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Angiogenesis inhibition and tumor-immune interactions with chemotherapy by a control set-valued method. (English summary)
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In the context of cancer, particularly malignant tumor growth, angiogenesis, the process of forming new blood vessels, is the primary mechanism by which a tumor becomes vascularized. Since angiogenesis is essential to tumor metastasis and the spread of cancer, there has been and continues to be significant research to further understanding of angiogenesis and its relation to tumor growth and invasion. Moreover, many cancer treatments and therapies target factors that promote tumor angiogenesis. To aid in the research efforts regarding angiogenesis, researchers in the mathematical sciences have developed a number of mathematical models of tumor angiogenesis. Some surveys of work in this area are given in [T. Alarcón, in *Mathematics, developmental biology and tumour growth*, 45–75, Contemp. Math., 492, Amer. Math. Soc., Providence, RI, 2009; MR2574186; H. M. Byrne, in *Mathematical biology*, 219–287, IAS/Park City Math. Ser., 14, Amer. Math. Soc., Providence, RI, 2009; MR2522052; H. A. Levine and M. Nilsen-Hamilton, in *Tutorials in mathematical biosciences. III*, 23–76, Lecture Notes in Math., 1872, Springer, Berlin, 2006; MR2208744].

In the article under review, the authors employ techniques from set-valued control theory, applied to a specific class of mathematical models for angiogenesis, to investigate cancer therapies that seek to inhibit tumor angiogenesis. The authors also give a second application of their techniques to investigate optimal control of immunotherapy of cancer. The article begins with a brief introduction describing some background on angiogenesis, its relation to cancer research, and some mathematical models of angiogenesis. Section two discusses the relevance of control theory to cancer therapy. The authors state that the primary relevance is to control for cancer therapy protocols that balance patient quality of life and effectiveness of treatment, here meaning minimization of cancer cell density. Also in section two is a brief review of control theory literature related to cancer research.

Section three describes the so-called set-valued approach to control. There are few mathematical details given but references, including a reference to another work by the first author, are provided where readers unfamiliar with set-valued analysis can find more information. In this section the authors establish notation, define the notion of a protocol (essentially a global solution to a certain nonlinear control system), and state two theorems used in the sequel. Theorem 1 establishes conditions for a protocol, specifically the minimal protocol defined as expression (7) in the paper, that result in a decreasing density of cancer cells. Theorem 2 is more complicated to describe in brief but deals with conditions to bring the cancer to a better stage. A proof is provided for the second theorem and a reference for a proof of the first theorem is given. At the end of section three the authors state that their two theorems formalize the clinically well established fact that success of a cancer treatment (mathematically, the existence of a protocol as defined in section three) is strongly dependent on how early in the progression of the disease the patient begins treatment (i.e. the initial conditions).

Sections four and five of the article present the applications mentioned above and interpret the results in terms of cancer treatments. A final conclusion section discusses

the strengths of the methods used in the article and addresses possible considerations for future research along the lines of investigation described in the article.

In the reviewer's opinion the article under review provides a short, useful introduction to some potentially valuable techniques in cancer research from a quantitative point of view. The techniques described in this article appear to be relatively easy to implement, and there are useful references for the non-specialist to seek out details not presented in the article, and further reading. The following related articles not cited in the work under review may also be of interest: [U. Ledzewicz, H. Mäurer and H. M. Schättler, Math. Biosci. Eng. **8** (2011), no. 2, 307–323; MR2793485; H. M. Schättler, U. Ledzewicz and B. Cardwell, Math. Biosci. Eng. **8** (2011), no. 2, 355–369; MR2793487].

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Note: This list reflects references listed in the original paper as accurately as possible with no attempt to correct errors.