Modeling and optimization of combined anticancer therapies

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The use of optimal control theory in mathematical modeling of cancer therapies has had more than five decades of history (see e.g. [1] for survey). The early literature is mainly focused on cancer chemotherapy, then modeling has been applied for novel cancer treatments such as anti-angiogenic therapy, immunotherapy, and gene therapy, and, recently, combination of chemotherapy and these modern modalities has become a subject of multi-input control optimization. Surprisingly, the most frequent form of combined therapy, which contains chemotherapy as a systemic treatment and radiation as a local therapy, is almost absent in the literature on system theory application to planning a war against cancer. One of the reasons is that both radio- and chemotherapy protocols are completely standardized. On the other hand, it is not clear how they should be combined to obtain the best effects in terms of patient survival. We present an explicit solution to the multi-input optimal control problem formulated for a simple model of cancer growth under the combined therapy. Then we extend this model with additional equations, describing pharmacokinetics and DNA repair of adjacent strand breaks and study alterations in optimal control strategies resulting from these processes. Ultimately, we compare the outcomes of the protocols found with the actual clinical ones, defined by Kaplan-Meier survival curves obtained with *in silico* tests. We discuss both structural and parametric sensitivity of the models and results obtained by our analysis and the role of parameter estimation for tumor growth models. Although the models taken into account are quite simple, we conclude that a careful judgment on a case-by-case basis is necessary to determine, if drug metabolism and/or DNA repair may be ignored in mathematical models. On the other hand, we have found that the role of parameter estimation for tumor growth models in the case of realistic protocols is the essential for prediction of efficiency of different therapy schedules. The talk is based on results presented in [2] and [3].

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