ISBN: 978-3-95450-231-8 ISSN: 2673-5490 doi: 10.18429/JACoW-IPAC2023-THPM065

PROTON FLASH IRRADIATION SETUP FOR PRECLINICAL STUDIES AT HZB

G. Kourkafas*, J. Bundesmann, A. Denker[1], A. Dittwald, T. Fanselow
Helmholtz-Zentrum Berlin für Materialien und Energie (HZB), Berlin, Germany
J. Heufelder, A. Weber, Charité – Universitätsmedizin Berlin, Germany
P. Mühldorfer, Berliner Hochschule für Technik, Berlin, Germany
[1]also at Berliner Hochschule für Technik, Berlin, Germany

Abstract

The HZB cyclotron continues to provide protons for eye-tumor treatment in collaboration with the Charité – Universitätsmedizin Berlin after 24 years and more than 4400 patients so far. With the perspective of broadening its research capabilities in the field of radiation therapy, intensive effort has been dedicated towards proton FLASH irradiation, which requires ultra-high dose rates or beam intensities.

By combining a fast and reliable switch-off mechanism, accurate dosimetry, and a double-scattering beam nozzle with a static 3D-printed range modulator, HZB is now able to deliver a dose rate above 150 Gy/s within a flat circular irradiation field of 18 mm diameter and a 27 mm spread-out Bragg peak with a distal fall-off of 1 mm in water. The reproducibility of the delivered dose meets the clinical acceptance criteria for a total irradiation time as low as 2.5 ms.

The first experiments with this setup were used on fibroblastic and sarcoma organoids. By adapting the design to a 35 mm lateral field and using optimal accelerator tuning to increase beam transmission, similar or even higher dose rates are expected, satisfying thus the FLASH conditions for eye-tumor treatment with protons.

INTRODUCTION

As a complement to its successful eye-tumor treatment with the Charité – Universitätsmedizin Berlin, the HZB cyclotron facility [1, 2] is exploring ways to incorporate proton FLASH irradiation into its research and clinical program, among other upgrade plans [3, 4]. The term FLASH is used to describe ultra-high dose rates in the field of radiotherapy, which for particles accelerators translates to high beam intensities with correspondingly fast and precise beam delivery systems [5].

Once the HZB cyclotron was proved to qualify for the currently acknowledged FLASH requirements [6], a suitable beam nozzle with a corresponding beam delivery system was designed for the irradiation of mice eyes under both conventional and FLASH conditions. The output beam provided a 5 mm spread-out Bragg peak with a mean dose rate of 70 Gy/s inside a 6 mm field within 200 ms [7].

Following a staged approach towards a clinical application, the next step is to accommodate larger irradiation volumes, while further expanding the achievable limits in terms of delivered intensity and irradiation time. The target parameters were adapted to suit the irradiation of organoids (three-dimensional cell clusters that can resemble the functionality of an organ) in well-type containers beyond 100 Gy/s in a time-scale of few milliseconds. This paper describes the implemented setup and the characterization of its output beam parameters, as planned to be used for preclinical studies.

MACHINE SETUP AND PERFORMANCE

From the two available injectors at HZB, the Tandetron (tandem accelerator) was used to feed the k = 132 isochronous separated-sector cyclotron with protons, providing an average beam current of up to 110 nA in continuous 5 ns-long bunches at 20 MHz with a final kinetic energy of 68 MeV. With an optimal operation of the alternative Van-de-Graaff injector, the average beam current can be raised by four times and the bunch duration minimized to 1 ns at the same repetition rate, however this option was not available at the moment of this study.

By utilizing an electrostatic deflector between the cyclotron and its injector, the beam can be switched on and off much faster than using a mechanical shutter, enabling shorter irradiation times and more accurate dose delivery. The control of this deflector is done using a FPGA board with a 10 kHz sampling rate, programmed in LabVIEW (NI, Austin, USA) to operate in two distinct modes:

1. fixed irradiation time, down to 1 ms
2. fixed applied dose

Once the beam exits the beam tube, the dose is monitored by two commercial transmission ionization chambers (T7861, PTW-Freinurg, Germany) and measured by an Advanced Markus Chamber connected to a UNIDOS webline electrometer (PTW-Freiburg, Germany). For the timescale of few ms, the delivered beam intensity can be significantly increased without damaging the vacuum window at the beam exit or reaching the radiation safety limits. Using a mm-focused beam and a fixed time of 100 ms, the mean dose rate at the plateau of the Bragg peak was measured versus the beam current, as shown in Fig. 1.

