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ADVANCES IN THE OPTIMIZATION OF MEDICAL ACCELERATORS*

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Abstract

Between 2016 and 2020, 15 Fellows have carried out collaborative research within the 4 M€ Optimization of Medical Accelerators (OMA) EU-funded innovative training network. Based at universities, research and clinical facilities, as well as industry partners in several European countries, the Fellows have successfully developed a range of beam and patient imaging techniques, improved biological and physical models in Monte Carlo codes, and also helped improve the design of existing and future clinical facilities. This paper presents three selected OMA research highlights: the use of Medipix3 for dosimetry and real-time beam monitoring, studies into the technical challenges for FLASH proton therapy, recognized by the European Journal of Medical Physics' 2021 Galileo Galilei Award, and research into novel monitors for in-vivo dosimetry that emerged on the back of the OMA network.

INTRODUCTION

The OMA network was built around 15 early stage researchers (ESRs) working on dedicated projects to maximize the benefits of the use of particle beams for cancer treatment [1]. The network consists of an international consortium of 41 partner organizations working in this field. It has provided a cross-sector interdisciplinary environment for beyond state-of-the-art research, researcher training, and new collaborations. The network has pushed technologies and simulation techniques significantly beyond the state-of-the-art and developed solutions that are now applied in clinical practice. OMA has also established a comprehensive and unique postgraduate training concept that can also be applied to other research areas and that was presented to educators at national and international learning and teaching events. The Fellows have benefited from a well-rounded training and successfully completed their projects within the network. This paper illustrates some of the research outcomes in the network.

SELECTED RESEARCH RESULTS

OMA has significantly advanced knowledge in proton/ion beam therapy and related key technologies. Research within the network was carried out by the Fellows across three closely interlinked work packages: Beam Imaging and Diagnostics, Treatment Optimization, and Facility Design and Optimization. A roughly equal number of Fellows has their main research focus on each work package, but there are also many collaborative links between the individual projects and work packages so that an overall optimization of ion beam therapy was achieved. The following sections present selected research highlights obtained across OMA.

Studies with MiniPIX-TimePIX Detectors

Recent advancements in accelerator technology have led to a rapid emergence of particle therapy facilities worldwide, affirming the need for enhanced characterization methods of radiation fields and radiobiological effects. The Clatterbridge Cancer Centre (CCC) operates a 60 MeV proton facility to treat ocular cancer and facilitates studies into proton-induced radiobiological responses [2, 3].

The Medipix3 is a hybrid pixel detector able to count individual protons with millisecond time resolution at clinical flux with near instant readout and count rate linearity. The system has previously demonstrated use in medical and other applications, showing wide versatility and potential for particle therapy.

OMA Fellows Jacinta Yap and Navrit Bal, together with their co-workers, have carried out measurements of the Medipix3 detector in the 60 MeV ocular proton therapy beamline at the CCC [4]. The beam current and lateral beam profiles were evaluated at multiple positions in the treatment line and compared with EBT3 Gafchromic film. The recorded count rate linearity and temporal analysis of the beam structure was measured with Medipix3 across the full range of available beam intensities, up to 3.12×10^{10} protons/s. The measurements allowed them to explore the capacity of Medipix3 to provide non-reference measurements and its applicability as a tool for dosimetry and beam monitoring for CPT. This is the first time the performance of the Medipix3 detector technology has been tested within a clinical, high proton flux environment.

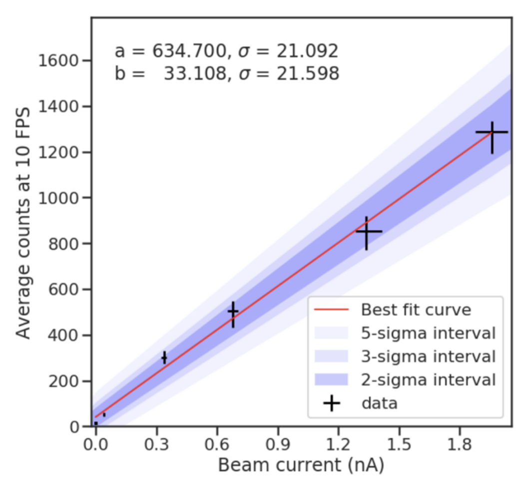

Figure 1: Count rate linearity over all active pixels recorded at 10 frames per second for 6 beam currents [4].

Figure 1 shows that the detector has a linear response across the entire tested range of beam currents from 0.012 to 1.97 nA. There is relatively large uncertainty of the

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average count rate due to the electrometer beam current measurements, dominated by the infrequent, manual readings. This is included in the residuals of the data and the variation in beam current which are both approximately in the order of 10%. It should be pointed out that measurement of the ultra-low beam currents would not be possible with other commonly used instruments with the precision of single protons.

