THE IRRADIATION SYSTEM FOR STUDYING BIOLOGICAL EFFECTS IN GLIOBLASTOMA CELL LINES AFTER EXPOSURE TO HIGH LET α PARTICLES APPEARING IN BNCT THERAPY*

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A biological sample irradiation system consisting of a 50 mm diameter ^{241}Am disc source was developed at the Heavy Ion Laboratory of the University of Warsaw. Prior to biological experiments, an investigation was conducted on the irradiation system to accurately assess the dose distribution within cells by analyzing the α-particle spectrum. A comprehensive numerical model of the irradiation system was developed to simulate and analyze the radiation process. The results of the numerical simulations were subsequently compared with measurements of α-particle energies emitted from the source and were found to agree within 4% agreement. The measurements were performed using a silicon detector under vacuum conditions and a track detector.

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1. Introduction

Recently, high-energy charged particles have emerged as an innovative therapeutic option in the cancer treatment [1]. Isotopes emitting ionizing radiation, characterized by short-range and high Linear Energy Transfer

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(LET), have become one of the solutions used in nuclear medicine. An example are α emitters used in targeted α therapy. In this approach, ^{225}Ac-labelled pharmaceuticals are administered into the post-surgical cavity [2]. Moreover, α particles are employed in the context of Boron Neutron Capture Therapy, a method used in the treatment of cancers that are difficult to treat with conventional methods. This therapeutic approach involves the administration of boron agents with a stable isotope, specifically ^{10}B. These agents selectively accumulate within cancerous tissues, then the tumor is exposed to a beam of neutrons with an appropriate energy level. The capture of thermal neutrons by the ^{10}B nuclei leads to the production of the ^{11}B isotope, which subsequently decays into high-energy α particles and ^{7}Li nuclei. The range of these highly ionizing particles is approximately 5 μm for ^{7}Li and 9 μm for the α particle, which is comparable to the size of a single cell [3]. This selective targeting ensures that only cancer cells are effectively destroyed. The BNCT therapy uses epithermal neutron beams with energies in the range of 0.5 eV–10 keV or thermal (< 0.5 eV) depending on the depth of the tumor in the patient's body. At the National Centre for Nuclear Research in Świerk, experimental research related to BNCT will use beams of thermal neutrons from the MARIA research reactor [4]. Both therapies have found their application in the treatment of brain tumors, including Glioblastoma multiforme (GBM). Consequently, the subsequent step of the project involves the determination of cell survival for two glioblastoma cell lines, M059K (CRL-2365) and M059J (CRL-2366), sourced from ATCC. This evaluation will be conducted in correlation with the dosage of α particles emitted by a flat ^{241}Am source. To ensure the precision and reliability of experiments, a detailed dosimetry of the irradiation setup was conducted to accurately determine the radiation doses deposited within the biological material. Due to limitations in reproducing the irradiation geometry in measurements, calculations of the dose deposited in the cellular sample were only feasible via Monte Carlo simulations. Consequently, in order to validate the simulation results, calculations were also conducted under conditions replicable experimentally. A detector used for ion measurements needs to be capable of operating under several limiting conditions such as vacuum, high temperature, strong magnetic fields, strong background radiation — mainly gamma and neutron radiation, *etc.* For example, semiconductor detectors, *i.e.* germanium, silicon, and diamond, are often used for measuring charged particles, with the use of the latter becoming more and more common. Semiconductor detectors have a good energy resolution of about 10 keV and a time resolution of about 1 ns, but are unable to operate correctly under a large ion flux. An alternative for the measurement of charged particles are polyllyl-diglycol-carbonate (PADC) detectors. The PADC detector is a plastic track detector possessing many specific advantages, which make

it a very useful diagnostic tool for the registration of particles. The reason for their popularity is, on the one hand, their high sensitivity to heavy charged particles (protons, deuterons, alpha particles or other heavy ions), and on the other hand, these detectors are not very sensitive to electromagnetic radiation and fast electrons. Another important advantage of these detectors is that they do not require any electronic devices, and hence the measurements of charged particles are not disturbed by electromagnetic radiation (X, γ) and E-M noise. A charged particle passing through such a material leaves a track of increased chemical reactivity extending along the particle's trajectory with a size of about 50 Å. These traces are visible under an electron microscope. However, after chemical etching, they can also be observed under an optical microscope.

To validate the MCNP calculations, several different measurements of the α particles were conducted. One of these measurements involved the use of a monolithic silicon surface barrier detector with a 21 mm diameter of active area in a vacuum environment, while another measurement utilized a plastic track detector under the air conditions of the ^{241}Am irradiation setup.

