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Book of Abstracts

Contents

Radiobiology / 1

Continuous Microdosimetric Photon Isoeffective Dose Model: experimental measurements

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This study presents the outcomes of combined radiobiological-microdosimetric experiments conducted in the same selected positions along the profile of a Spread-Out Bragg Peak (SOBP). The aim was to obtain the necessary parameters for a novel microdosimetric model for computing photon isoeffective doses in proton therapy [1-5]. This model, named Continuous Microdosimetric Photon Isoeffective Dose Model, depends on the first 3 moments of the lineal energy of microdosimetric spectra. In addition, these quantities are closely linked to Modified Linear Quadratic survival parameters that will be obtained from radiobiological experiments.

In this context, microdosimetric spectra measurements were conducted using two different Mini-TEPC microdosimeters in collaboration with Valeria Conte et al. (INFN). The sensitive volume of each microdosimeter was positioned at five predetermined measuring positions within solid water blocks, employing SOBP produced by a 148 MeV proton beam in the experimental room of the Trento Proton Therapy Centre.

Cell survival curves were generated at the same five designated positions, employing the same experimental setup used in microdosimetric experiments. These curves were constructed using doses of 0.5, 1.5, 3.5, 6, and 8 Gy, considering two different cell lines, JHU-11 and H460.

Radiobiological experiments involved the irradiation of two cell culture flasks at the same time positioned in the same way as the sensitive volume of the microdosimeter, so that they were exposed to a similar radiation field.

The model depends also on radiobiological parameters for a reference photon radiation. Survival curve for both cell lines were obtained using photons from the Xstrahl RS225 X-ray research irradiator available at TIFPA, considering the following doses: 0.5, 1.5, 3.5, 6, and 8 Gy.

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2

The beam test journey of the HEPD-02 detector at Trento Proton therapy center

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The HEPD-02, realized by the Limadou collaboration for the CSES-02 satellite, whose launch is planned for the end of 2024, will be the first detector operating in space to host a pixel-based tracker detector, as well as the largest LYSO bars realized for space applications.
The detector aims to observe electron fluxes in the energy range between 3 and 100 MeV and protons fluxes between 30 and 200 MeV, with an energy resolution better than 10% for 5 MeV electrons and an angular resolution better than 10% for 3 MeV electrons. The particle identification efficiency must be better than 90%.
The path to the design, prototyping, realization, and characterization of the detector heavily relied on the tests conducted at the Trento Proton Therapy Center. The tests began by characterizing the response of the designated pixel detector to low-energy nuclei, followed by using the beam to verify and characterize the tracking and calorimeter module responses. After detector integration, a final extensive campaign of tests was conducted to characterize and calibrate the detector and its read-out electronics. The contribution describes the tests performed, provides an overview of the main results, and outlines the plans for the next activities of the collaboration.

3

Microdosimetry at the proton therapy facility of Trento

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In the framework of the MICROBE_IT project funded by the 5th commission of INFN in the period 2021-2023, several microdosimetric measurements have been performed at the research beam lines of the proton therapy centre of Trento.
The detector employed is a new miniaturized Tissue Equivalent Proportional Counter characterized by a cylindrical sensitive volume of 1.0 mm in diameter and height designed to cope with high intensity beams such as those employed in clinical settings. With an overall external diameter of 1.53 cm and a water-equivalent thickness of approximately 0.79 cm, the detector is compact yet robust. It operates in a sealed mode, without the need for continuous gas flow.
The first measurement campaign has been carried out at the biological research line using the 148 MeV energy-modulated proton beam with the aim of performing a microdosimetric characterization of the radiation quality. The irradiation field had a diameter of about 6 cm, a modulation width of 2.5 cm and a range of about 13.5 cm. As a reference, at four depths along the depth-dose profile the

response function of our detectors has been compared to the one of a commercial spherical microdosimeter, the LET-1/2”Spherical TEPC produced by Far West Technology. In another measurement campaign, we characterized the radiation quality of different monoenergetic beams of the physics research beam line and the results have been compared with Monte Carlo simulations with the microdosimetric application of the Monte Carlo code TOPAS. Finally, pairwise measurements were performed in which we used our detector and an ionization chamber to simultaneously measure the microdosimetric spectrum and the dose at the same position. A new calibration technique based on the dose has been investigated.
The results from these measurement campaigns have been analysed and discussed in terms of shape of the microdosimetric spectra, and the average values of the distributions were derived and compared to track and dose-averaged LET obtained from Monte Carlo simulations. The microdosimetric spectra have been also used to perform a microdosimetric assessment of Relative Biological Effectiveness (RBEμ). The dose distribution of lineal energy, d(y), has been weighted with Loncol’s biological weighting function that was obtained by the convolution of the results of pairwise radiobiological and microdosimetric measurements.
The microdosimetric RBE has been used to calculate the RBE-weighted dose at different dose levels for the 148 MeV SOBP. From this analysis, it will be possible to observe the increase of the RBE-weighted dose at the end of the proton range especially when compared to the one weighted with a constant RBE equal to 1.1.

