Modeling the radiobiological effect of radiation using spheroids as an *in silico* model

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Context/aims: While our understanding of the hallmarks of cancer has advanced significantly, current therapeutic approaches, including radiotherapy, have not yet fully leveraged this knowledge. With the rapid progress in computational power and tools, there is now an opportunity to integrate and enhance radiotherapy practices through computational simulations.

Methods: In this study, we developed a computational model of cell growth using a Cellular-Potts Model (CPM). The model parameters were optimized to replicate the growth patterns observed in experimental data from a colorectal cancer cell line (SW837). We then integrated this model into the TOPAS-nBio software package, which simulates the irradiation process and the formation of radicals resulting from the radiolysis of water. TOPAS-nBio also allows for a realistic depiction of DNA structure, enabling us to assess both direct and indirect radiation effects, and their impact on cell survival due to double-strand breaks (DSBs). This created a comprehensive model coupling spheroid growth with radiation treatment.

Results: By incorporating oxygen diffusion into the model, we successfully simulated the behavior of different cell types in resource-limited environments. The cells respond to the environmental constraints, such as limited oxygen. The spheroid model replicates experimental observations, showing compaction as the number of cells increases. This leads to the formation of oxygen-deprived regions, corresponding to hypoxic and necrotic areas, while cells at the rim remain proliferative due to sufficient oxygen availability. Irradiation can be initiated at any chosen time, and spheroid size decreases with each exposure. Different treatment regimens produce morphologically distinct spheroids. Simulations of single-cell exposure to varying doses of X-ray irradiation show a uniform distribution of double-strand breaks (DSBs), with most damage caused by indirect effects, highlighting the need to simulate the chemical stage. The number of clustered DSBs provides a more accurate fit to the linear-quadratic (LQ) equation than the total number of DSBs alone.

Conclusions: The Cellular-Potts Model (CPM) successfully produced a spheroid that mirrors the compaction observed in experimental data and responds to oxygen levels, resulting in the formation of a layered structure with hypoxic and necrotic zones. The implementation of the irradiation phase was also successful, as spheroid volume decreased with increasing doses and the number of irradiations. These preliminary results provide a foundation for developing a comprehensive toolkit to simulate multicellular growth and DNA damage.