2. Irradiation setup

The experimental setup used for the irradiation of biological samples developed at the Heavy Ion Laboratory [5] consists of a ^{241}Am surface source with a 50 mm diameter and an activity of 1.96 MBq. The active component of the source consists of a mixture of pure gold powder and AmO_2 in the ratio of 1:0.0425. A layer of gold covers the source's surface. The source is affixed to the inner surface of a Petri dish lid using a 6 μm thick Mylar film. Cells seeded onto 30 mm diameter coverslips are positioned at the centre of the bottom part of the sterile Petri dish. A 5.8 mm air gap is left between the source and the biological sample on the coverslip. The detailed geometry of the setup is shown in Fig. 1.

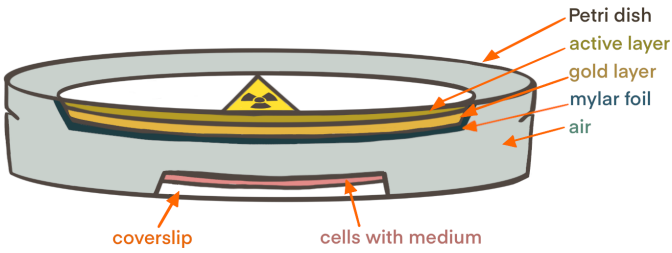

Fig. 1. Sketch of the α-particle irradiation setup (not in scale). From the top: active layer of the ^{241}Am surface source, protective gold layer, Mylar foil, air between the source and the biological sample, cells with medium, and coverslip. All elements are placed in a sterile Petri dish.

The proposed irradiation system represents an ideal tool for research on many different cancer cell lines after exposure to densely ionizing α particles. The foremost merit of this setup lies in its dimensions and its capacity to irradiate cells within a laminar chamber or an incubator, concurrently preserving sterility and providing optimal conditions for cellular functionality.

3. Monte Carlo simulations and measurements of energy spectra

A detailed model of the cell sample irradiation setup (Fig. 1) was prepared using the Monte Carlo N-Particle (MCNP) simulation framework [6]. Since the manufacturer of the alpha surface source provided only approximate information regarding the geometric parameters, such as the thickness of the active layer and the protective gold layer, a series of simulations were conducted using various values of these parameters, which were subsequently validated experimentally. The first measurement was an energy calibration, the geometry and experimental conditions were recreated in the MCNP. The Monte Carlo calculation included the GEB (Gaussian Energy Broadening) parameters calculated using FWHM of the peaks measured using a spectroscopic ^{241}Am source. Constants $a = 0.657$, $b = -0.272$, and $c = 0$ were determined from the equation

$$\mathrm{FWHM} = a + b\sqrt{E + cE^2}\,,$$

where E is the energy of the particle.

The next step was the measurement of the ^{241}Am surface source shielded by a 6 μm thick Mylar foil and a 2 cm diameter aluminum collimator. The distance between the source and the detector surface was 4.12 cm. In this case, the geometry was also reproduced in detail in MCNP leading to the determination of the average flux across the detector volume, expressed in units of $1/\mathrm{cm}^2$ (F4 type tally in MCNP). Subsequently, the values that best reproduced the results of the measurement were selected. Alpha-particle energy spectra of the ^{241}Am surface source obtained from measurements with a silicon detector (solid gold line) in the vacuum environment and calculated with MCNP (dashed grey line) are presented in Fig. 2. The integrals corresponding to the curves in Fig. 2 were ascertained and the discrepancy between them is 4%.

Finally, after checking the compliance of the measurements with Monte Carlo calculations, the obtained active layer (0.4 μm) and the protective gold layer (0.8 μm) were implemented in a numerical model of cell irradiation setup. The average energy deposition within the cellular layer is $4.53e+07$ MeV/g/s.

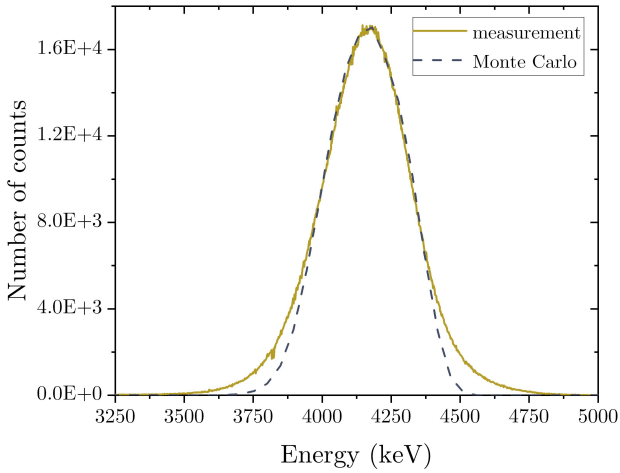

Fig. 2. (Colour on-line) The alpha-particle energy spectrum of ^{241}Am registered for a surface source shielded by a 6 μm thick Mylar foil in a vacuum zoomed on the main peak. Solid gold line: spectrum measured with a silicon detector. Dashed grey line: spectrum calculated with MCNP.

