Multi-scale in silico tumor modeling: experimental/computational integration

Tzamali E. [1#], **Oraiopoulou M-E.** [1,2], **Tzedakis G.** [1], **Spanakis M.** [1], and **Sakkalis V.** [1*]

[1] Institute of Computer Science, FORTH, Greece

[2] Institute of Electronic Structure and Laser, FORTH, Greece

Presenting author: Computational BioMedicine Laboratory, email: tzamali@ics.forth.gr
* Corresponding author: Computational BioMedicine Laboratory, email: sakkalis@ics.forth.gr

ABSTRACT

A large amount of research work together with recent advances in technology including novel imaging techniques and high resolution genomic studies advocate that tumors are incredibly complex, highly heterogeneous, self-organized biological systems spanning multiple temporal and spatial scales. More specifically, tumors involve processes at microscopic level, where molecular interactions like signaling and metabolic reactions occur, at cellular and mesoscopic level, where cells interact with each other and the local microenvironment, as well as processes that involve remodeling of the cancerous and adjacent tissue. The involved biological processes are strongly coupled and the challenge is to appropriately incorporate them into a complete description, utilizing the available knowledge and data to better understand and predict how tumors evolve and respond to therapy. The integration of mathematical and computational approaches with experimental data and advanced imaging techniques is more than important. Mathematical modeling is an indispensable tool for understanding these complex bio-processes, integrating the information from multiple biological experiments and clinical examinations, predicting tumor behavior and systematically testing different hypotheses. We focus on glioblastoma (GB), a malignant brain tumor with extremely poor prognosis for the patient. The disease is fatal mainly due to its extensive inter- and intra-tumor heterogeneity and its extremely complex biology that result in treatment failure and high recurrence potential. To better understand the implications of inter- and intra-tumor heterogeneity on GB progression and therapeutic outcomes, we developed a hybrid, discrete-continuous, stochastic-deterministic, agent-based mathematical model that captures both the overall tumor kinetics and the individual cellular behavior [1]. In vitro and in vivo patient-derived data are used in order to initialize, parametrize and validate the developed GB predictive algorithms. We give also particular emphasis on metabolism, the most fundamental subcellular process. Metabolic reprogramming, a hallmark of cancer, contributes to tumor development and introduces metabolic liabilities that can be utilized towards novel approaches and knowledge related to tumor growth, invasion and treatment response. We incorporate existing genome-scale metabolic modeling approaches that link genotypes with phenotypes into cell-centered, agent-based tumor growth models that account for the interactions among phenotypes and the spatiotemporally heterogeneous tumor microenvironment [2, 3].

As the complexity and understanding of tumor progression and therapeutic response is unlikely to be solved by a single, individual field of research, a strong synergy between natural sciences, mathematics, information technology, clinicians and experimentalists is more than important in understanding brain pathophysiology, tumor progression and therapeutic outcomes. In our studies, we adopt an iterative loop procedure between experiments and theory with the aim to ultimately converge on a model that is both validated and predictive and, which recapitulates with the best possible way GB complexity and individuality.

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