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Towards *in silico* oncology: Adapting a four dimensional nephroblastoma treatment model to a clinical trial case based on multi-method sensitivity analysis

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ABSTRACT

In the past decades a great progress in cancer research has been made although medical treatment is still widely based on empirically established protocols which have many limitations. Computational models address such limitations by providing insight into the complex biological mechanisms of tumor progression. A set of clinically-oriented, multiscale models of solid tumor dynamics has been developed by the *In Silico* Oncology Group (ISOG), Institute of Communication and Computer Systems (ICCS)-National Technical University of Athens (NTUA) to study cancer growth and response to treatment. Within this context using certain representative parameter values, tumor growth and response have been modeled under a cancer preoperative chemotherapy protocol in the framework of the SIOP 2001/GPOH clinical trial. A thorough cross-method sensitivity analysis of the model has been performed. Based on the sensitivity analysis results, a reasonable adaptation of the values of the model parameters to a real clinical case of bilateral nephroblastomatosis has been achieved. The analysis presented supports the potential of the model for the study and eventually the future design of personalized treatment schemes and/or schedules using the data obtained from in vitro experiments and clinical studies.

1. Introduction

In the last decades several computational models simulating the complex phenomenon of cancer have been developed [1–3]. Such models can be very helpful in improving fundamental insight regarding the involved biological processes and in learning lessons useful for further model development in particular when clinical translation is envisaged. However, values for the parameters of complex multiscale biological models are difficult to acquire through new experimentation in vivo or in vitro and are usually obtained from literature or have to be estimated based on clinical and basic science experience.

A 4D simulation model has been developed by the *In Silico* Oncology Group-National Technical University of Athens (ISOG-NTUA) integrating multiple levels of biological complexity to examine the effect of chemotherapy on nephroblastoma tumors [4,5]. The structure of the model has been analytically presented in previous publications [4–7]. In the present paper we use this modeling platform and employ sensitivity analysis, in order to examine the model behavior, identify critical pathway components and reaction steps of the involved biological processes and further test the impact of parameter perturbations on the model output behavior. Based on the inferences of the model sensitivity analysis, a thorough model adaptation is addressed.

Sensitivity analysis is an efficient tool for systematic identification of the particular parameters, perturbations of which have significant effects on the simulated biosystem behavior at the scale investigated, especially when it is not possible or practical to conduct numerous experiments on the living system itself. To understand the quantitative dynamical properties of a complex biological system such as cancer, analyzing the sensitivity of its parameters can provide valuable insight into model characteristics. Sensitivity analysis can also be used to provide insight into the robustness of a model in order for it to be used as a tool for decision making.

Three different methods of sensitivity analysis are presented with dissimilar theoretical foundations to increase confidence in the ranking of key inputs: a graphical, a mathematical and a statistical sensitivity analysis of the effect of model parameters on growth properties and therapy outcomes of the simulated tumor. The results of these three analyses are evaluated and compared.

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The sensitivity analyses presented, aim at identifying critical control points of the modeled mechanisms, guiding additional data collection or research, verifying and validating the model. A "comfort level" with the particular model has been developed as the model response is reasonable from the theoretical perspective. Successful model adaptation to an actual clinical Wilms' tumor bilateral case (SIOP 2001/GPOH [8]) guided by the sensitivity analysis has been achieved for three time instants and presented.

This study provides a cross-method approach to analyzing parameter sensitivity of a computational cancer model and proposes its application to clinical reality. In the future, the ability to precisely define a tumor's fundamental characteristics, and to predict a patient's response to medication is expected to allow tailoring of specific treatments to specific patients, i.e. personalized medicine.

2. Methods

2.1. The simulation model

One of our previously developed model has been employed in this study [4,6]; therefore in this paper, only a brief description of its basic concepts, as well as of some key methods of the model are included.

The simulation approach is a discrete (cellular automata), 'top-down' model with a clinical perspective. The verification and validation of the model is in progress in the framework of SIOP 2001/GPOH clinical trial [8].

