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Dosimetry of laser-accelerated carbon ions for cell irradiation at ultra-high dose rate

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Abstract. Charged particle radiotherapy is currently used in an increasing number of centres worldwide. While protons are the most widely used ion species, carbon ions have shown many advantages for the treatment of radioresistant tumours, thanks to their higher Linear Energy Transfer (LET) and Relative Biological Effectiveness (RBE). The complexity and the high cost of conventional carbon therapy facilities has stimulated the investigation of alternative acceleration approaches such as the processes based on high-power laser interaction with solid targets. Recent developments in ion acceleration have allowed to investigate for the first time the biological effects of carbon ions at ultra-high dose-rate (10^9-10^{10} Gy/s) using the GEMINI laser system at Rutherford Appleton Laboratory (RAL). Carbon ions were accelerated from ultrathin (10-20 nm) carbon foils and energy selected by a magnet allowing to irradiate the cells with an average carbon energy of 10 MeV/u $\pm$ 8%. A dosimetry approach specifically designed for these low-energy ions was employed, which was based on the use of unlaminated EBT3 Radiochromic films. The details of the dosimetry arrangement as well as the Geant4 simulation performed to predict the energy and the dose distribution at the cell plane will be reported.

1. Introduction

The use of particle beams in clinical radiotherapy is applied in an increasing number of particle therapy centres worldwide [1, 2]. Hadrontherapy, based on the use of protons and ions for cancer treatment, shows many physical and biological advantages with respect to conventional radiotherapy with X- and gamma rays, such as the higher ballistic precision in the radiation release which allows maximizing the damage to the cancer volume while sparing the surrounding healthy tissues. The higher Linear Energy Transfer (LET) of carbon ions at clinical energy (100-300 MeV/u) with respect to protons leads to an increased efficiency in cell killing associated to the more complex cellular damage in the target tumour.This enhanced radiobiological efficiency is measured by the LET-dependent Relative Radiobiological Effectiveness (RBE) which is up

to 3 times higher for carbons than for protons [3]. For all these reasons, the use of carbon ions for cancer treatment and radiobiological studies is particularly interesting in relation to malignancies showing high radioresistence, i.e. responding poorly to X-rays and protons. However, the particularly high costs of Carbon therapy facilities (even in comparison to the already expensive proton therapy) have limited severely its availability, with only a handful of centres in China, Japan, Germany and Italy currently providing this form of treatment. Furthermore, while compact proton treatment solutions based on state-of-the-art RF technology (inclusive of fully moveable beam around the patient) are currently becoming available, no such advance is foreseeable for Carbons in the immediate future. In this framework, the possibility to use carbon ions accelerated via laser-matter interaction for radiobiological studies is of significant interest, providing unique capabilities for investigating the response of cells to high-LET particles at ultra-high dose rate [4, 5]. This is now possible thanks to significant advances in carbon acceleration via volumetric acceleration mechanisms acting on the bulk of ultrathin targets, e.g. Radiation Pressure Acceleration (RPA) [6] , as recently reported in [7], within the activities of the UK wide A-SAIL consortium [8]. Experiments using the intense, ultrashort GEMINI laser at the Rutherford Appleton laboratory have shown that carbon ions and protons can be accelerated to comparable energies (up to 25-30 MeV/u) by irradiation ultrathin (10-20 nm) carbon targets. The high carbon energy and flux achieved are very promising in an applicative prospect, and, in the framework of the A-SAIL project, an experimental campaign aiming at irradiating for the first time biological samples with laser-accelerated carbon ions was recently performed with the GEMINI system using similar targets and laser parameters as reported in [7].The experimental setup, the dosimetry arrangement as well as the Montecarlo simulations carried out to guide the irradiation arrangement and aid the analysis of the data will be discussed in the following sections.

