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Radiation "bombs" in amyloids

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Abstract. This paper describes the steps required to study the impact of a proton beam in protein aggregation and the influence of gold nanoparticles as dose enhancement. For this purpose, we have developed a method to locate the deposition of high amounts of energy by the proton beam, what we called “radiation bombs". These objects were developed and designed using the TOPAS simulation toolkit. The crucial step is to understand the importance of performing the simulation with an appropriate physics list. In this paper is also proposed a way to simulate the radiation bomb, as future work.

Keywords: proton therapy, TOPAS MC, TOPAS n-Bio, amyloid-β

1 Introduction

1.1 Motivation

Radiotherapy is used to treat cancer resourcing to high doses of radiation with the purpose of killing cancer cells and tumors. One of the most promising approaches to cancer treatment is radiotherapy with protons or heavy ions. It delivers high dose to the target volume with the advantage of a lower exposure of healthy tissue, in comparison with conventional radiotherapy.

The penetration of nanoparticles of high-Z material into the cells is a way to enhance the radiation dose into the tumor, because of the production of large amounts of short range electrons, which leads to more DNA damage. The number and energy of secondary electrons, that are generated by proton interaction with nanoparticles, depend on the electron density and atomic number of nanoparticles: overall, the higher the atomic number of nanoparticles, the higher their effect in DNA damage. Gold nanoparticles have a significant effect on dose enhancement, strand breaks and cell killing incurred by proton beam irradiation, since gold is a high-Z material [1].

Brains of patients with Alzheimer´s disease present abnormal levels of amyloid-β protein, that progressively accumulate in the form of plaques between neurons, that are absent in healthy brain tissue (figure 1). Amyloid percursor protein (APP) is one of the most abundant proteins in the central nervous system and is sequentially cleaved by β and γ secretases, releasing amyloid-β. Amyloid β-sheet molecules can aggregate to form flexible soluble oligomers, as shown in figure 1, that are neurotoxic and may spread throughout the brain, disrupt cell function and lead to neuronal cell death [2].

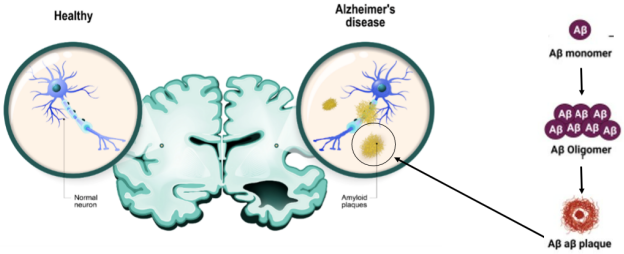

Figure 1: Amyloid β-sheet (Aβ) molecules aggregation and accumulation in the form of plaques, in brains of patients with Alzheimer´s disease. [3, 4]

1.2 Objective

The goal of this work is to apply Monte Carlo simulations in order to understand the impact of proton beam on protein aggregation and accumulation in brain cells.

2 Methods

Simulations were carried out using TOPAS [5, 6] (Tool for PArticle Simulation), a Monte Carlo tool layered on top of Geant4.

2.1 First step: irradiating liquid water with a proton beam

To better understand the simulation toolkit and the available tools, as well as to deepen the knowledge about the behaviour of protons, the first step was to study the simulation results when irradiating liquid water with a proton beam.

2.1.1 Simulation Geometry

We started by defining a simple box, with a half-length of 0.1 μm, filled with water, and by placing a proton beam of 100 keV (as blue in figure 6) at one end of the box. The simulations were performed using two different physics lists.

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2.1.2 TOPAS parameter: physics list

In a nutshell, the physics list gives the simulation information about the physical interactions that occur. For instance, what type of interactions (Compton, Photoelectric, etc.) it should simulate as well as the energy ranges it should consider.

We used the physics list *g4em-dna* that is optimised for electromagnetic interactions of particles with liquid water at the nanometer level and compared the results when using the *g4em-standard* physics list that simulates basic electromagnetic interactions with any material.

