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A mathematical study of the influence of hypoxia on phenotypic heterogeneity in cancer and its impact on radiotherapy effectiveness

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In the study of cancer evolution and radiotherapy treatments, scientific evidence shows that a key dynamics lies in the tumor-abiotic-factors interaction. In particular, oxygen concentration plays a central role in the determination of the phenotypic heterogeneity of the cancer cell population, both from a qualitative and geometric point of view.
Hypoxia acts as an environmental stressor promoting the selection of aggressive phenotypes and affecting therapeutic efficacy in a twofold way. On the one hand, selected cells are characterized by high resistance to hostile environments, resulting in the ability to survive in those areas in which the radiotherapy treatment is less effective because of the lack of oxygen (oxygen is responsible for the enhancement of the detrimental effect of ionizing radiation). On the other hand, selected cells present a low proliferative rate, thus being less exposed to radiotherapy action, which acts damaging the DNA of cells involved in the replication process.
In this talk, we present a continuous mathematical model to study the influence of hypoxia on the evolutionary dynamics of cancer cells. The model is settled in the mathematical framework of phenotype-structured population dynamics and it is formulated in terms of systems of coupled non-linear integro-differential equations. We consider a three-dimensional domain in which two dimensions are dedicated to the spatial representation while the other one features the phenotypic state related to the expression of the hypoxia-resistance gene. Numerical simulations are performed using Galerkin finite element methods, implemented in Python with FEniCS tool, with the aim to test different vessel dispositions, allowing to represent various biological situations (without the constraint of radial symmetry), such as cancer mass developing in well-oxygenated or highly inhomogeneous tissues and tumor cords growing around single vessels. Then, the effects of radiotherapy treatment are included in the model and numerical simulations are driven to analyze the influence of the heterogeneity in oxygen concentration and phenotypic distribution of cancer cells on the treatment effectiveness. Various therapeutical protocols, differentiated per doses and timing, are considered.
The computational outcomes show that the mutual interactions between the tumor mass and the oxygen distribution can result in a geometric characterization of tumor niches differentiated by phenotypic characteristics that determine a heterogeneous response to radiotherapy. The analysis of the study results provides suggestions about possible therapeutic strategies to optimize the radiotherapy protocol in light of the phenotypic and geometric inhomogeneities of the tumor.