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

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Several studies show that the combination of high-Z nanoparticles and external radiotherapy leads to an increased radiation effect in tumoral cells without increasing the patient dose. The objective of this work is to develop simulation tools that allow a better understanding of radiobiology results obtained in cell irradiation studies in the presence of multi-functional nanoparticles. In these proceedings we summarize the methodology that is being developed to make realistic simulations of the irradiation of monolayer and spheroid human glioblastomas multiforme cell cultures, taking into consideration different concentrations of the gold nanoparticles. Based on these simulations, microdosimetric dose distributions will be obtained as well as the temporal distribution of G-values yields for different reactive oxygen species. The microdosimetric distributions in cells will be used to predict cell survival fractions, using mathematical models of the biological effects of radiation. The results obtained in the simulations will be compared with the biological *in vitro* and *in vivo* experimental results.

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1. Introduction

To improve the effects of radiation in cancer treatment, the enrichment of tumors with high-Z nanoparticles (NPs) has been proposed. It as been observed that the presence of NPs increases both the direct and indirect effects of radiation [1]. Depending on whether the incident radiation is photons, protons, or heavy ions we can have different interaction mechanisms with the NPs, leading to the emission of secondary radiation. This secondary radiation when interacting with neighboring NPs can further increase the production of radiation in a cascading process. Ionization processes are particularly relevant since they lead to atomic de-excitation with the emission of X-rays and Auger electrons. The very low energy (~eV) component of Auger spectrum has electrons with very short ranges (~nm), which gives them a high linear energy transfer and thus a significant radiobiological effect. Due to the very short range, the energy deposition of these electrons will essentially be inside the cell.

The emission of more secondary radiation in the presence of NPs also enhances the production yields of reactive oxygen species (ROS), thus increasing the indirect effects of the radiation. Although the mechanisms underlying the physical and chemical stages in the presence of NPs are apparently well known, it is unclear how they contribute to the observed biological effects.

Here we report on the methodology that is being implemented for the modeling of dosimetric and radiobiological effects concerning the preclinical evaluation of multifunctional gold NPs (AuNPs) as radiosensitizers in proton therapy of glioblastoma multiforme (GBM). This study is one of the main activities of the *In-beam Time-of-Flight (TOF) Positron Emission Tomography (PET) for proton radiation therapy (TPPT)* project. The specific goals of the dosimetric studies in this work are to develop realistic simulations of human GBM cell cultures, considering different concentrations and cellular distributions of the AuNPs and different irradiation conditions.

2. Methodology

The process of modelling the effect of AuNPs on the biological response of GBMs will be divided into the following steps: i) Development and implementation of 2D and 3D computational models of GBM cell lines in the Monte Carlo simulations, ii) Simulation of microdosimetric distributions and ROS distributions in GBM cell lines, and iii) implementation of the biological effects model for cell death and strand breaks.

2.1 Implementation of computational models in MC simulations

The simulations are performed using the TOol for PArticle Simulation software (TOPAS) [2], more specifically, the extension TOPAS-nBio [3], which is layered on top of the Geant4 Monte Carlo toolkit [4].

To implement realistic simulations beyond simple spherical geometries, we are developing an algorithm that imports real cell images to the TOPAS geometry file. The process works as follows: a stack of 2D images is obtained from confocal microscopy and each of them is pre-processed to improve quality, and then segmented to allow for the identification and separation of the different cell components (the nucleus and the cytoplasm). A specific number is assigned to each component and written in a binary file that will be used as input in TOPAS. In the parameter file of the simulation, the number of voxels in each dimension x and y, the number of slices z, and the voxel dimension must be defined. It is important to define how the number in the binary file is converted to a specific material. For that, the extension MaterialTagNumber is used.

All the process, from segmenting the image to import it to TOPAS, was tested and done with an example of a confocal microscopy image taken from ImageJ software [5]. The results of each step of the described process are illustrated in Fig. 1.

Figure 1: Process to convert a confocal image to a computational model. Left: Original image; Middle: Segmented image; Right: Geometry in TOPAS.

As a first real test of this algorithm, computational phantoms of two different cell lines of GBM (U373 and U87) that are being used within the TPPT project will constructed from confocal images. The total number of AuNPs per cell will be estimated from the measured uptake obtained by inductively coupled plasma-mass-spectrometry (ICP-MS) and knowing the average dimension of a single AuNP (~4.3 nm diameter). The number of AuNPs will be randomly distributed in the cytoplasm.

Several incident beam configurations will be considered according to the irradiation campaigns foreseen by the TPPT project. These include a few hundred kV X-ray source, a ^{60}Co source, and a proton beam of 18 MeV and other typical clinical energies. Particular attention must be paid to the characterization of the incident beams: energy spectrum, beam width, field size and shape.

To simulate the physical interactions between the radiation and the cells, we will use two different lists: the Geant4-DNA [6] and the Livermore [7] lists. Production of fluorescence and Auger electrons, the Auger Cascade, and the PIXE process are included in the simulations.

