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MODEL FOR CANCER THERAPY WITH PENALTY ON THE COST OF TREATMENT

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Abstract: For a biologically validated mathematical model for tumor anti-angiogenesis developed by Hahnfeldt et al [3] the scheduling of angiogenic inhibitors is analyzed as an optimal control problem. In the objective a weighted balance between tumor reduction and the total amount of angiogenic inhibitors given is considered. Bifurcations of optimal solutions are illustrated numerically.

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1. Introduction

Tumor anti-angiogenesis is a cancer treatment approach that targets the vasculature of a growing tumor. A solid tumor, after going through an initial state

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of avascular growth, starts the process of *angiogenesis*, i.e., the recruitment of surrounding host blood vessels in order to facilitate its own supply of nutrients. Anti-angiogenic treatments bring in external inhibitors to disrupt this process and thus indirectly effect the tumor which, deprived of necessary nutrition, regresses. These inhibitors, like endostatin, are very expensive biological agents. Since there also always is a need to keep side effects under control, the question how to administer a given amount of inhibitors in an optimal way arises naturally and this leads to optimal control problems.

In this paper we consider such a problem for a biologically validated, two-dimensional model of ordinary differential equations developed in 1999 by Hahnfeldt, Panigrahy, Folkman and Hlatky, [3], a group of researchers then at Harvard Medical School. In [5] we gave a complete solution (in terms of a regular synthesis of optimal controls [2]) for this model for the problem how to schedule a given amount of inhibitors in order to maximize the tumor reduction achievable. In this paper we consider a modified objective that better balances the total amount of inhibitors given with the benefit to be gained in tumor reduction. Rather than specifying the total amount of inhibitors a priori, we incorporate this amount as a penalty term in the objective and then minimize a weighted average between the inhibitors given and the minimum tumor volume. Based on our earlier results optimal controls are determined. Depending on the weight that is given to the inhibitors in the objective bifurcations in the structure of optimal controls arise and will be illustrated numerically.

2. Mathematical Model [3] and Synthesis of Optimal Solutions [5]

We briefly review the underlying mathematical model of Hahnfeldt et al [3]. The growth of the tumor volume p is modeled as Gompertzian with variable carrying capacity of the vasculature q,

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

where ξ denotes a tumor growth parameter and dynamics for the endothelial support is given in the form

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

Here bp models the stimulation of the vasculature by the tumor and the term $dp^{\frac{2}{3}}q$ models endogenous inhibition of the tumor (see [3]). The exponent $\frac{2}{3}$ arises since these inhibitors are being released through the tumor surface. The coefficients b and d are growth constants. The terms μq and Guq describe,

respectively, loss to the endothelial cells through natural causes (death etc.), and loss of endothelial cells due to additional outside inhibition. The variable u represents the control in the system and corresponds to the angiogenic dose rate while G is a constant that represents the anti-angiogenic killing parameter. In [4, 5] we solved the following optimal control problem:

(P1) for a free terminal time T, minimize the value $J_1(u) = p(T)$ subject to the dynamics (1) and (2) over all Lebesgue measurable functions $u : [0, T] \to [0, a]$ that satisfy a constraint on the total amount of anti-angiogenic inhibitors to be administered, $\int_0^T u(t)dt \leq A$.

It is shown in [5] that an optimal singular arc $\mathcal{S}$ is the center piece for the synthesis of optimal controls. In the variables (p, x) with $x = \frac{p}{q}$ this curve $\mathcal{S}$ can be parameterized in the form

$$p^2 + \left(\frac{bx(\ln x - 1) + \mu}{d}\right)^3 = 0 \qquad \text{for} \quad x_1^* < x < x_2^*\,, \tag{3}$$

and the singular control that keeps the system on the singular curve is given as a feedback function of x in the form

$$u_{\sin}(x) = \frac{1}{G}\left[\left(\frac{1}{3}\xi + bx\right)\ln x + \frac{2}{3}\xi\left(1 - \frac{\mu}{bx}\right)\right]. \tag{4}$$

Furthermore, there exists exactly one connected arc on the singular curve $\mathcal{S}$ along which the singular control is admissible, i.e., satisfies the bounds $0 \leq u_{\sin}(x) \leq a$.

The admissible singular arc becomes the center piece of the synthesis of optimal solutions illustrated in Figure 1. The important curves are the admissible portions of the singular curve (solid curve), portions of trajectories corresponding to the constant controls $u = 0$ (almost horizontal dash-dot curves) and $u = a$ (almost horizontal solid curves), and the line $p = q$ (dotted black line) where the trajectories achieve the maximum tumor reduction. This diagram represents the optimal trajectories as a whole and each of the different curves gives a different optimal trajectory depending on the actual initial condition. The thick lines in the graphs mark one specific such trajectory. The corresponding optimal control starts as full dose $u = a$ until the corresponding trajectory reaches the singular arc, then varying partial doses according to the singular control are given until all inhibitors are exhausted. Only along this segment a significant tumor reduction commences. Then the optimal trajectory still follows a trajectory for the control $u = 0$ until the diagonal $p = q$ is reached where due to aftereffects the minimum tumor volume is realized.

