On the need of using MC Simulations to optimize the design of a clonogenic assay to measure RBE as a function of LET and minimize the measurement uncertainty.

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Background: We used GAMOS/Geant4 to optimize the design of a clonogenic assay for a proton therapy active scanning machine, with the novelty of including a detailed calculation of the uncertainty in the calculation of RBE.

Material and Methods: Based on using a jig-shaped shield, GAMOS/Geant4 has been used to select the optimal combination of energy, measurement positions on the Bragg curve, beamlets spacing and exposure times to irradiate five cell lines with different doses and LET values.

After selecting the optimal energy, we had to face a problem that is specific to active scanning: the width of a single beamlet has sigma greater than the diameter of the cell wells, and no moving collimators can be used to change the shape of the beam as a mean to control which wells are irradiated. To solve this problem, a complex distribution of beamlets for the 150 configurations (5 cell lines x 5 dose values x 6 LET values) is necessary. This optimization has been done with Geant4 to have an accurate simulation of the beam dispersion that allows us to calculate dose inhomogeneity at the cell plane.

The optimization of the configuration must take into account not only the reduction of proton beam time (and therefore cost) but also the effect that the selected parameters will have on the expected uncertainty of the RBE results. To our knowledge there is no published work that minimizes the RBE uncertainty in the design.

To get a good estimate of the RBE uncertainty we have used the detailed GAMOS simulation of the proton beam and have added to it several RBE phenomenological models (included in GAMOS) with different input values of α_x and β_x for each cell line obtained from a previous irradiation of our cells in a photon beam from a 6MV LINAC.

Preliminary results: We have selected an energy of 70.2 MeV, as it is the one with highest LET values, up to 29 KeV/um and its LET spectrum at the cellular plane is the narrowest one and has a negligible influence in the RBE uncertainty.

The complex distribution of beamlets designed to irradiate 8 cells with each of the 150 configurations takes only around 2.5 hours of beam time.

In summary, we have developed a new free-to-use tool based on Geant4 to optimize the design of clonogenic assays which consider the uncertainties from all the contributing factors to the RBE result.