

**An *in silico* spatiotemporal simulation model of the development and response of solid tumors to radiotherapeutic and chemotherapeutic schemes *in vivo*.
Normal tissues response to radiotherapy *in vivo* . Clinical testing.**

Vassilis P. Antipas*

Thesis Consultants: Georgios S. Stamatakos*, Nikolaos K. Uzunoglu*

**In Silico Oncology Group, Microwave and Fiber Optics Laboratory, School of Electrical and Computer Engineering, National Technical University of Athens,
9, Iroon Polytechniou, GR 157 80 Zografos, Greece. Email: vantipas@gmail.com*

Abstract

Considerable research efforts have focused on the mathematical / computer modeling of the response of tumors and normal tissues to various therapeutic modalities but, unfortunately, current models of such dynamic processes need substantial improvement due to the complexity of the problems addressed and the paucity of large series of clinical data. This thesis presents an effort to overcome a number of current modeling shortcomings by addressing the actual clinical tumor and the surrounding normal tissue *in vivo*. Therefore, the proposed model simulates the spatiotemporal response of a tumor under different radiotherapeutic and chemotherapeutic fractionation schemes. Modeling of the *in vivo* response of slowly responding normal tissues to radiotherapy is also addressed. The special case of glioblastoma multiforme (GBM) has been considered as an application paradigm. Concerning chemotherapy, the effect of the temozolomide agent has been computer modeled. The salient points of the model are the following. The imaging data of the patient (e.g. MRI T1 slices), the exact histopathologic type of the malignancy as well as pertinent genetic (e.g. p53 gene status) data are

appropriately collected and introduced into the simulation software. The proposed 4-D simulation model which refers predominantly to the cell – tissue level is based on the cell cycle, the oxygen and nutrient supply (as estimated from the imaging data), the cell loss factor, the alpha and beta radiobiological parameters of the linear quadratic (LQ) model and the pharmacokinetic and pharmacodynamic parameters of the drug. Especially for the normal tissues, the tissue homeostatic tendency has been primarily taken into account. All parameters used in the model have already been defined and can in principle be determined either experimentally or clinically. Therefore new mathematics dictated parameters of ambiguous physical meaning are avoided. The chiefly *discrete mathematics* employed include the generic stochastic Monte Carlo technique, cellular automata constructs, Euclidean geometry metrics etc. Visualization of the simulation predictions has been achieved using virtual reality techniques. The model predictions have shown good agreement with both reason and clinical experience. An at least semi-quantitative agreement of the simulation predictions with the outcome of the RTOG Study 83-02 has strengthened the potential of the model. Long term quantitative testing and adaptation are ongoing. Therefore, after completion of the necessary long term tests and eventual improvements the proposed modeling platform could serve as a patient individualized *decision-support system*. In this way the medical doctor could make his or her final decision on the selection of the most promising therapeutic scheme by taking into account both, the predicted outcomes of all simulated regimens as well as his or her own medical knowledge and expertise. It is noted, however, that such a computational platform does not intend to replace the medical doctor's input but to add the possibility to investigate the impact of specific treatment-induced perturbations. Such a system could also serve as an educational platform for professionals and patients by means of virtual reality demonstrations of the likely natural development and treatment responsiveness of specific cancers so that all groups might positively contribute to the discussion about treatment procedure.

Key words: *in silico* oncology, cancer, slowly responding normal tissues, tumor growth, radiotherapy, chemotherapy, fractionation, simulation, modeling, visualization, neovasculature