Modeling adjuvant chemo- and radiotherapy

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***Short Abstract* — Surgery that removes solid tumors can be preceded or followed by adjuvant radio – chemo- or radiochemotherapy. These therapies can be administered in a different order. In this work we present analysis of different therapy protocols, aimed at finding a hypothetical optimal one and checking what results it yields in a heterogeneous population of patients. Moreover, we discuss differences in modeling results between a standard linear-quadratic model of radiotherapy and an approach that takes into account dynamic effects of radiation.**

***Keywords* — adjuvant therapy, radiotherapy, chemotherapy, Kaplan-Meier curves, optimal control.**

I. Background

THE The development of adjuvant anticancer therapies is largely empirical, based on the outcome of a prospectively designed randomized clinical trials. One of the most intensively explored areas in the clinic is comparison of the effectiveness of postoperative (or preoperative) radiotherapy to the effectiveness of postoperative (or preoperative) radiotherapy combined with chemotherapy.

Dynamical models of cancer growth employ a variety of modeling techniques, from ordinary differential equations to agent-based models. Therapy is incorporated in tem in the form of control variable, thus facilitating formal approaches to optimize therapy protocols or comparison of different ways to model chemo- and radiotherapy [1-2]. In this work, we focus on two different approaches to model radiotherapy and include it in a combined protocol with chemotherapy. The comparison is based on patient survival curves obtained through simulation of tumor growth for a population of heterogeneous patients, differentiated by parameters corresponding to the tumor growth rate and responsiveness to therapy.

II. The Model

One of the most widely used models, generally accepted by clinicians, is the Gompertz model. In this work, chemotherapy is incorporated in it in the simplest form, without taking into account cell-cycle specificity nor drug resistance phenomenon, as one of the control variables $\gamma(t)$ and the simplest pharmacokinetics model. The effects of radiation therapy are most often described by the so called Linear-Quadratic (LQ) model and switches in state trajectory, following radiation events. While this has been tested as well, in an alternative model version we also take into account repair of radiation-induced DNA damage with the half time μ then the decay rate R, following the line of reasoning presented in [3]. Denoting by $N(t)$ tumor size and by $d(t)$ the radiation dose rate at time t, and the system under consideration is described by the following set of equations:

$$\dot{N} = -\rho N log\frac{N}{N_\infty} - c\gamma N - (\alpha d + \beta d f)N \quad (1)$$

$$\dot{\gamma} = -\lambda\gamma + u \quad (2)$$

$$\dot{f} = -\mu f + d \quad (3)$$

Where (2) represents pharmacokinetics and (3) fast repair mechanisms, following irradiation events.

III. Model Analysis and Conclusions

Two main questions arise in such approach to modeling: (i) what are the differences in tumor growth dynamics under standard therapy protocols between standard LQ model and the one given by (3) and (ii) how should intertumor heterogeneity be incorporated for analysis of protocols efficacy for a given population of patients.

In recent years many reports have showed a correlation between a metabolism of cancer cells and tumor malignancy (e.g., [6]). In the case of breast cancer it has been found that isoleucine, threonine, glutamine and linoleic acid, measured in serum before therapy had started, allow to differentiate patients with respect to predicted outcome of adjuvant chemotherapy [7]. Therefore, we used patient blood morphology data to create a distribution from which model parameters, corresponding to tumor growth rate and its responsiveness to therapy, were sampled. Thus, a population of virtual patients was created. Therapy protocols were simulated for each patient, with a predefined threshold of tumor size defining patient death. Subsequently, survival curves were calculated. The results showed that blood morphology can be used to estimate parameters in tumor growth models, making it possible to model a heterogeneous population of patients.

Acknowledgements: This work was partially funded by NCN grant DEC-2016/21/B/ST7/02241.

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