Available patient-individualized medical data are used to define the area of interest at the 'top' (organ) level. This area is discretized by a 3D cubic mesh (a regular grid of geometrical cells). The elementary volume of the mesh is called "geometrical cell" (GC). Each occupied GC is initialized with a population of biological cells (Number of Biological Cell- NBC) which is defined based on typical solid tumor cell densities (e.g. 10^9 cells/cm^3) [9], unless more specific information for a particular tumor is available (tissue level). The biological cells in each occupied GC are distributed in a finite number of *states*, namely five categories defined according to their mitotic potential: STEM cells with theoretically unlimited mitotic potential, LIMP cells with LImited Mitotic Potential, terminally differentiated cells with no mitotic potential, necrotic and apoptotic cells. Many biological phenomena (cellular level) such as cell cycling, division, quiescence, differentiation, repopulation, apoptotic and necrotic death, chemotherapeutically induced death are incorporated in the model, as illustrated in the cytokinetic diagram presented in Fig. 1. Pharmacokinetics and pharmacodynamics (hypo-cellular level) of the chemotherapeutic drugs used, [10–18] determine the fraction (or number) of lethally hit cells which enter a rudimentary cell cycle (Fig. 1) leading to apoptotic death, as well as their actual time of death.

The simulation algorithm supports the division of tumor volume into different metabolic regions (e.g. necrotic and proliferative) based on available imaging data and the handling of each region separately. Nevertheless, as a first approximation, in the present paper spatially homogeneous tumors constituted of equivalent cell category populations throughout their whole volume are considered. Also, space and time-independent transition rates are used throughout the tumor region for the relative short time interval simulated (in the range of a chemotherapeutic scheme duration), compared to the tumor's lifetime.

An automatic methodology has been developed and adopted for the tumor's constitution initialization in order to avoid latent artificial tumor growth behaviors as described analytically in previous publications [4,5]. Other information from histopathological or molecular data when available can be incorporated appropriately in the model by redefining the model parameters values and lead to a refined clinical adaptation [4]. The sensitivity analysis guides the redefinition of model parameters' value and leads to a more well-founded model adaptation. In Fig. 2 a simplified activity diagram of the algorithm is presented. At each computational time step the discretizing mesh is scanned. The scan could be considered as two separate scans; the first applies the rules of the cytokinetic model and the second performs a geometrical reconstruction in the tumor region: shrinkage or expansion of the tumor conformal to its initial shape, in the absence of any special information for the mechanical properties of the surrounding tissues.

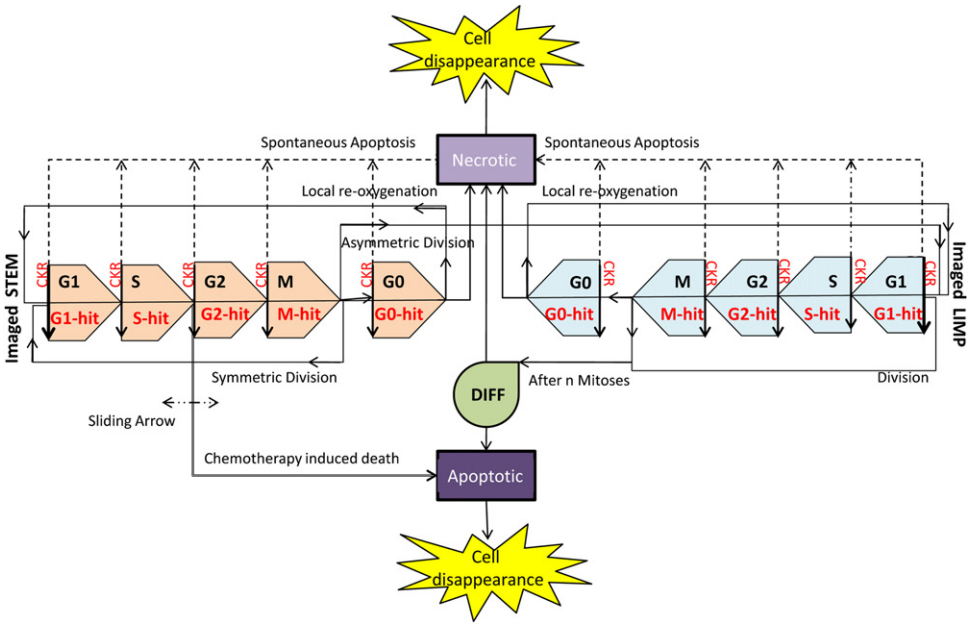

Fig. 1. Generic cytokinetic model for tumor response to chemotherapy. LIMP: LImited Mitotic Potential cells. DIFF: Terminally differentiated cells. G1: Gap 1 phase. S: DNA synthesis phase. G2: Gap 2 phase. M: Mitosis phase. G0: Dormant phase. Hit: Cells lethally hit by chemotherapy. CKR: Cell kill ratio of the chemotherapeutic drugs. The sliding arrow indicates the point of the cell cycle at which cells are led to apoptosis and depends on the drugs' mechanisms of action.