Optimal and Realizable Suboptimal Protocols for Tumor Anti-Angiogenesis and Combination Treatments

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In this talk we address the problem of how to design optimal treatment protocols for some novel cancer therapies with a focus on mathematical models for tumor anti-angiogenesis. This is a relatively new cancer treatment approach that aims at depriving a growing tumor of the network of blood vessels and capillaries 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 1 to 3 mm in diameter, this no longer is true and deprived of the necessary nutrients for cell duplication 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* [8] to recruit surrounding, mature, host blood vessels in order to develop a network of blood vessels and 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 [9]. Overall angiogenesis is based on a complex balance of tightly regulated stimulatory and inhibitory mechanisms. Anti-angiogenic treatments exploit 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 the genetically stable endothelial 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 [11] 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.

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 [10] 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. The dynamics of these systems describe the growth of the tumor volume and its vascularization under the effects of control functions representing the dosage of the angiogenic inhibitors. Several modifications of this model have been introduced and analyzed as dynamical systems in the literature since then, e.g., [6, 7].

Naturally, in all medical applications either resources are limited (and very expensive in the case of anti-angiogenic treatments) or potential side-effects need to be kept tolerable (like in chemotherapy). While applications of optimal control to mathematical models arising in biomedical problems have had a long history with the early focus on models in cancer chemotherapy, there has been a strong resurgence of this methodology in the analysis of newer models. This especially holds for novel treatment approaches to cancer like anti-angiogenesis discussed here or models describing the immune response to viruses (e.g., HIV [12]) or cancer and resulting immunotherapies (e.g., [4, 5]), a second approach currently intensively pursued in medical research. Regarding anti-angiogenesis, in [7] the question how to schedule angiogenic inhibitors in such a way as to realize the maximum tumor reduction possible was posed as an optimal control problem by Ergun et al.: 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 [15] we gave a complete theoretical solution to this problem for all possible initial conditions for the model formulated in [10] and various modifications were analyzed in [13, 15, 19, 21]. This solution is given in the form of a so-called synthesis of optimal controlled trajectories. Such a synthesis provides a full "road map" of how optimal protocols look like depending on the initial condition in the problem, both qualitatively and quantitatively, and is illustrated for the model by Hahnfeldt et al. in Fig. 1. The thick curves in the graph mark one specific such trajectory. In this case the initial value p_0 for the tumor volume and q_0 for the endothelial support are high and require to immediately start with the treatment. The optimal trajectory therefore initially follows the curve corresponding to the control $u = a$ representing the maximum dose. Note that, although inhibitors are given at full dose along this curve, this shows very little effect on the number of the cancer cells in a sense of decrease. Once the trajectory corresponding to the full dose hits a specific curve, the so-called singular arc $\mathcal{S}$, it is no longer optimal to give full dose and the optimal controls

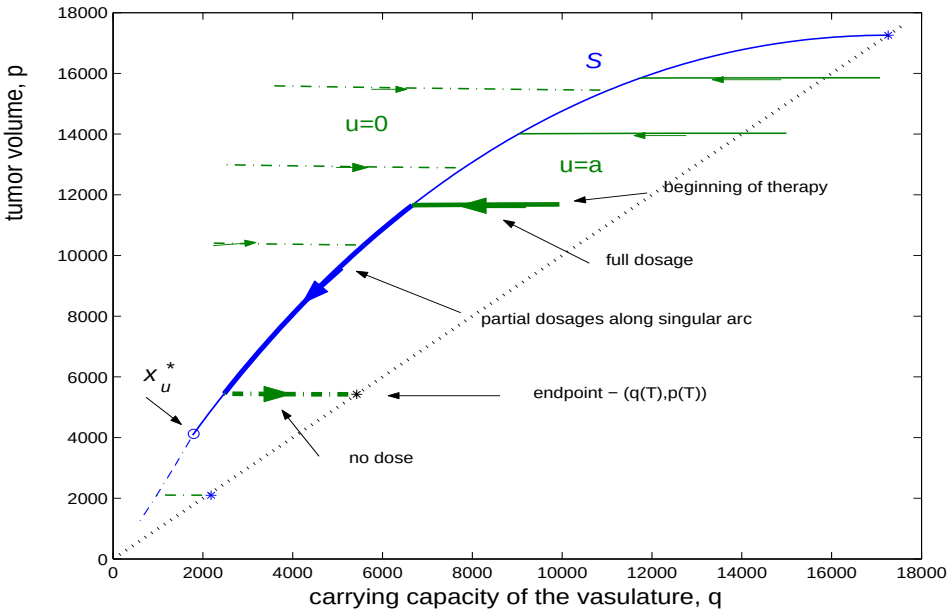

Figure 1: Synthesis of optimal controlled trajectories for the model by Hahnfeldt et al. [10]

here switches to a protocol of specific time-varying partial doses that depend on the current states $p(t)$ and $q(t)$ of the system, the singular control. The optimal trajectory then follows the singular arc until all inhibitors are exhausted. At this time therapy is over, but due to after effects the maximum tumor reduction is only realized as the trajectory for the control $u = 0$ crosses the diagonal $p = q$.

However, with the current state of medical technologies a protocol of state dependent time-varying partial doses is not realizable. Hence the question as to what are good, but simple and realistic strategies arises. Using the theoretically optimal solution as a benchmark allows 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 talk we present the theoretically optimal solutions and then discuss structures of simple, but very close to optimal, suboptimal protocols. For example, giving all inhibitors at a constant dosage already leads to a generally very good suboptimal strategy if one takes as dosage the averaged value of the optimal control [16]. This protocol comes within 1% of the optimal value for one of the models. This can still be improved upon by giving inhibitors at piecewise constant dosages and calculating the optimal dosages and durations for a small but fixed amount of segments. We also consider strategies that rather than allowing to optimize the time periods, a priori fix this structure in time like, for example, giving daily or semi-daily doses with rest periods during the night. Overall, 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.

These aspects become even more prominent in models for combination therapy that augment anti-angiogenic treatment with chemotherapy. The model for that treatment then also includes a killing term on the primary tumor volume which introduces a second control into the system. Due to the multi-control aspect, even with simplified dynamical equations, this becomes a challenging problem mathematically. On the other hand, additional medically relevant questions like the proper sequencing of the drug have to be addressed. Initial results about the structure of optimal controls for such a model will be presented and some open problems will be formulated.

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