4

Beam and treatment monitoring in FLASH and CONV regimes for PT applications

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With this contribution we want to report about the interest we have in the Trento facility related to research activities we are carrying on in the context of several INFN, CREF and Sapienza projects.

The first activity that would profit from the collaboration with the Trento facility and the availability of a research proton beam delivered both at FLASH and Conventional rates is related to the development of a beam monitoring system exploiting the fluorescence of air induced by the beam at FLASH intensities. While the detection operating principle has been already validated using electron beams, the applications to PT irradiations is still stopped by the unavailability of proton beams at FLASH intensities. Whenever possible we would like to come to Trento to test the detector response using protons delivered in both regimes to ensure that the technique has a good potential also for the case of proton therapy treatment monitoring.

In the same context, we would like to exploit the Trento facility for our studies related to the monitoring of PT treatments using the prompt photon detection, the secondary charged and neutral particles produced (especially in the case of ^{12}C ions treatments) using a novel detection multimodal technique (the MULTIPASS approach for the PT monitoring) based on scintillating fibres properly arranged and readout in a compact way. For the study of the detector performance, the use of proton beams is of paramount importance to characterise the detector response to protons and study the prompt photons in proton therapy.

Finally the Trento facility would be the ideal place where to test the novel scintillating materials that are under development in the SBAI Department of Sapienza University of Rome: such materials have shown promising performance in terms of light yield and time resolution that exceed the current best products that are available on the market. While the evaluations have been done, so far, using mainly cosmic radiation, we are interested in benchmarking the novel materials against proton beams of therapeutic energy.

5

Study of SEU effects in readout circuits of silicon micro-strips detectors developed in 110 nm UMC technology.

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At INFN-Torino, ASICs for readout of several detectors were designed and are under development using the 110 nm CMOS UMC. This technology has been chosen for its lower cost even if there was not a systematic characterization for what concerns the radiation tolerance. Total Ionizing Dose and Single Event Upset (SEU) effects measurements are important studies to characterize ASICs and then also this new technology. Proton beams with different current intensities can be used to investigate the SEU effects as a function of particle flux and to study the dependence of the upsets rate to the clock frequency applied to the circuits. Ion beams of different energies allow the measurement of the cross section for SEU. However, the two techniques are correlated (H. Hutinen and F. Faccio, NIMA, 450, 2000). Among others, the development of full-size prototypes for the custom readout circuit of silicon double-sided microstrips of PANDA Micro Vertex Detector is a good tool to know the behavior of this technology under radiation. Some years ago, the development of this readout started with a full-size prototype named PAStA. It is a triggerless circuit and implements the Time over Threshold (ToT) technique to determine the charge and time information, it features 64 channels and presents a global controller that is common to all channels, it collects the data from the channels and distributes the configurations to the registers. The clock frequency was limited to 120 MHz. Two techniques (TMR-Triple Modular Redundancy and HE-Hamming Encoding) are applied in the configuration registers, and they were tested with ion beams at the SIRAD facility (INFN-LNL) and with proton beams in the experimental room of INFN-TIFPA, in Trento. Results from these measurements shown the robustness of these two techniques against SEU effects and collect information on the 110 CMOS nm technology under radiation (D. Calvo et al. https://doi.org/10.22323/1.370.0126). Recently a new full-size prototype named ToASt_v1 has been designed and produced. ToASt has 64 channels, grouped in 8 regions with local buffering, then the corresponding FIFOs outputs are stored in the Global Readout FIFO. Each channel provides the event timestamp and implements the ToT. The master clock frequency is 160 MHz, the circuit can work at different clock frequency (up to 200 MHz) anyway. A configuration serial link running at 80 Mb/s provides access to the channel and global configuration registers. In this new ASIC configuration registers the TMR is implemented. Evaluation of the cross section for SEU has been performed with ion beams detecting only upsets from logic 1 to logic-0. The motivation is connected to a triplication error in the Verilog code that was corrected in the ToASt_v2 submitted to the foundry the past February. The characterization with proton beams become more interesting to provide information for different clock frequencies also in anticipation of use of ToASt in other experiments.

6

The Proton Radiography experiment

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Abstract

In recent years we have been witnessing a growing scientific interest in proton Radiography (p-Rad). The p-Rad systems, currently used in-vivo for proton range verification, operate by integrating the particle signal thus having limited spatial resolution together with a high dose.
The main goal of this experiment is to develop, starting from the 'proton Computed Tomography' (pCT) system already build by INFN-Florence, a 'single-event'p-Rad apparatus capable of acquiring radiographies in less than 1s with a dose up to a thousand times lower (down to about 20 microGy) and a significantly better spatial resolution compared to the 'integrating'systems. To reach this target the calorimeter of the present pCT system will be upgraded replacing the YAG:Ce detectors with faster plastic scintillators.
Together with the proton Radiography apparatus, this collaboration aims to increase the accuracy of the proton therapy treatments working on two other lines which make extensive use of the present pCT apparatus.
The first one is dedicated to the acquisition of tomographies of medical prostheses to measure their 3-dimensional distributions of the proton Stopping Power (relative to water) (SPR). This information will help to overcome some of the issues in the treatment plan definition when non-biological materials are present in the irradiation area (xCT measurement saturation in case of metals and unknown SPR).
Moreover, using the pCT apparatus to produce 3D SPR images of a biological phantom, the x-ray CT (xCT) calibration in proton treatment planning could be verified using the pCT map as reference. This study aims to conduct a multi-centre survey with the participation of four European proton therapy/research centres.