2.2 Second step: add amyloid to the simulation

Since we want to study the impact of radiation on protein aggregation, the next step was to add an amyloid to the simulation. For that, we used TOPAS extension TOPAS-nBio.

2.2.1 TOPAS extension TOPAS-nBio: PDB4DNA application

In TOPAS-nBio, using PDB4DNA application, we are able to input a DNA geometry in a specific file extension, simulate the irradiation of this structure and obtain an output file, containing the single strand and double strand breaks for every primary particle emitted, as shown in the diagram in figure 2.

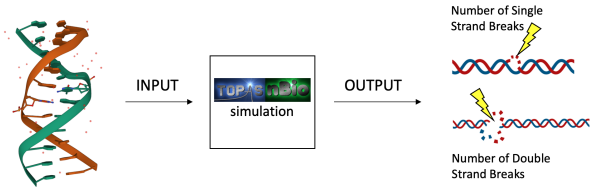


Figure 2: Overview Diagram of an TOPAS-nBio example.

In order to simulate amyloids instead of DNA, the base code in c++ had to be changed, so it would be possible to input a protein structure and simulate the breaks induced by radiation. The base code was specifically designed to read DNA structures by considering its double stranded structure and its residues. Hence, the changes in the base code had to enable the simulation to read molecule structures other than DNA structures. For that, we generalised the base code to any molecule structure, by changing for example some if statements.

The input file of the amyloid is obtained from the RCSB Protein Data Bank [7], with identifier 2M4J [8], where we extract a file that specifies the geometry of the amyloid. This file is called a pdb file and it gives us, for example, the x,y and z coordinates of each atom of each molecule strand.

In order for the TOPAS simulation to compute the number of strand breaks, it extracts the spatial coordinates of each atom of the amyloid from the pdb file. In addition, it simulates the spatial coordinates of each energy deposition as well as the amount of energy deposited, by the particles. With this information, the simulation considers a certain energy deposition to result in a strand break, if it occurs close to an atom of the amyloid and the deposited energy is higher than the energy necessary to break a bond between two atoms.

2.2.2 Simulation Geometry

The simulation geometry is illustrated in figure 3 and consists of two boxes filled with water. The smaller box is called a detector and inside of it is the amyloid. So, the simulation will only consider energy depositions that occur inside the detector. The box has 1000 Å× 1000 Å× 1000 Å and the amyloid 50 Å× 50 Å× 14 Å of dimension.

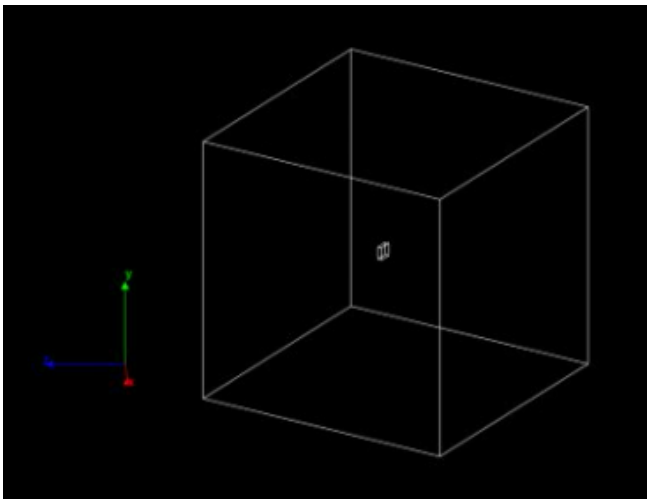


Figure 3: View of the geometry defined in for an amyloid structure 2M4J [8] shown in the centre of the figure, inside a water cube. Box/Amyloid volume ratio: 30 000.

We simulated the total number of strand breaks of the amyloid induced by a proton beam from energy 100 keV to 12.5 MeV.

2.3 Third Step: increase amyloid size

The third step consisted of repeating the same amyloid structure from the protein data bank along the x, y and z axes in order to increase the probability of occurring an energy deposition near an atom of the amyloid, leading to a strand break.