4. Track detectors

PADC detector samples of the CR-39 TASTRAK type, which were irradiated with alpha particles in the ^{241}Am irradiation setup were analyzed using a semiautomatic system composed of an optical microscope connected to a PC by means of a CCD camera (Nikon DS.-Fi2, 5.24 Mpix) and suit-

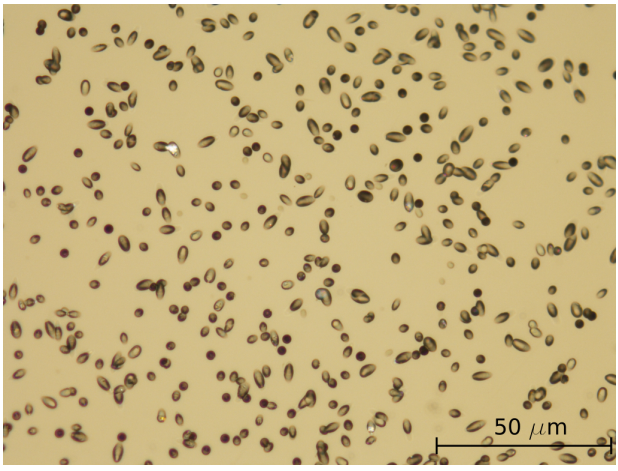

Fig. 3. Image of a track detector irradiated with a dose equal to 0.5 Gy, taken by optical microscope.

able software (Nikon–NIS–Elements BR 4.00.03—64 bit). Irradiated track detector is presented in Fig. 3. Alpha particles emitted from the entire surface of the source were recorded by trace detectors after passing through the air. Through appropriate selection of the parameters of the etchant solution, the scanned detectors that were irradiated with helium ions provided parameters of an etched pit, such as track diameter and track mean gray level [7, 8]. Both these parameters can be found quickly with good accuracy, and give enough information to determine the track density of the incident charged particles. Figure 4 illustrates the relationship between the track density and the detector surface area for the deposited doses. The black trend lines demonstrate the uniformity of cell sample irradiation, a crucial aspect of radiobiological research.

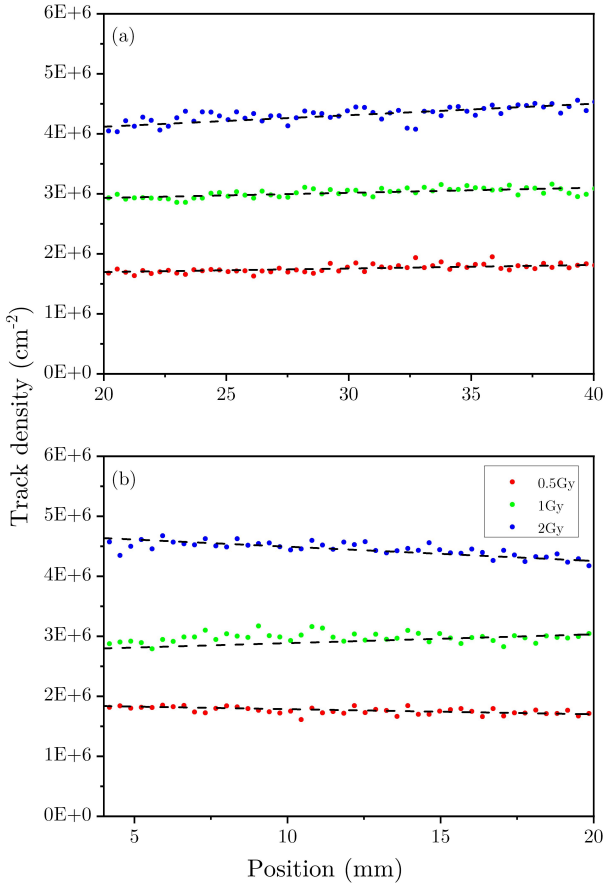

Fig. 4. (Colour on-line) Horizontal (a) and vertical (b) scans of track detectors irradiated with three different doses. Dashed black lines are trend lines. Uncertainties of experimental points are 5%.

5. Summary

A detailed model of an experimental ^{241}Am surface source setup dedicated to biological sample irradiation was prepared in MCNP. The calculations yielded the dimensions of the active part of the source and the protective gold layer. Results of Monte Carlo calculations of α-particle spectra were compared with experimental data. Measurements were performed with a silicon detector in vacuum conditions. The measurement and Monte Carlo results agree within 4%. Additionally, the track detectors were irradiated in a biological sample setup, in the air environment, which allowed for the determination of track density depending on the radiation dose. The surface ^{241}Am source enables homogeneous irradiation of biological samples.

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