7

Activation of the p53 pathway in combination with photon or proton irradiation for the treatment of brain tumours

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p53 is a critical tumour suppressor protein and its encoding gene, TP53, is the most frequently mutated gene in human cancer. Activating the p53 pathway is regarded as a plausible strategy to increase radiosensitivity of cancer cells and reduce carcinogenesis. One of the strategies is to inhibit

the interaction of p53 with its negative regulator MDM2, which represents a promising clinical strategy to treat p53 wild-type tumours. Blocking the MDM2/X–p53 protein–protein interaction has been widely recognized as an attractive therapeutic strategy for the treatment of various cancers. p53 is a multifunctional transcription factor that can be activated by cellular stresses, such as hypoxia and DNA damage. Upon activation, p53 acts as a tumour suppressor and responds to cellular damage by mediating cellular responses such as cell proliferation, cell cycle arrest, DNA repair, metabolism, angiogenesis and apoptosis.
The influence of radiation on the p53 pathway, and in particular the differences between photon and proton irradiation, are not yet fully understood. The aim of this study is to investigate the impact of the MDM2 inhibitor drug, AMG 232, in combination with photon or proton irradiation in brain cancer cell lines. Both its anti-cancer and radiosensitizing effect will be investigated by assessing its functionality on a p53 wild type (wt) and p53 mutated (mut) cell line with the aid of various assays. Grade 4 brain tumour cell lines Glioblastoma Multiform (GB) and Medulloblastoma (MB) were selected for this study.

8

Proton-induced Radiation Damage Effects on Silicon Photomultipliers for HEP and space experiments

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Silicon Photomultipliers (SiPMs) are single-photon sensitive detectors that continue to attract increasing interest in several industrial and scientific applications that require fast detection speed, high sensitivity, compactness, insensitivity to magnetic fields and low bias voltages. SiPMs are also replacing photomultiplier tubes (PMTs), hybrid photodiodes (HPDs), or other in high-energy physics (HEP) experiments, and for the readout of scintillators in gamma-ray detectors for space. In such applications they receive a significant dose of particles (e.g. protons and neutrons) and X and gamma rays.
While the effects of radiation in silicon detectors are well-studied [6], the literature is not as much concerning Avalanche Photodiodes (APDs) and photon-counting detector, working in Geiger-mode (like SPADs and SiPMs). Indeed, there has been recently an increasing interest in assessing such effects on both SPAD-arrays and SiPMs for HEP and space-experiments.
During the last years, at FBK (Trento, Italy) we have been developing many different technologies for SiPMs and SPADs, optimized for different applications. Such technologies are based on different silicon starting-materials (with different doping species), made with different internal structures and cell pitch (i.e. SPAD pitch).
Given the big interest in SiPM for harsh radiation environment application, we irradiated several SiPM chips, each one containing few 1x1mm2 SiPMs, with protons at the Trento Proton Therapy Centre (TPTC), in 3 different irradiation campaigns, in 2020, 2021 and 2023. During these sessions the SiPMs were irradiated as a bare chips, on a custom support, or irradiated mounted on custom PCBs, and connected to measurements systems placed inside the experimental room. We used the "dual-ring"setup, to have uniform fluence on a large area area, thus to irradiate all the SiPM chips with the same dose and be able to compare the effects of irradiation on several technologies. This is typically working with protons at 148 MeV, but the energy in our case has been lowered with 10 foils of RW3 wafer equivalent material down to 74 MeV. We verified the beam profile to be uniform on a spot of 8 cm in diameter. We placed the PCB containing the SiPMs in a 3D printed box, with a motorized shutter, which was open during proton irradiation (to avoid plastic in the proton path) and closed during online measurements, to have the measurement in dark condition. In the box we also placed a 4-LED illuminator board (470 nm). After each irradiation step we measured the current-voltage (IV) curves of all SiPMs (in dark and with illumination). We compared the radiation damage effects on the detectors after each irradiation step to identify the main behaviors and the most radiation tolerant technological splits and layouts

9

Towards real-time dose control during cancer radiation therapies based on full-organic wearable dosimeter