The simulation geometry is illustrated in figure 4 and consists of the same box as in figure 3, with the amyloid structure increased and repeated along the axes. The box has 1000 Å× 1000 Å× 1000 Å and the amyloid Å× Å× Å of dimension.

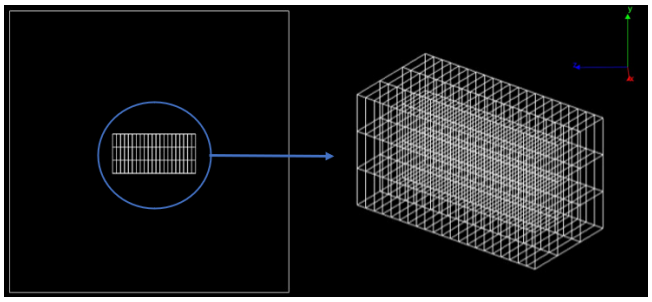


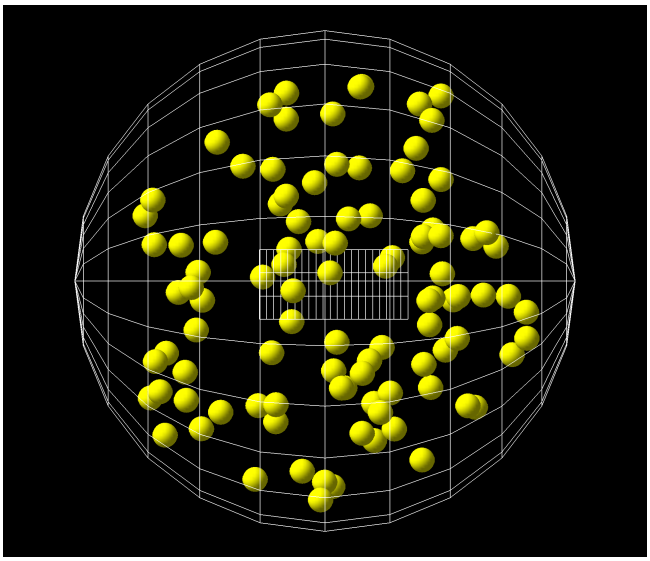
Figure 4: Geometry defined for the amyloid structure 2M4J [8] increased in size along x, y and z axes. Box/Amyloid volume ratio: 150.

We simulated the total number of strand breaks of the amyloid induced by a proton beam from energy 100 keV to 12.5 MeV.

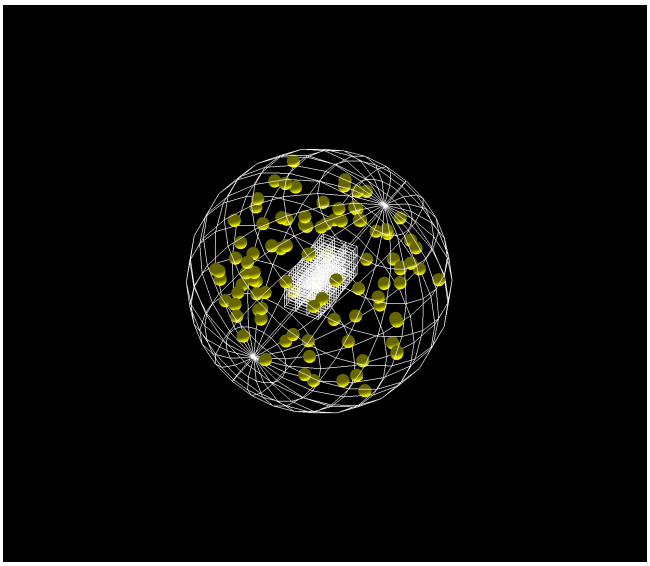
2.4 Fourth Step: add gold nanoparticles

To do the radiation bomb simulation, we defined a sphere filled with water. It contains the previous amyloids and additional randomly distributed gold nanoparticles (yellow), as shown in figure 5. We are placing them near the amyloids since gold is a high-Z material, which will improve the concentration of the radiation dose into the amyloids, because of the production of large amounts of short range electrons, which leads to more strand breaks and ultimately to more protein damage.