In order to the test the system's repeatability for the shortest available irradiation times, the statistical fluctuation of the dose from 30 measurements at 90 nA was measured for different target doses. The results plotted in Fig. 2 indicate that the clinical requirement of < 2% dose uncertainty is achieved above 10 Gy which corresponds to a total delivery

* georgios.kourkafas@helmholtz-berlin.de

ISBN: 978-3-95450-231-8 ISSN: 2673-5490 doi: 10.18429/JACoW-IPAC2023-THPM065

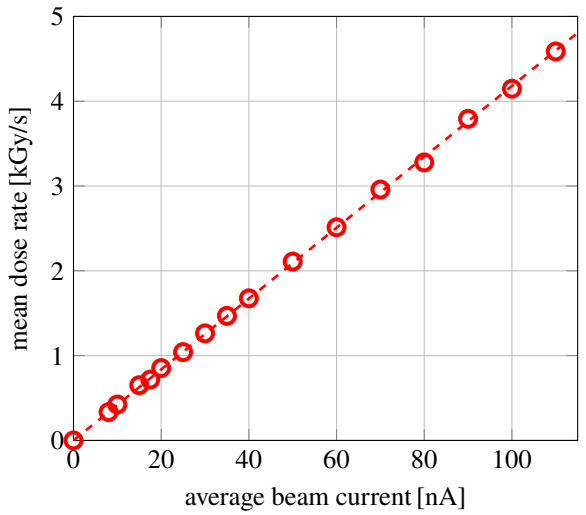

Figure 1: Measured mean dose rate against average beam current for a focused beam at full energy.

time of 2.5 ms. Correspondingly, an irradiation time of 1 ms results in 4% dose fluctuation, while even for 0.2 ms the inaccuracy stays below 14%. The performance can easily be improved by upgrading the sampling rate of the FPGA board.

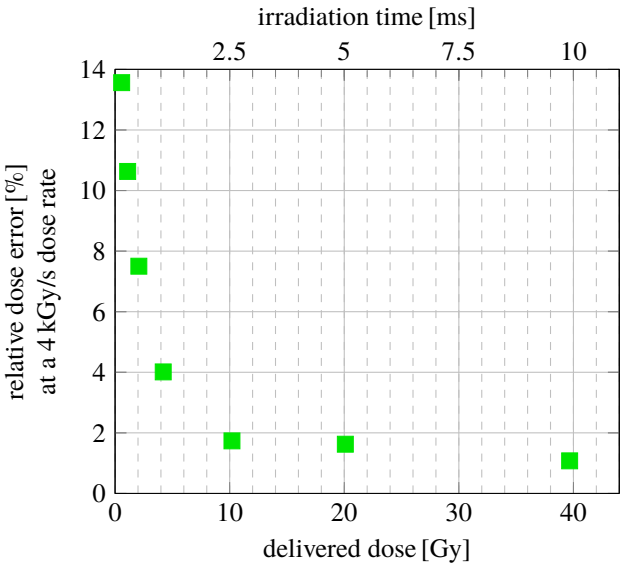

Figure 2: Relative dose error for different target doses and corresponding irradiation times using a 90 nA beam current.

BEAM NOZZLE AND OUTPUT BEAM CHARACTERIZATION

In order to apply the achieved performance into preclinical applications that require larger fields and a full energy modulation, an 80 cm-long nozzle with an efficient scattering and modulating design was installed, shown in Fig. 3.

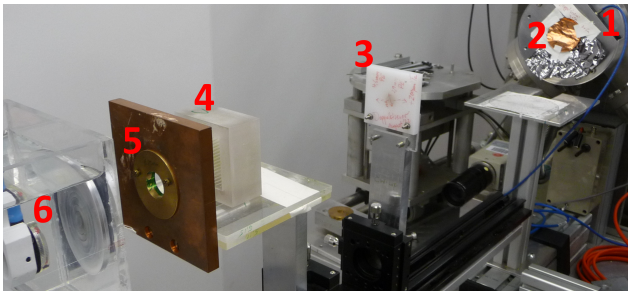

Figure 3: Beam nozzle with a dual-ring double scattering scheme (elements 2 and 3) and a static modulator (4). The beam travels from the vacuum window (1) to the dose chamber (6) through a collimating aperture (5).