To simulate the water radiolysis, some variables as the ramification rates and dissociation schemes must be defined, using the TOPAS-nBio extension. This extension can output spatial-temporal distributions of G-values, that is the number of each chemical species produced per 100 eV of energy deposited at given time and point. From the G-values yields is possible to verify which chemical species are more affected and which stage of radiolysis is more relevant in the presence of NPs.

2.2 Microdosimetric radiobiological models

The microdosimetric quantities obtained by simulation according to the methodology described by Kim *et al.* [8] are the input parameters for applying the cell survival models. Two models are, for now, being considered: the Local Effect Model (LEM) [9] and the Microdosimetric Kinetic Model (MKM) [10], where both assume that the cell nucleus is the principal target.

The application of these models to AuNP radio-enhancement is made considering the probability, p, of interaction between the radiation and the NPs and the radial dose per ionization from a single AuNP, d_{AuNP} [8]. The number of lethal events in the nucleus L_n follows a Poisson distribution as a function of dose. Thus, the surviving fraction is determined by $S = \exp(-\langle L_n \rangle)$.

According to the LEM, the number of lethal events L_n is a function of the absorbed dose d in an infinitesimally small volume inside the nucleus,

$$L_n = \begin{cases} \alpha d + \beta d^2, d \leq D_t \\ (\alpha + 2\beta D_t)d - \beta(D_t)^2, d \geq D_t \end{cases}, \quad (1)$$

where $d = D(1 + p d_{\text{AuNP}})$, being D the prescribed dose in Gy, and α and β are the coefficients in the Linear Quadratic model (LQM) [11] for the reference radiation; D_t is threshold dose, above which the LQM fails. The principal assumption of the LEM is that the probability of damage happening depends on the quantity of local energy deposited and not on the particles that deposit that energy.

The MKM assumes that the nucleus is divided into small independent domains with density ρ and radius r_d, and the summation of the local effect in all domains determines the survival probability [8]. In this model, the number of lethal events depends on the average absorbed dose in the nucleus D_n and on the dose-mean linear energy $\bar{y}_D$:

$$\langle L_n(D_n) \rangle = \left(\alpha + \frac{\beta \bar{y}_D}{\rho \pi r_d^2} \right) D_n + \beta D_n^2, \quad (2)$$

where $D_n = [\sum_{i=1}^{n} D(1 + p(d_{AuNP})_i)]/n$, being n the number of the nucleus' sub-volumes and $(d_{\text{AuNP}})_i$, the total radial dose per ionization from all GNP deposited at i-th sub-volume. The dose-averaged lineal energy, $\bar{y}_D$, is the first moment of the dose distribution within the nucleus. This distribution can be scored following the method described in [12].

3. Ongoing work and future prospects

Currently, we are are optimizing the application of the conversion process to confocal images of two cell lines of human GBM and, simultaneously, we are developing the TOPAS application that allows to score the microdosimetric quantities needed by the LEM and the MKM. For now we are applying these models to a simple geometry as a spherical cell with AuNPs in the cytoplasm. In the future, we want to apply the LEM and the MKM to the more realistic geometries for 2D and 3D models obtained from confocal images.

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References

[1] S. Lacombe, E.Porcel and E.Scifoni, Cancer Nanotechnol. **8**(1):9, 2017.
[2] J. Perl, J.Shin, J.Schumann, B.Faddegon and H.Paganetti, Med. Phys. **39**(11):6818–37, 2012.
[3] J. Schuemann, A.L.McNamara, J.Ramos-Mendez, J.Perl, K.D.Held, H.Paganetti, S.Incerti and B. Faddegon, Radiat. Res. **191**(2):125–138, 2019.
[4] S. Agostinelli *et al.* (Geant4 Collaboration), Nucl. Instrum. Methods A **506**:53, 2003.
[5] C.A. Schneider, W.S. Rasband and K.W. Eliceiri, Nat. Methods **9**:671-675, 2012.
[6] S. Incerti *et al.* (Geant4-DNA Collaboration), Med. Phys., **45**(8):722-739, 2018.
[7] G4EmLivermorePhysics: https://geant4.web.cern.ch/node/1619
[8] H. Kim, W. Sung and S. J. Ye, Radiat. Res. **195**(3):293-300, 2021.
[9] M. Scholz and G.Kraft, Radiat. Res., **161**(5):612-620, 2004.

[10] R.B. Hawkins, Med. Phys., **25**:1157–70, 1998.

[11] S. J. McMahon, *Phys. Med. Biol.*, **64** 01TR01, 2019.

[12] I. Kyriakou, D. Emfietzoglou, V. Ivanchenko, M. C. Bordage, S. Guatelli, P. Lazarakis, H. N. Tran, and S. Incerti, J. Appl. Phys. **122**:024303, 2017