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Modeling the radiobiological effects of gold nanoparticles in proton therapy of glioblastomas

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MOTIVATION

The combination of high-Z nanoparticles (NP) and external radiotherapy leads to an increased radiation effect in tumoral cells without an increase of the patient dose (Figure 1).

However, it is not yet clear how the sequence of physical, chemical, and biological mechanisms contributes to the observed synergic effect.

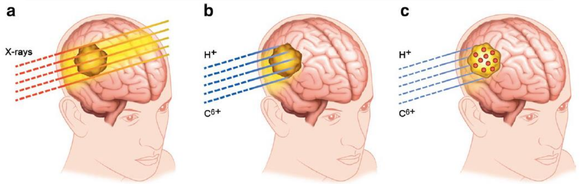

Figure 1. Effect of NPs in tumoral cells [1].

OBJECTIVE

Develop realistic simulations of the irradiation of monolayer (2D) and spheroid (3D) human glioblastomas multiforme (GBM) cell cultures, taking into consideration different concentrations and cellular distributions of the gold nanoparticles (GNPs).

TOol for PArticle Simulation

The simulations will be implemented based on TOPAS [2] software more specifically the extension TOPAS-nBio [3] that includes models of the physical and chemical processes induced by radiation at the DNA scale.

Figure 2. a) TOPAS e **b)** TOPAS-nBio.

METHODOLOGY

To built the simulation is necessary define four sections:

Geometry

The construction of the computational cell models will be developed based on confocal microscopy images of the biological samples.

Original Image → Segmented image → Binary File → Import to TOPAS

Source

We simulate irradiations with different types of radiation:

- X-ray spectra with 50 and 150 kVp
- Cobalt-60 beam
- Proton beam with 80 keV, 18 MeV and 150 MeV

Physics List

To simulate the physical interactions, we define two different lists:

- Geant4-DNA list
- Livermore list

We also include in the simulations the production of fluorescence and auger electrons, the Auger Cascade and the PIXE process.

Output

The dose distributions at the subcellular scale will be obtained, as well as the temporal distribution of the reactive oxygen species (ROS).

[1] S. Lacombe, et al., "Particle therapy and nanomedicine: state of art and research perspectives", *Cancer Nanotechnol*, 2017.
[2] J. Perl, et al., "Topas: an innovative proton monte carlo platform for research and clinical applications," *Med Phys*, 2012.
[3] J. Schuemann, et al., "Topas-nbio: An extension to the topas simulation toolkit for celular and sub-cellular radiobiology," *Radiat Res*, 2019.
[4] H. Kim, et al., "Microdosimetric-Kinetic Model for Radio-enhancement of Gold Nanoparticles: comparison with LEM", *Radiat Res*, 2020.

RADIOBIOLOGICAL MODELS

The simulations outputs will be used to predict cell survival fractions (S), using standard mathematical models of the biological effects of radiation as Local Effect Model (LEM) and Microdosimetric Kinetic Model (MKM) [4]. Both models assume that the cell nucleus is the principal target, and it is divided into small independent domains. The application of this models to GNP radio-enhancement is done considering the probability of interaction (p) and the radial dose per ionization from single GNP (d_{GNP}).

LEM

The number of lethal events (L_n) is a function of the absorbed dose in infinitesimally small volume in the nucleus (d):

$$L_n(d) = \begin{cases} \alpha d + \beta d^2, & d \le D_t \\ (\alpha + 2\beta D_t)d - \beta D_t^2, & d > D_t \end{cases}$$

$$d = D(1 + p\, d_{GNP}) \qquad S = \exp(-\langle L_n(d)\rangle)$$

MKM

The number of lethal events (L_n) depends on the average absorbed dose in the nucleus (D_n) and on the dose-mean linear energy $(\overline{y_D})$:

$$\langle L_n(D_n)\rangle = \alpha^* D_n + \beta D_n^2 \qquad \alpha^* = \alpha + \frac{\beta \overline{y_D}}{\rho \pi r_d^2}$$

$$D_n = \frac{\sum_{i=1}^{N} D(1 + p(d_{GNP})_i)}{N}$$

$$S = \exp(-\langle L_n(D_n)\rangle)$$

RESULTS

The results obtained in the simulations will be compared with the biological in vitro and in vivo experimental results, which will include evaluation of cell viability and survival. Moreover, the simulated ROS yields will be also compared with the experimentally determined values.

So far, we did the definition of geometry on TOPAS, represented in figure 3c.

In the future, we will use this complex and realistic geometry to obtain more accurate results when compared to those obtained when using simple geometries.

Figure 3. a) Original Image **b)** Segmented Image **c)** Geometry defined on TOPAS.

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