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LOCAL CONTROLLABILITY OF MODELS OF COMBINED ANTICANCER THERAPY WITH DELAYS IN CONTROL

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ABSTRACT

In the paper [1] we present conditions of controllability for the original Hahnfeldt et al. model [2] to which two control variables describing two treatment modalities have been introduced and those variables may exhibit different delays. Nowadays antiangiogenic therapy is considered as an essential component of multidrug cancer therapy, especially with chemotherapy. Although tumor eradication in such combined therapy may be still the primary goal the chaotic structure of the angiogenically created network leads to another target for antiangiogenic agents. Namely using angiogenic inhibitors to normalization of the abnormal vasculature (the so called pruning effect) facilitate drug delivery [3]. Smaller dose of anti-angiogenic agents (bevacizumab 5 mg/kg) shows significantly different (higher) median survival from chemotherapy alone in the treatment group when the dose 10 mg/kg can even increase survival compared to chemotherapy alone in the treatment group. The continuous treatment with angiogenic inhibitors ultimately leads to a decrease in tumor blood flow and a decreased tumor uptake of co-administrated cytotoxic drugs. In the periodic therapy the main goal of anti-angiogenic agents is to normalize tumor vasculature. Yet another difficulty in planning treatment protocols in the combined therapy is related to pharmacokinetic-pharmacodynamic (PK/PD) properties of antiangiogenic and cytostatic agents. Modeling of those effects leads to extension of the model by additional differential equations for PK and introduction of additional nonlinearities for PD description. We overcome this problem by including time-delays different for both types of agents. Although such description is far from accurate illustration of biological processes behind PK/PD phenomena but for the simplified model used in this paper it is adequate way of modeling the important changes in effects of therapy caused by them. Pharmacokinetic factors may also contribute towards mechanisms of resistance. The half life time for cytostatic drugs is rather short usually few hours but for example for commonly used Cisplatin it changes from 30-100 hours (mean: 65). For antiangiogenic agents the half life may vary over a wide range (for example from 15 minutes for angiostatin up to 20 days bevacizumab). Yet another reason for including delays in control variables describing effects of chemotherapy is related to the idea of normalization of vasculature using angiogenic inhibitors (as discussed above). The cytostatic agents should be administered with delay necessary for pruning vessels by antiangiogenic drugs. A question which of the goals mentioned above could be reached in finite treatment horizon may be answered, at least theoretically, by analysis of controllability of dynamical systems used as models of the processes of tumor growth in the presence of vascularization. Controllability is a qualitative property of dynamical control systems and its meaning,

roughly speaking, is following: a dynamical system is controllable if it is possible to steer it from an arbitrary initial state to an arbitrary final state using the set of admissible controls. In the existing literature there are many different definitions of controllability strongly depending on the class of dynamical control systems. In the paper [1], we consider relative constrained local controllability for second-order finite-dimensional semilinear stationary dynamical systems described by the set of two ordinary differential state equations with delays. To our knowledge, the problem of controllability for such models is absent in the literature except of our previous studies in which controllability of the simplified model [4] of this class for antiangiogenic therapy [5] and combined therapy [6] have been studied. The results are based on theorems proved in [7] for nonlinear systems without delays. The theorems have been extended in [8] for the case when control variables have multiple delays. The idea of the theorems is that under suitable assumptions constrained global relative controllability of a linear associated approximated dynamical system with delays implies constrained local relative controllability near the origin of the original semilinear second-order dynamical system with delays.

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