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Mechanical flexibility, portability, low cost of fabrication, scalability onto large areas and human tissue equivalence are crucial properties which make organic and hybrid semiconductors excellent candidates for the development of wearable proton dosimeters. Among others, their employment in the medical field (i.e. during proton therapy treatments) to monitor in real-time and in-situ the dose delivered to the patients is extremely interesting.
In the last years the scientific community has put big efforts to look for alternative technologies, with the aim to overcome the main limitations presented by conventional materials and to achieve novel important properties requested by novel applications. We recently reported the results achieved with an innovative fully-organic indirect detector, where a flexible phototransistor (OPT) based on dinaphtho[2,3-b:2′,3′-f]thieno[3,2-b]thiophene (DNTT) is coupled with a plastic scintillator based on polysiloxane (i.e. homopolymer polymethylphenylsiloxane and polyvinylphenyl-co-phenylmethyl). This preliminary test has been performed at LABEC Ion Beam Center (INFN-Firenze, Italy) under 5 MeV proton beam to mimic the end-of-range conditions typically present at the border of the target during the prostate cancer treatment. To describe the detecting signal, we developed a kinetic model able to precisely reproduce the dynamic response of the device under irradiation and to provide further insight into the physical processes controlling it.
Here, the assessment of this technology as flexible personal dosimeter will be shown. With this aim, the detector has been tested in actual clinical conditions employing an anthropomorphic phantom mimicking the human pelvis, and a therapeutic proton beam provided by the TIFPA proton therapy center (Trento Institute for Fundamental Physics and Applications, TN, Italy) typically employed for prostate cancer treatment (energy in the range [70-200] MeV) (Figure a). The detector has been placed in two different positions in accordance with the Monte Carlo simulation shown in Figure b: (i) centered on the target of the beam (i.e. in the prostate position) and decentered from it, in the region surrounding the tumor (i.e. the rectum which is one of the organs at risk that would benefit from a real-time monitoring of the impinging radiation). The gafchromics reported in Figure b showed the positions of the detector during the tests. The dynamic curve shows that this device is able to monitor in-situ and in real-time the presence/absence of radiation for the accurate recording and mapping of the dose delivered during a treatment plan.
Finally, the detector has been characterized as dosimeter when placed centered in the target position under 200 MeV proton beams and, as reported in Figure c,d, it presents dose linearity and provides a stable response even after hard and long-lasting proton irradiation (up to 2 · 10^10‘ protons, 30 min of operation).

10

Evaluating the Reliability of AI Accelerators with Proton Experiments

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Applications based on Artificial Intelligence (AI) are being employed in several fields, including medical diagnosis, drug discovery, robotics, and autonomous vehicles. Enabling robots and vehicles to perform tasks autonomously can be useful in several scenarios, particularly for space exploration and satellites 1. This success can be attributed in great part to advances in AI models, such as Convolutional Neural Networks (CNNs) and, more recently, Transformer models [2,3].

Due to their size and complexity, modern AI models require parallel accelerators, such as Graphics Processing Units (GPUs) or Tensor Processing Units (TPUs). The architectures of these devices are optimized to perform highly parallel computations efficiently by employing a large number of computing cores. While this kind of architecture can accelerate parallel applications, a fault in a shared or critical resource may affect multiple output elements. Additionally, the large number of computational resources in accelerators further increases the likelihood of SEUs. Unfortunately, radiation-hardened devices are extremely expensive, offer poor performance, and have low power-efficiency, which make them unsuitable to run large AI models. Therefore, in order to safely deploy Commercial-Off-The-Shelf (COTS) devices in space, it is mandatory to ensure both reliability and availability.

Our past research has evaluated the reliability of several AI accelerators under different types of radiation [4,5]. This includes measuring the response of devices to radiation-induced Single Event Latchups (SELs), the effects of Total Ionizing Dose (TID), and creating realistic fault models based on Single Event Upsets (SEUs) observed during experiments with radiation. Further, our previous work has analyzed how faults propagate through AI models, providing insights into the effects of radiation on AI applications [5]. Despite continuous efforts into this field of research, there are several aspects of radiation-induced effects that must be more thoroughly evaluated.

The Trento Proton Therapy Center facility could provide interesting experimental data, advancing the knowledge of the reliability of AI accelerators against protons. Performing experiments at the facility would allow us to evaluate state-of-the-art AI models with new and efficient AI accelerators in realistic settings. For instance, as shown in Figure 1, in previous beam experiments we investigated how Silent Data Corruption (SDC) propagates through the layers of AI models, such as the Data-efficient image Transformers (DeiT). These results showed that radiation-induced SDCs start as errors with relatively high magnitude (red bars), which are then spread to subsequent layers. As the error spreads, however, the error magnitude quickly reduces (red bars), while the ratio of affected elements (blue bar) quickly increases. In other words, AI models quickly dilute the error into the elements of a layer, taking few layers to propagate the error to most elements. With further experiments, we could better identify the root causes of radiation-induced misclassifications in AI models.