2. Experimental setup

The experiment was conducted at the Rutherford Appleton Laboratory, Science and Technology Facilities Council, United Kingdom using the GEMINI laser system which is able to deliver $\sim$12 J in a single shot at a pulse duration and central wavelength of 45 femtoseconds and 0.8 μm, respectively. The GEMINI laser system was focused into ultrathin carbon foil targets (10-25 nm), at intensities $\sim$ 6x10^{20} W/cm^2, by f/2 parabola. A double plasma mirror system was used for pulse contrast enhancement, and the pulse polarization was controlled by use of a wave plate. The ions (protons and carbon) accelerated from the target were selected using the experimental arrangement shown in figure 1 (left). A 0.9 T magnet coupled with a 500 μm wide slit was placed at about 50 mm from the target to energetically disperse the particles. The cells were placed in air at about 1 cm from a 50 μm kapton exit window. A target-cells distance of about 200 mm (figure 1) was chosen so that doses of order of 1 Gy could be delivered to the cells in a single exposure.The ion beam parameters in terms of energy spectrum and flux were measured by using a Thomson Parabola Spectrometer (TPS) coupled with BAS-TR Image Plates (IP). Moreover Radiochromic films, of EBT3 and HD-V2 type, were used in a stack configuration to measure the proton energy and spatial distribution.

Cells were grown as monolayers within a specifically designed dish on a 3 μm thin mylar foil. Before irradiation the dish was placed horizontally, closed with another mylar window and the 7 mm-thick gap between the two mylar windows was filled with a small amount of cell culture medium. The dish was then placed inside a small chamber provided with a 3 μm Mylar window in order to enhance the isolation of the cells from the laboratory environment as well as to flip, by means of a motorized mechanism, the dish vertical during the shot and remove the cell medium from the central part of the dish, i.e. our region of interest (figure 1 (right)). Glioblastoma stem cells (GBM), i.e. cancerous brain cells, which are particularly resistant to radiation [9, 10], were then irradiated with carbon ions reaching the cells at an energy around 10 MeV/u.

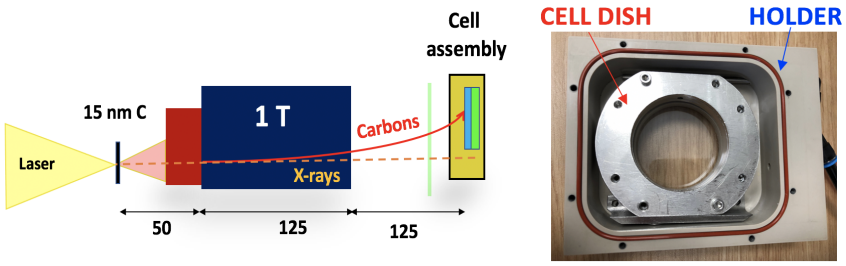

Figure 1. Scheme of the experimental setup (left). Image of the holder and the dish (right).

3. Dosimetry arrangement

The shot-to shot dose delivered to the cells in this type of experiment is typically detected using RadioChromic films (RCF) [11, 12] placed just behind or in front of the biological samples. RCFs, if previously calibrated with a known source, can be used as absolute dosimeters providing a measurement of the dose delivered for each shot. EBT3 RadioChromic films can be used for ion dosimetry in a dose range from 25 cGy up to 10 Gy, i.e. the typical doses needed for radiobiological studies. EBT3-RCFs are composed by a 28 μm thick active layer (A.L.) sandwiched between two 125 μm matte-polyester substrates(S.L.) as reported in [13].
The response to radiation of the RCF, i.e. the active layer colouring, strongly depends on the type of radiation, i.e. photons, protons or ions, on its LET and on the dose. The darkening level of the active layer after the RCF exposure to a fixed radiation dose is a function of the LET for the specific type of radiation used [14, 15, 16]. As a consequence, the dose calibration of RCFs has to be obtained for the specific ion species and energy required. In the experiment described here, carbon ions with energy up to 10 MeV/u were used to irradiate biological samples. The RCFs were placed just behind the 3 μm Mylar window on which the cell monolayer had been grown (see figure 2). Figure 2 also shows the dish structure with the two mylar windows (dark blue squares), the cell monolayer (light blue squares) and the gap between the two Mylar foils (sky blue square) filled with the air (grey square) when the dish is placed vertical during the irradiation.