Following the principles described in [8], a dual-ring double scattering scheme with copper, tantalum and high-density polyethylene was used to create a homogeneous irradiation profile large enough to cover the cell containers at the target location. A 20 mm-wide collimating aperture was used at the end of the nozzle to confine the scattered beam. The established expertise of HZB in producing 3D-printed static modulators [9] was employed to produce the ridge filter depicted in Fig. 4, which was positioned 12 cm upstream the target location.

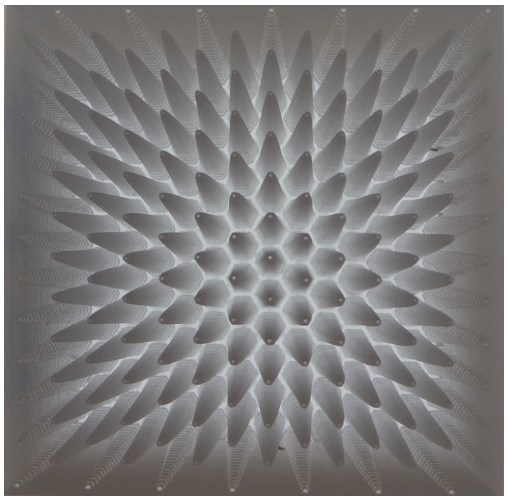

Figure 4: Close-up photo of the 3D printed ridge-filter modulator. The peaks are pointing downstream.

The depth-dose profile was measured using a water phantom as illustrated in Fig. 5, after an entrance window of 2.4 mm water-equivalent thickness. A full energy modulation with a 26.8 mm range, ±1.5% ripple and 1 mm distal fall-off (90%-10%) is observed, satisfying the clinical acceptance requirements.

The transverse beam profile was captured with a CCD camera behind a luminescent screen at different locations along the spread-out Bragg peak as described in [10] and is plotted in Fig. 6. A very homogeneous field of 18 mm is measured at the entrance of the irradiated volume, with a deviation of less than 2 mm until the end of the proton

ISBN: 978-3-95450-231-8 ISSN: 2673-5490 doi: 10.18429/JACoW-IPAC2023-THPM065

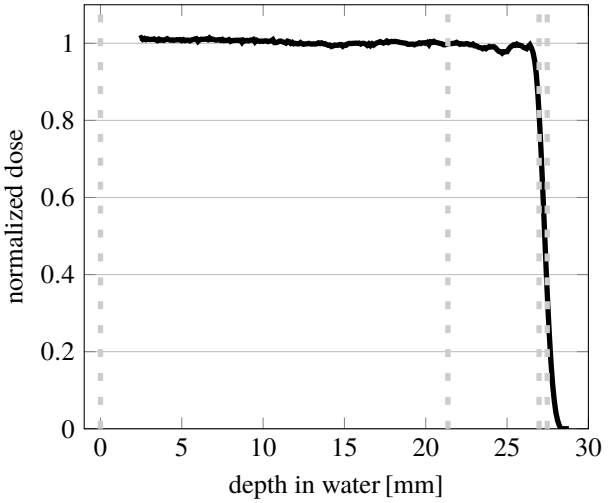

Figure 5: Measured depth-dose profile in water, normalized to the middle of the spread-out Bragg peak. The transverse beam profile was captured at the locations of the dashed vertical lines.

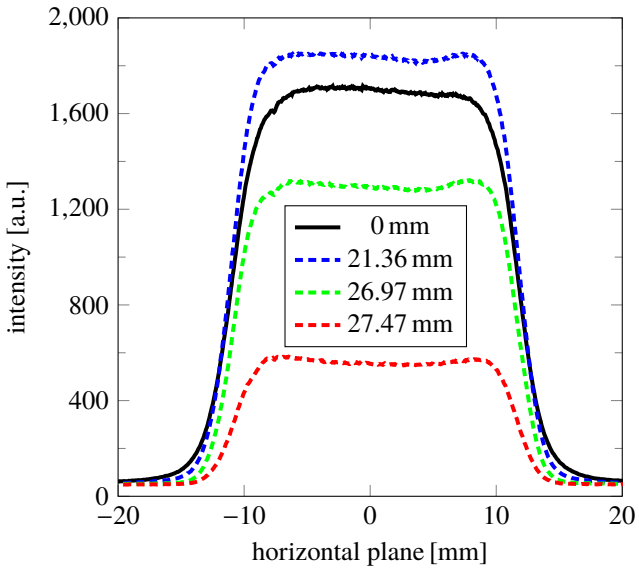

Figure 6: Horizontal beam profile at various locations along the spread-out Bragg peak.

range. The intensity of each profile varies according to the dose curve shown in Fig. 5, which could not capture the first millimeters, where the spread-out Bragg peak has not yet fully risen to its plateau level.