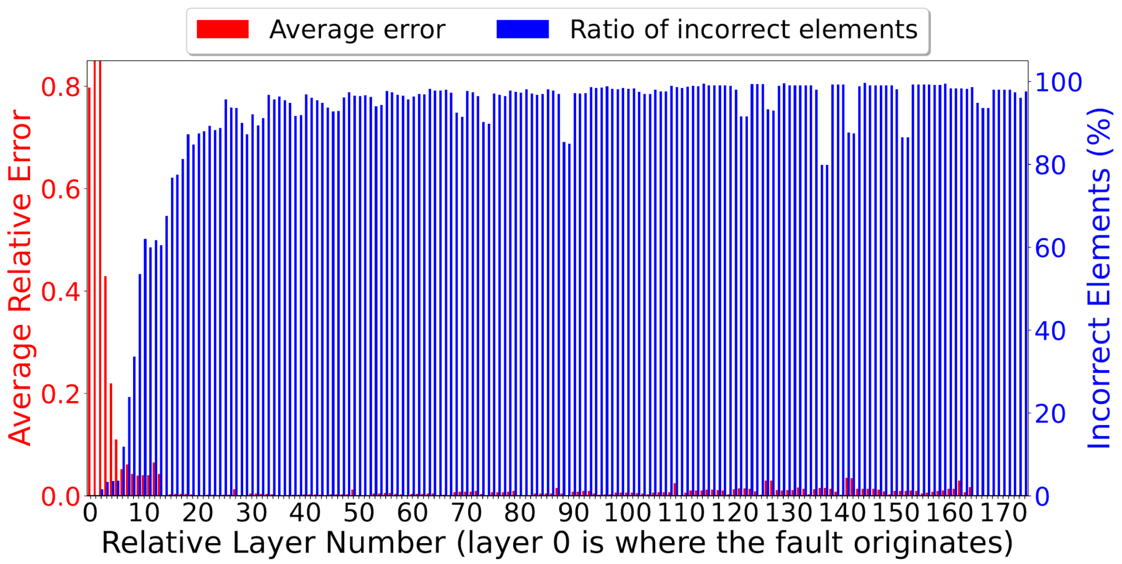

Figure 1: Propagation of SDCs throughout the layers of Data-efficient image Transformers (DeiT).

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11

p21: a new player in colon cancer cell radioresistance.

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Radiation therapy is the most effective cytotoxic therapy to treat localized solid cancers. With the introduction of charged particle radiotherapy (such as proton therapy), the area of irradiated healthy tissue surrounding the tumor was further decreased. Unfortunately, radiotherapy resistance remains a major obstacle in tumor eradication, thus making it crucial to disentangle the complex molecular mechanisms underlying tumor resistance.
The cyclin-dependent kinase inhibitor p21, encoded by the CDKN1A gene, is a tumor suppressor critical for reducing cellular proliferation in response to different stress signals, including DNA damage. Interestingly, it has been demonstrated also an oncogenic role of this protein, due to its anti-apoptotic and pro-survival functions.

With the aim of elucidating the chain of events that takes place in the cell upon irradiation and better evaluate the role of the p21 pathway in response to both X-rays and proton therapy treatments, the molecular mechanisms activated upon X-rays and proton beam irradiation were studied.
As a model, we used the HCT116 colon cancer cell line and its derivative HCT116 p21KO generated using the CRISPR-Cas9 gene editing technique.
Results from our laboratory performed on these two isogenic colon cancer-derived cell lines suggest a role for p21 in radioresistance. In fact, HCT116 p21KO cells were more sensitive to both X-rays and proton beam irradiation in comparison with their parental counterpart. Moreover, to better mimic the shrinkage effect of radiation therapy on solid cancers, 3D spheroids were also used. HCT116 parental, and p21KO cells spontaneously formed spheroids in ultra-low attachment plates. Notably, while parental spheroids showed a reduction in diameter 10 days after X-rays and proton irradiation but still maintained a proper 3D organization, the p21KO spheroids completely disaggregated. Furthermore, the viability of the p21KO spheroids drastically dropped in response to X-rays and proton irradiation, and the analysis of PARP cleavage and activation of Caspase 3 highlighted an increase in apoptosis, particularly in p21 null cells.
Taken collectively, these data suggest that the absence of p53-dependent responses through p21 enhances the sensitivity to irradiation. This study revealed a dichotomy in p21 role: in addition to its canonical tumor-suppressive role, it seems to hold a radioprotective function in these cancer cells that, when depleted for p21, are considerably more prone to apoptosis. These findings could set the stage for future studies based on therapies targeting p21 in combination with charged-particles radiotherapy.