To facilitate the progression of Medipix3 toward clinical implementation, further testing is recommended to fully characterize the cluster properties, signal uniformity, sensitivity across the detector, activation levels, dose rate thresholds, energy dependence, stability, spatial resolution and dosimetric calibration factors. These should be performed at different facilities, across the full treatment energy range and with different particle types.

Challenges for FLASH Proton Therapy

There is growing interest in the radiotherapy community in the application of FLASH radiotherapy, wherein the dose is delivered to the entire treatment volume in less than a second. Early pre-clinical evidence suggests that these extremely high dose rates provide significant sparing of healthy tissue compared to conventional radiotherapy without reducing the damage to cancerous cells. This interest has been reflected in the proton therapy community, with early tests indicating that the FLASH effect is also present with high dose rate proton irradiation. In order to deliver clinically relevant doses at FLASH dose rates significant technical hurdles must be overcome in the accelerator technology before FLASH proton therapy can be realized. Researchers from the OMA partners PSI, University of Manchester and Liverpool, under the leadership of S. Jolly from UCL have investigated possible ways to overcome current technical challenges and pave the way for FLASH proton therapy. Their publication in *Physica Medica* [5] won the 2021 Galileo Galilei award for the best paper in the *European Journal of Medical Physics* in the year 2020 which was also recognized as one of the most cited papers in that journal for the period 2018 – 2022.

Amongst the important challenges discussed in the full article is proton beam delivery in particular spot scanning. While the average beam current requirement for double-scattered systems still holds, the actual delivered current will be significantly higher since one must account for the dead time between spots, for switching energy layers, and for the variation of beam current required in each layer/spot to create a uniform dose distribution. In addition, rather than having a "static" magnetic beamline that does not have to adjust whilst the protons are delivered to the patient, with spot-scanning the beamline is "active": steering magnets within the nozzle must direct the pencil beam to the desired spot within the treatment volume and every magnet within the entire beamline must also adjust to match the beam energy for a given energy layer.

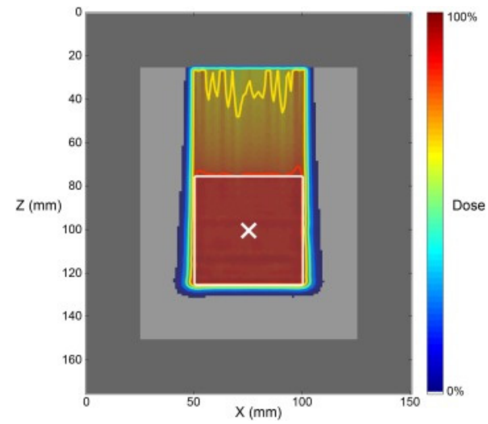

Figure 2: Longitudinal dose distribution (in z) for the central slice of the spot-reduced "van de Water" treatment plan; beam enters from above. The colours indicate the fraction of the maximum dose within the plan. Note the dose uniformity within the treatment volume despite the reduction in number of spots by 2 orders of magnitude, from [5].

For a spot-scanning system the total number of spots and energy layers is critical in establishing a baseline for the overall speed of the system. Due to the open questions about how FLASH treatment might be delivered, delivery of a single 4 Gy fraction applied using a single field is assumed; multiple-field treatments are expected to reflect the issues seen in single-field delivery.

In order to provide greater spot and layer switching time, an optimized treatment plan for a 1 liter volume was recalculated using the method described in [6]. This spot-reduced "van de Water" plan reduced the number of energy layers to 16, with a maximum number of spots in any layer of 310, partly through variations in the beam spot size from 2–20 mm. A longitudinal slice through the resulting dose distribution is shown in Fig. 2. In combination with a large energy acceptance, a very fast change of energy could be faster than the lateral shift of the pencil beam. This can be achieved by using by a rapidly-adjusting degrader or by using a ridge- or pin-filter.

Significant development will be required to enable FLASH delivery, particularly if the goal is to adapt existing spot-scanning systems for use at FLASH dose rates to clinically relevant volumes. This includes developments in magnet scanning speed and dosimetry before such systems can be realized. The hybrid approaches already being pursued — particularly the use of scanned beams with patient-specific range modulators — are likely to pave the way to clinical proton FLASH delivery. The challenges for the different accelerator types in operation were clearly identified and compared in the full study.

Gas Jet Monitor for In-vivo Dosimetry

In hadron beam therapy, knowledge of the detailed beam properties is essential to ensure effective dose delivery to the patient. Clinical settings currently implement interceptive ionization chambers which require daily calibration and suffer from slow response times. With new and emerging treatment techniques using ultra-high dose rates, there

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is a demand for the development of novel beam monitors, which are fast, non-invasive and calibration-free. Current methods to carry out this characterization require multiple systems each imparting a slight disturbance to the particle beam as it passes by. This disturbance can alter the intended transverse dose profile of the beam, ultimately creating slight deviations from a patient's treatment plan. QA methods are mostly disruptive measurements and do not allow treatment to take place at all whilst they are being conducted.