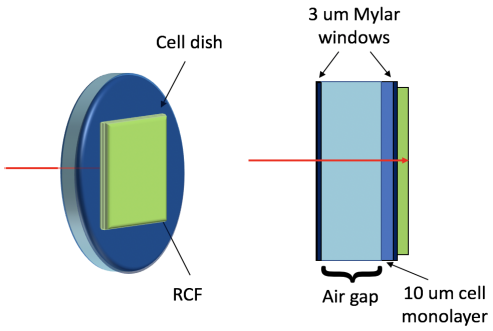

Figure 2. Scheme of the cell dish (in blue) and RCF (green box) arrangement during the irradiation. The RCF was placed just behind the dish, i.e. in contact with the Mylar window (dark blue box) to minimize the cells-dosimeter distance.

In order to accurately measure the dose delivered to the cells with the minimum uncertainty possible the dose measured by the RCF active layer need to be as comparable as possible to the real dose delivered to the cells. This has been evaluated simulating by means of the Geant4 toolkit [17], a 10 MeV/u monoenergetic carbon ion beam incident on the cell dish and retrieving

the depth dose profile along the different layers of the EBT3 film (figure 3(left). The monolayer cell has been modelized as a 10 μm-thick water layer and the real EBT3 active (A.L.) and substrates layer (S.L.) densities has been used in the simulation code.

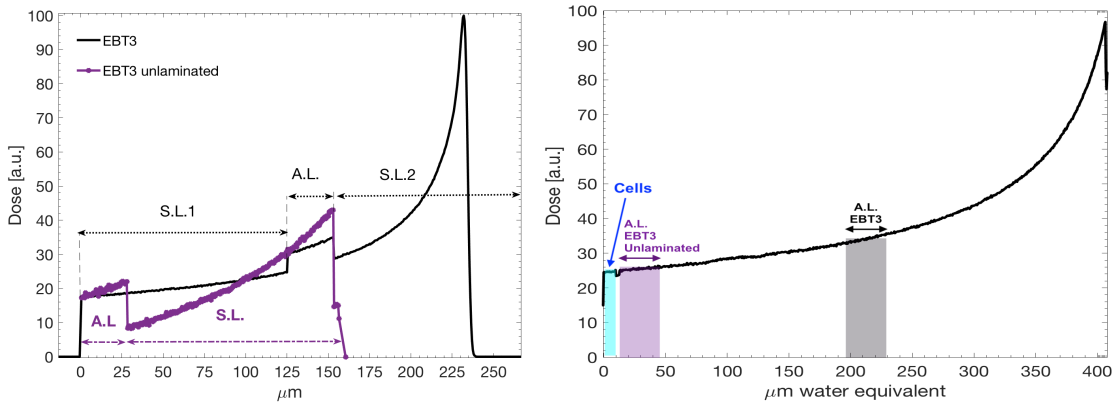

Figure 3. Normalized depth dose profile along the material composing the EBT3 RadioChromic films (black line) and the EBT3 unlaminated (purple line) (left). Normalized depth dose profile in water equivalent thickness [18] showing the position of the cells (light blue box) and of the active layer for the EBT3 (grey box) and for the EBT3 unlaminated (purple box) (right).

As can be seen in figure 3 (right) showing the depth dose profile in water equivalent thickness [18], the dose released from 10 MeV/u into the cells (light blue square) differs by about 30 % from the dose delivered to the EBT3 active layer (grey box). Such difference does not allow to measure with accuracy the dose delivered to the cells. Moreover, the energy and the LET reaching the active layer is much lower than the incident energy 10 MeV/u due to the energy loss in the front RCF substrate (S.L.1). For such reason an alternative type of EBT3-RCF has been used for dose measurement in the present experiment, namely unlaminated EBT3 RadioChromic films composed of just one substrate (S.L) and the active layer (A.L.).The material composition as well as the thickness for both the active layer and the substrate of the unlaminated custom RCF is exactly the same as the EBT3. The depth dose profile in the unlaminated EBT3-RCF material and water equivalent thickness evaluated with the Geant4 simulation is also shown in figure 3. It is clear that, the unlaminated EBT3 provides a much more faithful measurement of the dose released to the cells, with a difference of $\sim$ 2% between the dose released to the cells and the one delivered to the EBT3 active layer.