12

Validation of Trento's Proton Centre for FLASH Radiotherapy: A Comparative Analysis, Insight from Zebrafish

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Radiotherapy is one of the main treatment options for cancer patients. The delivery of radiation sources and the reduction in damage to the surrounding healthy tissues have made significant progress in recent years. Particularly, the emergence of Ultra High Dose Rate (UHDR, also known as FLASH) radiotherapy is encouraging because it enhances treatment efficacy while minimizing side effects. Unlike conventional radiation therapy, which irradiates the target for an extended period, FLASH radiotherapy delivers radiation in ultra-high doses per fraction, potentially sparing the surrounding normal tissues while maintaining tumor control. In addition, irradiating in conditions with reduced oxygen concentration (hypoxia) may confer advantages by exploiting the differential response of tumor cells to radiation. Hypoxia, a common feature of solid tumors, has been associated with increased radioresistance and reduced efficacy of conventional radiotherapy. However, the FLASH regime may overcome the radioresistance associated with hypoxia, resulting in improved tumor control and reduced normal tissue toxicity.
In this study, we conducted a comparative analysis with what was recently obtained by a research group based in Dresden to examine similarities and disparities in irradiation outcomes. Experiments were performed on 1 day post fertilization zebrafish embryos. To evaluate the impact of oxygen

concentration on irradiation efficiency (both conventional and UHDR) and healthy tissue sparing effect, zebrafish embryos were irradiated in normoxia or hypoxia (2.5% O2). To do so, approximately 2 hours before irradiation, about 30 embryos for each experimental condition were placed in 0.5 ml Eppendorf tubes filled with 200 µl low melting agarose and around 300 µl E3 embryo medium. Hypoxia was applied by placing the embryos within the InViVO2 hypoxic chamber (Ruskin) for 90 minutes in order to reach the desired Oxygen concentration (measured using the Presens Oxygen sensor). After this incubation, Eppendorf tubes with the embryos were sealed and moved to the Trento Proton Therapy Centre for irradiation. Both normoxic and hypoxic zebrafish embryos were irradiated with conventional and UHDR proton beam with a total radiation dose of 30 Gy. After irradiation, the embryos were moved to 96-well plates and maintained under normal conditions (28 ℃) with medium exchange every other day. We acquired images daily until 120hpf by analyzing five biological endpoints (pericardial edema, curved spine, head diameter, embryo length, and eye diameter). All malformations were scored and normalized with the controls.
Preliminary results suggest that the FLASH regime may have a potential protective role towards damages, particularly on spinal damage.
Taken together, these preliminary results confirm that irradiation in hypoxic conditions appears to play a protective role on healthy tissues, particularly evident when combined with the FLASH regime.

13

Comparative study of the effects induced by innovative radiotherapy treatments in zebrafish

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Conventional radiotherapy (RT) is based on the administration of photon beams in the form of low Linear Energy Transfer (LET) radiation (X-rays), which deposit a relatively small amount of energy on the target and disperses it to the surrounding healthy tissue, due to scattering phenomena, differently from high LET radiation (protons), which is delivered directly on the target with minimal dispersion on the close non irradiated tissues. The increased effectiveness of charged particles compared to photons is quantified by the Relative Biological Effectiveness (RBE), that represents a key parameter to compare different radiation qualities for prescribed doses. In recent years, it is grown the necessity of RT protocols improvement. Hence, the therapeutic use of proton beams, alone or in combination with radiomodifiers, requires the development of high performance and reliable in vivo models for preclinical research. In this scenario, the zebrafish embryo is a powerful and versatile model for assessing the effect of ionizing radiation with different LET values. We previously showed the radioprotective role of curcumin in combination with conventional X-rays, by the analysis of mortality, morphological alterations, and identifying the molecular mechanism underlying this biological effect in zebrafish. Based on this, distinct batches of 24 hours post-fertilization (hpf) zebrafish embryos were exposed to protons at the same X-rays dose range (0-15 Gy). Sister batches were pre-treated from 6 to 24 hpf with curcumin, at concentrations of 2,5 and 5 µM, and subsequently irradiated using the abovementioned dose range. Moreover, batches of 6 hpf embryos were either used as untreated controls or subjected to single treatment with curcumin following the same experimental setting used in the combined treatment. Treated and control embryos were carefully examined by daily stereomicroscope observation until 120 hpf, to estimate the mortality rate, developmental delay, morphometric parameters, hatching and heart rate values. Among these, the pericardial edema (PE) measurement was used to calculate a Protection Rate (PR) value in combined vs single treatments. Our experiments, comparing protons vs photons beam as single treatments at the isodose, showed that the damage inflicted by protons is greater than that inflicted by photons, in terms of malformed embryos percentage and PE/spinal curve (SC) incidence. Moreover, curcumin pre-treatment produces a major recovery in combination with protons than with photon irradiation.

A PR value has been calculated in terms of PE diameter ratio at 72 and 96 hpf for both curcumin concentration, showing better protection performance using higher curcumin concentration.
Keywords: zebrafish; radiations; curcumin.