The STFC-funded project JetDose will develop a new in-vivo dosimetry system based on the re-application of technologies pioneered by the QUASAR Group at the Cockcroft Institute/University of Liverpool. The underpinning technology was originally developed for use with low energy antiproton beams and most recently adapted for gas jet profiling for the high luminosity upgrade of the Large Hadron Collider at CERN [7, 8]. In this system, a supersonic gas jet is fired across the high intensity proton beam at the LHC, see Fig. 3. The gas molecules have little-to-no effect on the proton beam, however the proton beam excites the gas molecules; this excitation can be imaged, which in turn provides a complete non-invasive two-dimensional profile image of the proton beam.

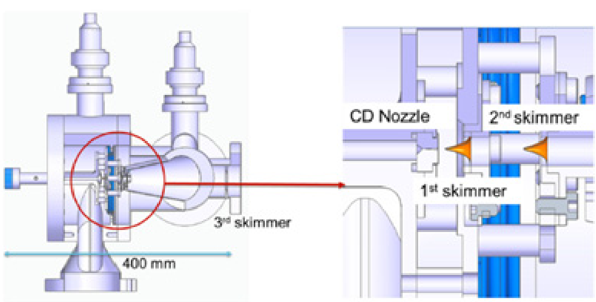

Figure 3: Conceptual compact design of the optimized dosimetry monitor.

JetDose will redirect this technology at the medical accelerator sector, by optimizing it for the different challenges found in a treatment facility. The non-invasive means of producing a profile image will allow the monitor to be run online alongside treatment operation. As the intensity in the images directly depends upon the beam intensity, and therefore the dose, an image collected with this system provides an in-vivo dose map of the beam being delivered to the patient. The focus of the project is on the design, development, and testing of an optimized medical version of the system with OMA partners CCC, Fondazione CNAO, beam instrumentation company D-Beam and leading OEM manufacturer IBA. A prototype monitor has been setup at the Cockcroft Institute's DITAlab and measurements with beam are planned later this year.

RESEARCHER TRAINING

The OMA Fellows received a comprehensive training within a unique international network. They have gained a broad insight into both, academic and industrial aspects associated with medical accelerators, with opportunities to undertake specific training and secondments within the network.

The fundamental core of the training consisted of dedicated cutting-edge research projects for each Fellow at their host institution. To complement this, the network provided opportunities for cross-sector secondments for all Fellows. An intra-network secondment scheme enabled them to spend time working at other institutions within the network, receiving hands-on training in specific techniques and a broader experience in different sectors. Another important aspect of the training is a series of network-wide events comprising several schools, topical workshops and an international conference, which were all open to the wider scientific community.

This interdisciplinary training concept was directly based on the successful programs developed within the DITANET, oPAC and LA^{3}NET projects [9-11]. OMA has organized two Researcher Skills Schools, three international Schools on Medical Accelerators (4-9 June 2017 at CNAO, Italy) [12], Monte Carlo Simulations (6-10 November 2017 at LMU Munich, Germany) [13], and on Particle Therapy (1-5 April 2019 at TU Vienna with Medaustron as local host [14]. The network has also organized three Topical Workshops on Facility Design and Optimization at PSI in Switzerland [15], Diagnostics for Beam and Patient Monitoring [16], and Accelerator Design and Diagnostics [17]. Presentations from all training events are available via the respective event indico page. On 28 June 2019 an outreach Symposium on Accelerators for Science and Society was held at the Arena and Convention Centre in Liverpool with talks live-streamed on the day and now available on-demand via the event website [18]. The network also organized an international Conference on Medical Accelerators and Particle Therapy in Seville, Spain in September 2019. This event summarized and promoted the scientific results of the project and discussed remaining challenges and established a basis for future collaboration [19].

The research results of the OMA project have been widely disseminated via scientific journals, international events, and the project website www.oma-project.eu. This was complemented by targeted social media campaigns about cancer therapy and a quarterly newsletter, the *OMA Express*, which can be accessed via the project website [1].

SUMMARY AND OUTLOOK

The OMA project has delivered excellent results with significant impact in the field of medical and particle and radiation physics. The network has achieved all of its ambitious targets with only minor deviations over the four year project duration. Research has advanced knowledge in proton and ion beam therapy and several examples were given in this paper. The results are expected to contribute important knowledge to the development of the next generation of medical accelerators. A comprehensive training program and interdisciplinary outreach and communication which has reached millions around the world were additional successes.

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