protocols for a Class of Mathematical Models of Tumor Anti-Angiogenesis, *J. of Theoretical Biology*, **252**, (2008), pg. 295-312

[14] MAURER, H., BÜSKENS, C., KIM, J.-H.R. and KAYA, C.Y., Optimization methods for the verification of second order sufficient conditions for bang–bang controls, *Optimal Control Applications and Methods*, **26**, (2005), pp. 129–156

[15] SWIERNIAK A., GALA G., GANDOLFI A. and d'ONOFRIO A., Optimization of angiogenic therapy as optimal control problem, Proceedings of the 4th IASTED Conference on Biomechanics, Acta Press, (Ed. M. Doblare), (2006), pp. 56-60