14

Characterization of thin silicon detectors for applications in conventional and flash irradiations

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Detector technology based on thin (~ 50 μm) silicon sensors is gaining interest for the possible applications in beam monitoring, quality assurance, treatment verification and dosimetry in radiation therapy. Compared to gas ionization chambers, thin silicon sensors feature superior sensitivity, allowing to measure single particles, increased spatial resolution, much faster signal collection times and crossing time resolutions of tens of picoseconds. In addition, the large electric field in the small thickness limits the effects of charge volume recombination at the ultra-high dose rates foreseen in FLASH modalities.
Thanks to the INFN-CSN5 projects MoVeIT, SIG and FRIDA, the University and INFN group of Torino has been exploring various applications aimed at enhancing treatment delivery or contributing to new developments in this field. Several sensors of various thicknesses (15, 25, 45 and 60 μm), both with and without moderate gain, were designed and characterized on particle beams both at TIFPA and CNAO, demonstrating the capability of tracking single protons and carbon ions with crossing time resolutions as good as 20 ps. The applicability to beam monitoring at FLASH dose rates has been verified with electron beams at the CPFR facility in Pisa, where good signal linearity has been observed up to doses of 10 Gy in 4 μs pulses.
Large area sensors (2.7x2.7 cm^2) segmented in strips and a custom front-end readout chip (ABACUS) were developed to build a detector for counting beam particles over the cross section of a pencil beam, demonstrating the capability of operating up to clinical rates and measuring the beam position and profile with resolutions comparable to radiochromic films.
Smaller sensors and a custom analog readout were employed to develop a self-calibrating system to measure, with negligible beam perturbation, the particle's energy through a time-of-flight technique, allowing the measurement in a few milliseconds with an uncertainty of less than 1 mm range in water.
The excellent time resolution has been exploited developing readout systems based on fast Time to Digital converters to provide a full 4D tracking of beam particles at high rates. This has allowed to perform measurements of the CNAO beam time structure at the nanosecond level as well as acquiring Prompt Gamma Timing distributions, a useful technique for the in vivo verification of the particle range in the patient correlating in time the detection of the primary particle and of the emitted photon.

15

Microtubules as IR target

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Radiotherapy is a rapidly evolving domain encompassing various aspects, including the utilization of diverse beam types (protons, heavy ions, X-rays, electrons) and delivery methods, such as the emerging FLASH modality. To enhance clinical decision-making, a comprehensive understanding and modeling of physical, biophysical, and biological processes are essential. Initial and pivotal investigations often involve monolayer cell cultures. We study the microtubule (MT) network as a target of Ionizing Radiation (IR), in addition to DNA, traditionally recognized as the primary target of IR-induced damage. MTs present novel avenues for modeling. Our focus lies on studying MT occupancy and curvature, which correlates with the acetylation mechanism of lysine amino acid at position 40 of α-tubulin.
We acquired 3D STORM images employing a SAFe360 module (Abbelight) integrated with an inverted bright-field Olympus IX71 microscope, achieving a resolution of approximately 20nm. Confocal microscopy images were obtained using the Laica Stellaris 5 system. Subsequently, STORM and confocal images were analyzed using ImageJ software for filament reconstruction and curvature calculation. Statistical analyses were conducted using MATLAB.
We analyzed STORM and confocal images of non-cancerous and cancerous human mammary cells irradiated with different beam types protons vs. X-rays in a dose range from 4 to 15 Gy. The analysis aims to quantify MT area occupancy, perform filament reconstruction, and assess MT curvature. Statistical tests were conducted for each population. From the results it is clear that super-resolution microscopy techniques could bridge molecular integrity with geometric and spatial properties.
This is particularly significant as MTs, comparable in size to DNA, are viable candidates for energy distribution simulations using similar computational approaches. These findings offer insights into the fundamental mechanisms governing cell proliferation and survival.

Radiobiology / 16

A proton minibeam setup in the TPBL and the MIRO project

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Minibeam irradiation is seen as a new frontier for exploiting the advantages of proton beams, as well as other types of radiation, towards increasing the therapeutic ratio on clinical treatments. In this context a novel INFN project has been recently launched called MIRO - Minibeam Radiation, dedicated to the investigation of beam design and radiobiological effectiveness of electron and proton

minibeam irradiations. The first part of this project carried on at the Trento proton beam Laboratory (TEPBL) was the setup of a dedicated line for irradiation through a specific collimator, which, being able to serve both for protons (70 MeV) and electrons could allow a link between the local investigations and those performed with electrons in Pisa. This first setup was firstly characterised by extensive simulations and then used for experimental measurements through EBT films. The agreement between simulation and measurements was very promising and it was possible realised a peak to valley dose ratio (PVDR) uin the setup, larger of 3.5, uo to 5 mm depth after the collimator, thus allowing in principle irradiation of biological samples in the range relevant to mini beam radiobiology research. Further design of more opimized collimators is also proposed, through dedicated simulations.

17

Characterization of FOOT silicon microstrip detectors with protons.

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The FOOT (FragmentatiOn Of Target) multi-detector experiment aims at improving the accuracy of oncological hadrontherapy for tumor treatment. It studies the nuclear fragmentation due to the interactions of charged particle beams with patient tissues. Among the FOOT detection subsystems detectors, the Silicon Microstrip Detector is part of the charged-ions-tracking magnetic spectrometer. The MSD has been exposed to proton beams at Trento facility to study the response in terms of collected signal, noise and detection efficiency. In this presentation we will present some of the results obtained from these studies.

