Mathematical Methods and Models in Biosciences
June 15–20, 2025, Sofia, Bulgaria
https://biomath.math.bas.bg/biomath/index.php/bmcs

Modeling radiotherapy response to tumor heterogeneity and its microenvironment

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Research has revealed that the interaction between tumors and abiotic elements is crucial for therapy outcome. Notably, hypoxia serve as an environmental stressor that not only promotes the emergence of more aggressive cell types but also influences therapeutic effectiveness in a twofold way. First, the cells that adapt to these harsh conditions exhibit a high resistance to environmental stresses, enabling them to persist in regions where radiotherapy is less effective due to insufficient oxygen, being the latter an element essential for amplifying the damaging effects of ionizing radiation. Second, these adapted cells tend to have slower proliferation rates, rendering them less susceptible to radiotherapy, which primarily targets dividing cells by damaging their DNA.

This talk introduces a continuous mathematical model designed to investigate the influence of hypoxia on the evolutionary dynamics of cancer cells. The model is based on [1] and is developed within the framework of phenotype-structured population dynamics. It is expressed through a system of coupled nonlinear integro-differential equations and encompasses a four-dimensional domain: one dimension for time, two for spatial representation, and one for the phenotypic state, which describes the metabolic response of cells to environmental stress in terms of resistance. Furthermore, the model integrates radiotherapy by examining how both oxygen spatial distribution and the phenotypic characteristics of the tumor influence treatment outcomes.

The primary objective is to generate a reliable epigenetic map of the tumor within its microenvironment and to exploit it to explore alternative radiotherapy schedules beyond the standard of care. This approach aims to account for the evolving phenotypic heterogeneity and capitalize on the well-known reoxygenation effect. Preliminary numerical simulations indicate that strategically timed treatment schedules can significantly improve therapeutic outcomes and may provide valuable insights for designing future clinical trials.

References

[1] G. Chiari, G. Fiandaca, M. E. Delitala, Hypoxia-related radiotherapy resistance in tumors: treatment efficacy investigation in an eco-evolutionary perspective, *Frontiers in Applied Mathematics and Statistics*, 9:1193191, 2023.