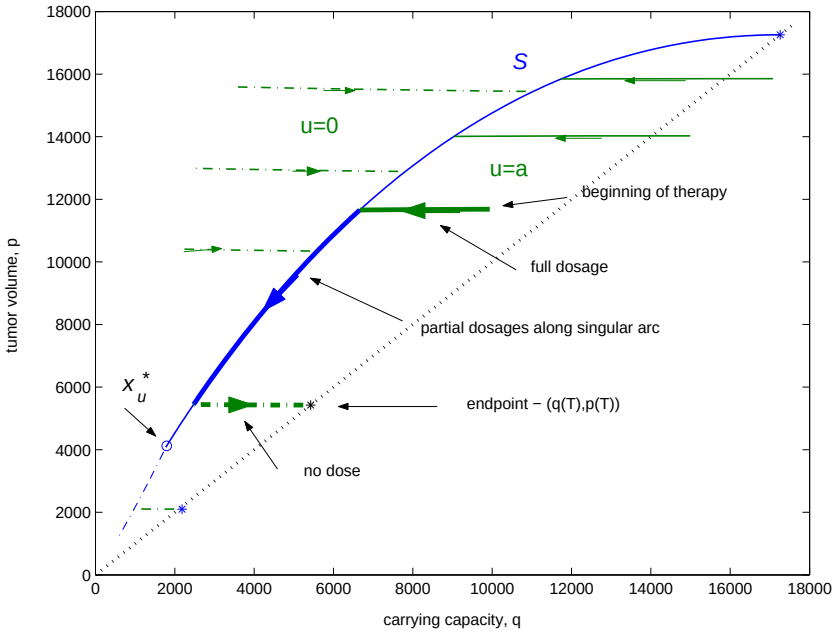

Figure 1: Synthesis of optimal trajectories

3. Optimal Control with a Modified Objective

Minimizing the tumor volume with a constraint on the amount of available inhibitors does not put a cost on the usage of angiogenic inhibitors and thus optimal solutions exhaust all available inhibitors regardless of incremental benefits. In the formulation below we add the integral of u with a positive weight κ as a measure for the cost of the treatment to the objective in order to balance the total amount of anti-angiogenic inhibitors administered with a reduction in tumor size over time.

(P2) For a free terminal time T, minimize

$$J_2(u) = p(T) + \kappa \int_0^T u(t)dt \tag{5}$$

over all Lebesgue measurable functions $u : [0, T] \to [0, a]$ subject to the dynamics (1) and (2).

It can be shown that the qualitative structure of optimal solutions does not change. The reason is that the extra multiplier associated with the isoperimetric

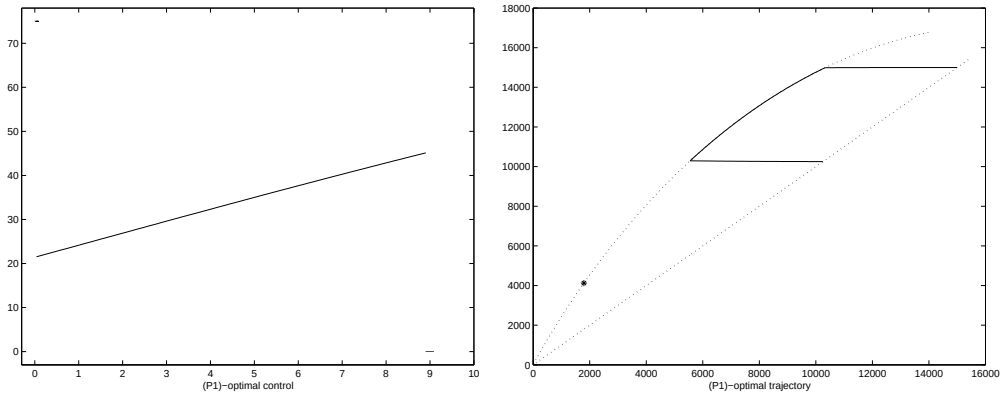

Figure 2: $(P1)$-optimal control (left) and corresponding optimal trajectory (right)

constraint in the original model $(P1)$ is constant and its role now is being taken over by the coefficient κ. Hence the computations and subsequent analysis with some modification carry over. In particular, *the singular curve and its admissible portion are the same* and *the concatenation structure of optimal controls is identical for both problems*. But there is a significant quantitative difference in how long the optimal solutions stay on the singular arc. Now optimal trajectories leave the singular arc at an optimal time τ_* when the incremental benefit of tumor reduction equals the incremental penalty incurred by the use of additional inhibitors. It is not difficult to compute the optimal time τ_* numerically by introducing a 1-dimensional parameter τ that measures for how long the trajectory follows the optimal solution of the problem $(P1)$. As before, the optimal control then ends with a segment for $u = 0$ until the diagonal $p = q$ is reached. We thus simply need to minimize the resulting parameterized objective.