3.1. Geant4 simulation

The setup shown in figure 1 has been simulated by using the Geant4 (Geometry And Tracking) [17] Montecarlo toolkit to predict the particle distribution at the cell plane (figure 4).

A realistic proton and carbon source has been simulated as input of the simulation by using the energy spectra measured with the TP coupled with the IP and considering an isotropic angular distribution within the aperture of the selection magnet. The IP calibrations reported in [19, 20] and [21, 22] have been used to convert the IP raw images in absolute flux respectively for protons and carbon ions. The beam accelerated from ultrathin foils consisted primarily of protons and C^{6+} ions, which reached comparable energies of up to $\sim$20 MeV/n, depending on target thickness and pulse polarization, consistently with previous observations [7].

A start-to-end simulation, i.e. from the source down to the cell position, has been performed aimed at predicting the energy dispersion of protons and carbon ions as well as their dose distribution at the cell plane. Due to the comparable energies per nucleon that proton and

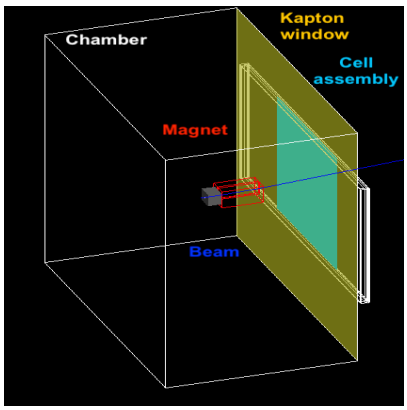

Figure 4. Snapshot of the experimental setup modelized by means of the Geant4 simulation toolkit.

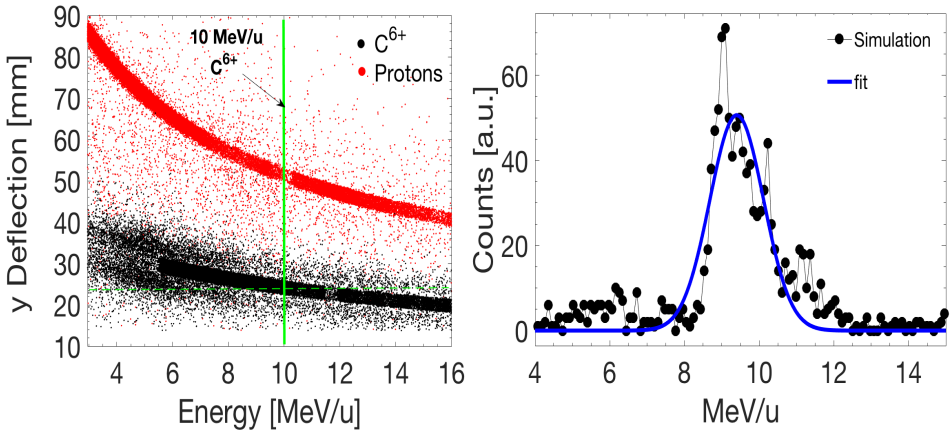

Figure 5. Simulation of the energy dispersion at the cell plane as resulting from the magnetic deflection of the dipole for protons (red points) and C^{6+} ions (black points). The reference vertical position for 10 MeV/u carbon ions on the cells is also shown (dashed green line) (left). Energy distribution within the region of interest (black points) obtained with the Geant4 simulation and gaussian fit (blue line) (right).

carbon ions can obtain in this regime, so it is necessary to ensure that, at the position of 10 MeV/u carbon ions on the cell dish, corresponding to $\sim$ 12 MeV/u carbon ions accelerated from the target, no protons reach the cells. The Montecarlo simulations allow in fact to take into account of the particle energy loss into the traversed materials, i.e. the kapton and mylar windows and the air gaps. Figure 5 (left) shows the energy dispersion in the vertical direction for protons and carbon ions at the cell plane. As can be seen, no protons are expected to overlap with the 10 MeV/u carbon ions (green dotted line in figure), demonstrating the absence of proton contamination in cell irradiation.