We simulated the total number of strand breaks of the amyloids induced by a proton beam of energies from 100 keV to 17.5 MeV, with and without the presence of gold nanoparticles. Moreover, since the *g4em-dna* physics list only includes reactions with water and not with other materials we had to use the physics list *g4em-standard* option 4.



(a) Simulation geometry: 2D perspective.



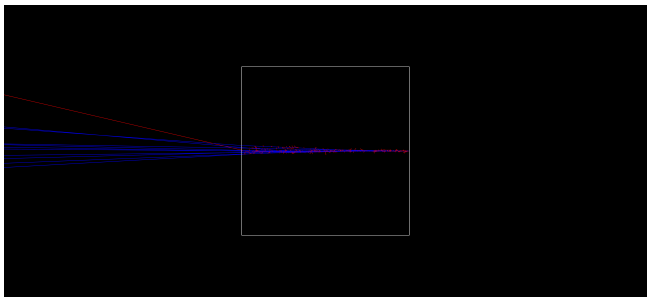
(b) Simulation geometry: 3D perspective.

Figure 5: Radiation bomb Simulation geometry. The added gold nanoparticles are depicted in yellow.

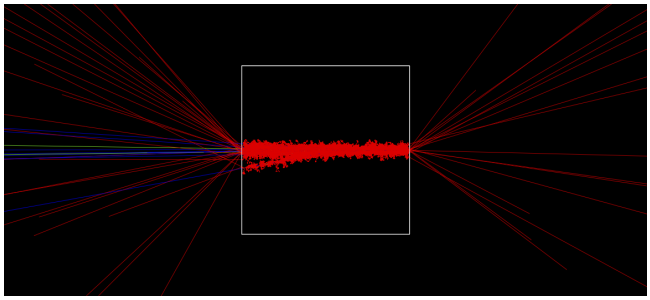
3 Results and Discussion

3.1 First Step: proton beam irradiating box filled with water

The graphical simulation results are shown in figure 6. When comparing figures 6b and 6a, a much larger amount of secondary electrons (in red) is observed when using the g4em-dna physics list, which is a predicable result, since, as mentioned, the g4em-dna physics list is optimised for reactions in water at a nanometer scale.



(a) Simulation performed with the physics list g4em-standard option 4.



(b) Simulation performed with the physics list g4em-DNA.

Figure 6: Simulation in TOPAS [5, 6] of a 100 keV proton beam (blue) interacting with a box filled with water, using two different physics lists.

3.2 Second Step: add amyloid to the simulation

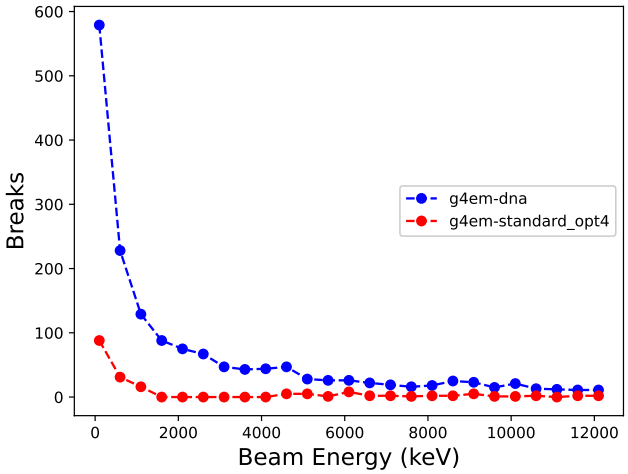


Figure 7: Total number of strand breaks on the amyloid induced by a proton beam from energy 100 keV to 12.5 MeV, using two different physics lists. Number of simulated events: 10^4.