We illustrate the differences for the initial condition $(p_0, q_0) = (15,000; 15,000)$ and for some specific numerical values considered in [3, 5], but the conclusions are generally valid. The optimal control for $(P1)$ is given by $u = a$ until time $\tau_1 = 0.04$ (days), then follows the singular control until $\tau_2 = 8.91$ and then ends with $u = 0$ at the optimal final time $T = 9.09$; the control and corresponding trajectory are shown in Figure 2.

Figure 3 shows the graphs of the objective I for various values of the weight κ in the penalty term. The penalty term is dominant for large values of κ and in these cases the function I will be increasing as shown for the case $\kappa = 21.5$. This

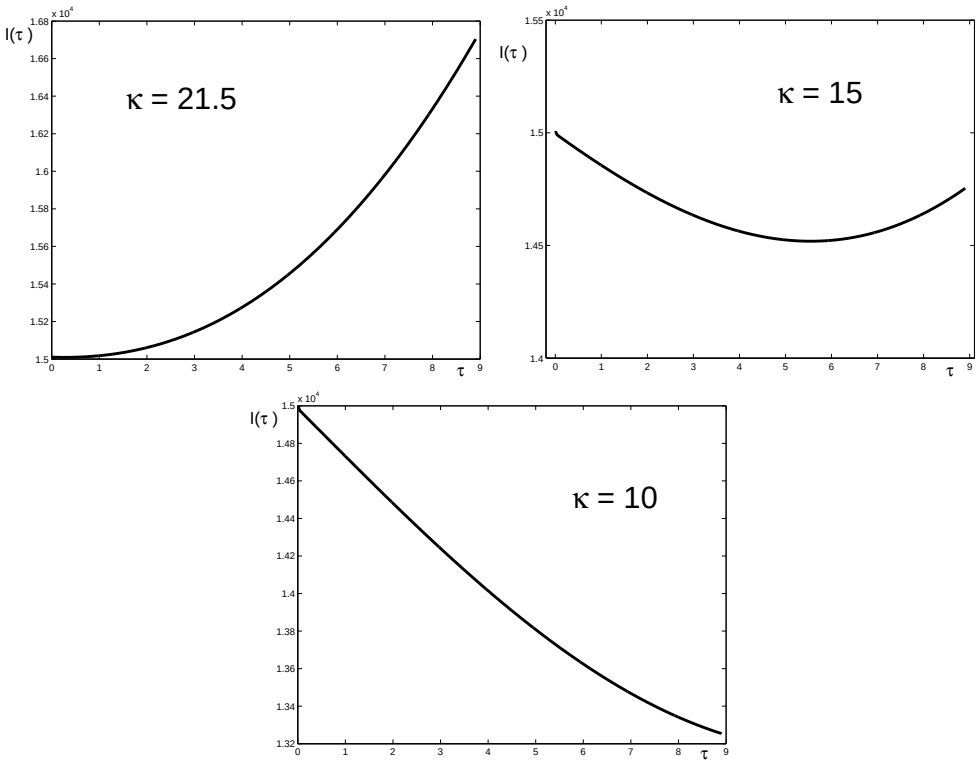

Figure 3: Graphs of the function I for $\kappa = 21.5$ (top left), $\kappa = 15$ (top right), $\kappa = 10$ (bottom)

simply means that for this problem formulation and such a high weight, it would be "optimal" in the sense of minimizing the objective to do nothing, i.e., the best parameter value is given by the left end point $\tau = 0$. As κ decreases below a threshold κ_1^* $(P2)$-optimal control are of the form **a0** and do not yet include a piece on the singular arc until for some coefficient κ_2^* the $(P2)$-optimal trajectory follows the $u = a$ trajectory until it hits the singular arc $\mathcal{S}$ and immediately bounces off with control $u = 0$. As κ decreases below κ_2^* the minimum is achieved for a parameter $\tau > \tau_2^*$ and thus now $(P2)$-optimal controls are of the type **as0** as for problem $(P1)$, but the optimal control follows the singular arc only until time τ. As κ decreases further eventually the minimum is realized at the time τ_3^* when the singular control has used up exactly the amount A given as constraint in problem $(P1)$. In this case the $(P1)$ and $(P2)$-optimal controls are identical.

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