Figure 6 (left) shows the image of one unlaminated EBT3 irradiated at the cell position and acquired with the scanner EPSON V750. The images were recorded with a spatial resolution of 50 μm (1200 dpi). The pixel values in each point of the images were converted in optical density and then in dose using the dose calibration performed with the carbon ions accelerated by the Tandem at the Laboratori Nazionali del Sud (INFN-LNS). The carbon energy spatial

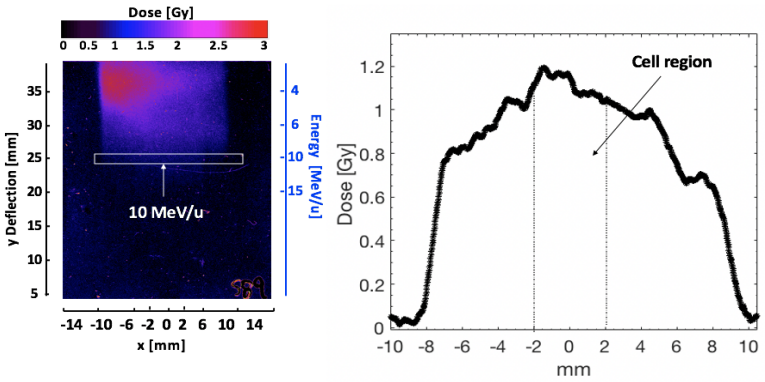

Figure 6. Image of the unlaminated EBT3 irradiated with carbon ions during one shot. The region corresponding to 10 MeV/u carbon ions is also shown (white square) (left). Dose profile along the region highlighted as retrieved by applying the dose calibration. The region where the cells were plated, having a. $\sim$ 4 mm width, is also indicated (right).

dispersion as resulted from the magnetic deflection and calculated by means of the simulations is also reported in the right blue axis of figure 6 (left). The region corresponding to 10 MeV/u carbon ions is also indicated in figure 6 (left) with a white box. The dose profile in x-direction along such region is then shown in figure 6 (right).
Considering a 4 mm width cell region (as indicated in figure 6 (right)), an average dose of 1 Gy with a standard deviation of 0.2 Gy is obtained.
Geant4 simulations were also used to estimate the energy spread of carbon ions over the region of interest, as shown in figure figure 5 (right). By fitting the energy distribution with a gaussian function a FWHM of 1.6 MeV/u is obtained corresponding to a $\Delta E/E$ of about 15% (figure 5 (right)). The energy range (9.5 $\pm$1.6 MeV/u) estimated with the simulation can be then used to evaluate the pulse duration and the dose rate at the cell position, which are unique characteristics of such beams. Considering the $\Delta E/E \sim 15$ % and the target-cell distance of 200 mm as shown in figure 1, one estimates a pulse duration of $\sim$ 400 ps. Finally evaluating the ratio between the average dose delivered per shot, namely 1 Gy, and the pulse duration, i.e. 400 ps, an avarage dose rate of 2.5×10^9 Gy/s is obtained, confirming the peculiarities of such beams.

4. Conclusions

Irradiations of biological samples by means of 10 MeV/u laser-accelerated carbon beams have been performed for the first time during the experiment here reported. The experimental setup employed has been described in details in this contribution together with Geant4 simulations carried out to optimize the beam parameters, such as energy spread and dose distribution, and ensure a good beam quality for cell irradiation. Particular care was placed on the choice of detector for dose measurements in light of the low-energy of carbon ions used for the irradiation. A confident prediction of beam energy distribution and dose profile are important requirements towards an improved control and accuracy of the beam delivery, for high-quality radiobiology studies in an unique parameter space of potential interest to future clinical applications.

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