We can see in figure 7 the results, after adding the amyloid to the simulation. Overall, when using the *g4em-dna* list, a higher number on strand breaks is obtained. This result is excepted since as observed previously, the *g4em-dna* list simulates much more secondary electrons than the *g4em-standard* list. With an increase in secondary electrons, the probability to occur an energy deposition near the amyloid, thus, to occur a break, is higher. Moreover, a higher number of strand breaks is observed for energies around 100 to 200 keV, while for energies above 4 MeV, the graph forms a "plateau", which means that we have roughly a constant number of strand breaks for higher energies.

3.3 Third Step: increase amyloid size

Te resultas after incresing the amyloid size are similar to the ones obtained in the previous step. Overall, when using the *g4em-dna* list, a higher number on strand breaks is obtained.

3.4 Fourth Step: add gold nanoparticles

The results obtained with the radiation bomb simulation are depicted in figure 8. As we can observe, there is a downward trend for both curves and a slightly higher number of strand breaks when using gold nanoparticles. We expect to obtain a higher number of breaks with the presence of gold nanoparticles near the amyloid, since the reaction of radiaton with gold produces a high amount of secondary electrons, thus, overall, increases the production of electrons. However, the results show a very small difference of strand breaks. In fact, the difference is so little that we are not able to confirm with certainty that it is due to the addition of gold nanoparticles.

As observed throughout this work, the most suitable physics list for this simulation would be the g4em-dna, nevertheless, for radiation to react with gold we had to use the g4em-standard physics list. Since the second physics list simulates much less electrons than the first one, we would expect to observe a more noticeable difference between the curves in graph 8, when using the g4em-dna physics list.

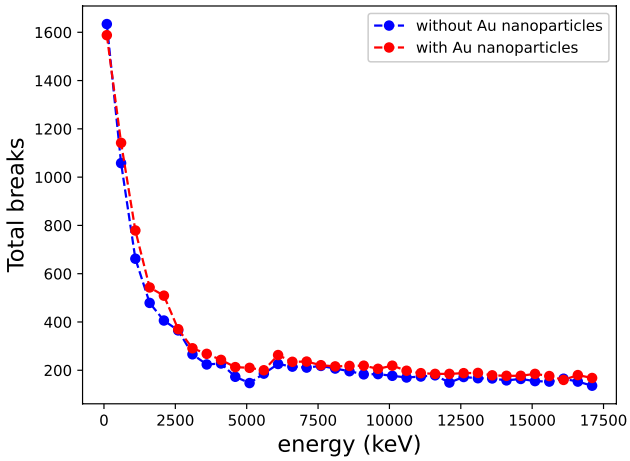


Figure 8: Total number of strand breaks on the amyloid induced by a proton beam from energy 100 keV to 17.5 MeV, with and without the presence of gold nanoparticles. Simulation performed with the physics list g4em-standard option 4 . Number of events: 10^5

4 Conclusions and Future Work

From this work we are able to take several conclusions:

1. It is very important to study the impact of different physics list in the simulation, since it can considerably influence the results.

2. We are able to get better simulation results in liquid water at the nanometer level with the *g4em-dna* physics list.

3. The number of strand breaks is the highest for energies around 100 keV and becomes constant for energies approximately above 4 MeV.

4. By adding gold nanoparticles, we obtained a slightly higher number of strand breaks, although we were expecting a substantially larger difference. It is important to note that with the obtained results, we are not able to conclude properly about the influence of gold nanoparticles in the simulation.

4.1 Method Limitations/ Future work

As we have been illustrating, the g4em-dna physics list is able to optimally simulate the physical interactions in water at the nanometer scale while the *g4em-standard* does not. With that in mind, we are working on simulating the radiation-bomb with the two physics lists, specifying the *g4em-standard* physics list to the gold nanoparticles. This way, the results will probably be improved and should also provide a more realistic picture of the effect of these particles and the potential damage induced in the amyloid structures.

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