This setup was measured to deliver a mean dose rate of 1.5 Gy/s for an average beam current of 1 nA. By extrapolating this value up to the beam currents exhibited in Fig. 1, it is safe to expect that 150 Gy/s can be reached and surpassed. A further improvement of the scattering scheme with a quadruple-ring design is currently investigated, which aims to increase the nozzle transmission to approximately 2 Gy/s per nA. This upgrade together with the machine optimization shall enable FLASH dose rates within a 35 mm field for eye-tumor therapy.

CONCLUSION

The developed setup facilitates FLASH irradiation of 18 mm-wide cell cultures in well-type containers, with irradiation times down to 2.5 ms and mean dose rates that can be extrapolated up to 150 Gy/s at full modulation, while meeting the clinical requirements. Experiments with fibroblasts, sarcoma and uveal-melanoma organoids are already being performed by the Charité – Universitätsmedizin Berlin. Further upgrades are being planned in order to simultaneously shorten the irradiation time, improve the dose accuracy, increase the transmission efficiency through the nozzle and achieve higher dose rates.

REFERENCES

[1] A. Denker *et al.*, "Status of the HZB Cyclotron", in *Proc. 22nd Int. Conf. on Cyclotrons and their Applications (Cyclotrons'19)*, Cape Town, South Africa, Sep. 2019, pp. 253–255. doi:10.18429/JACoW-CYCLOTRONS2019-TUC02

[2] I. Seibel *et al.*, "Local Recurrence After Primary Proton Beam Therapy in Uveal Melanoma: Risk Factors, Retreatment Approaches, and Outcome", *Am. J. Ophthalmol.*, vol. 160, no. 4, pp. 628–636, 2015. doi:10.1016/j.ajo.2015.06.017

[3] A. Rousseti *et al.*, "Preclinical proton minibeam radiotherapy facility for small animal irradiation", presented at the 14th International Particle Accelerator Conf. (IPAC'23), Venice, Italy, May 2023 paper THPL043, this conference.

[4] A. Denker *et al.*, "Upgrade plans and new target stations for the HZB cyclotron", presented at the 14th International Particle Accelerator Conf. (IPAC'23), Venice, Italy, May 2023 paper THPM129, this conference.

[5] S. Jolly *et al.*, "Technical challenges for FLASH proton therapy", *Physica Med.*, vol. 78, pp. 71–82, 2020. doi:10.1016/j.ejmp.2020.08.005

[6] G. Kourkafas *et al.*, "Towards FLASH Proton Irradiation at HZB", in *Proc. Cyclotrons'19*, Cape Town, South Africa, Sep. 2019, pp. 202–204. doi:10.18429/JACoW-CYCLOTRONS2019-TUP021

[7] G. Kourkafas *et al.*, "FLASH proton irradiation setup with a modulator wheel for a single mouse eye", *Med. Phys.*, vol. 48, no. 4, pp. 1839–1845, 2021. doi:10.1002/mp.14730

[8] Y. Takada, "Dual-Ring Double Scattering Method for Proton Beam Spreading", *Jpn. J. Appl. Phys.*, vol. 33, no. 2, pp. 353–359, 1994. doi:10.1143/JJAP.33.353

[9] G. Kourkafas *et al.*, "A 3D RANGE MODULATOR FOR ULTRA-SHORT PROTON FLASH IRRADIATION", *Physica Med.*, vol. 94, no. 4, pp. S64–S65, 2022. doi:10.1016/S1120-1797(22)01578-2

[10] S. N. Boon *et al.*, "Performance of a fluorescent screen and CCD camera as a two-dimensional dosimetry system for dynamic treatment techniques", *Med. Phys.*, vol. 27, no. 10, pp. 2198–2208, 2000. doi:10.1118/1.1289372