18

Test of amorphous silicon detectors on the Trento Proton Beam Line

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Hydrogenated amorphous silicon (a-Si:H) is a well
known material for its radiation resistance and for the possibility
of deposition on flexible substrates like Polyimide (PI). The HASPIDE collaboration is developing a-Si:H devices both for
dosimetry of clinical beams than flux measurement of other beam types.
In this framework a test has been carried out at the Trento Proton Beam Line to test the capabilities of the prototypes in measuring the proton fluxes. Some resulta on device sensitivity, linearity of the reponse and measurement uncertainty will be presented.

19

Dosimetric characterization of ultra-high dose rate proton beams for FLASH radiotherapy using calorimetry

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The recent discovery of the "FLASH"effect occurring delivering beams at average dose-rates exceeding 40 Gy/s and with a total irradiation time of < 300 ms, is leading to a growing interest in establishing the dosimetric and monitoring techniques that still assure the high level of accuracy needed for the clinical translation of FLASH radiotherapy [Romano et al., Med. Phys. 2022).
An experiment was recently carried out at the experimental room of the of the Trento Proton Therapy facility using ultra-high dose rate (UHDR) proton beams accelerated at 228 MeV by a IBA Proteus 235 cyclotron [Tommasino et al., NIM A 869 (2017) 15–20].
Aim of the experiment was to dosimetrically characterize the high energy UHDR proton beams using a newly developed portable graphite calorimeter specifically optimized for UHDR beams. The new dosimeter is an innovative and compact device recently developed at the National Physics Laboratory (NPL), which is the UK National Metrology Institute, acquired at the INFN Catania Division in the framework of the INFN CSN5 national call "FRIDA". The calorimeter is a portable secondary standard dosimeter composed by a simplified structure consisting of a central graphite core, 2 mm thick and 16 mm of diameter. The cylindrical core is connected to a single thermistor which forms one arm of a DC Wheatstone bridge providing, upon previous calibration, the measurement of the temperature rise during the irradiation, which is proportional to the absorbed dose [G. Bass et al., Br. J. Radiol. (2023)]. The calorimeter has been also calibrated in terms of absorbed dose at NPL under reference conditions using a Co60 source. Its response in terms of temperature increase upon irradiation and hence of absorbed dose was investigated varying the following beam settings: i) the beam current (from 10 nA up to 500 nA) and, hence, the average dose rate (up to 250 Gy/s) keeping the same total dose delivered; ii) the delivered dose (0.3-20 Gy) by changing the irradiation time (from 10 ms to 1 s), keeping the same beam current. The calorimeter was placed in air at the isocentre, at 2-3 meters far from the exit window. Before reaching the calorimeter, the proton beams were traversing the in-transmission double gap ionization monitor chamber supplied by the DE.TEC.TOR. company (named FLASHQ). The FLASHQ served as monitoring system during the whole experiment, thanks to a calibration in dose carried out using the IBA reference PPC05 ionization chamber placed at the same position of the calorimeter. No significant deviation from the linearity was observed for both the PPC05 and the in-transmission chamber at the explored rates. Alanine dosimeters were used to provide absolute dose measurements at the same irradiation point, whereas EBT-XD radiochromic films were used to evaluate the transversal dose distributions at the detector position and the beam uniformity.
After systematically demonstrating the dose rate independence of the calorimeter with UHDR proton beams and comparing it against the alanine dosimeters, absolute dose measurements at different proton beam currents were performed demonstrating the reliability and accuracy of the calorimeter for UHDR proton beam dosimetry. This system provides a very promising tool for accurate evaluation of dose in the perspective of future radiobiology and preclinical measurements.

20

The effect of particle therapy on tumour angiogenesis

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Non-small cell lung cancer (NSCLC) is the most prevalent type of lung cancer, which remains the leading cause of cancer-related mortality worldwide. Anti-angiogenic drugs, such as recombinant endostatin (RE), have been intensely studied to inhibit tumour angiogenesis in NSCLC, leading to mixed and often disappointing results in (pre)clinical trials. Despite the fact that previous studies revealed distinct differences in angiogenic effects between proton and photon irradiation, combination treatments with RE and proton therapy remain underexplored.
Therefore, this in vitro study investigates the up- and down-regulation of angiogenic processes in three cells lines that are relevant to the NSCLC tumour microenvironment (human lung fibroblasts (HLF), Human Umbilical vein endothelial cells (HUVEC) and lung adenocarcinoma (A549) cells) after low and high doses of 230 MeV proton (Trento Proton Therapy Centre) and photon irradiation (NRF iThemba LABS), combined with RE. In addition, the impact of the combination treatment is evaluated on cell migration, tubulogenesis, invasion and cell proliferation. Thus far data analysis from these experiments has revealed that cell migration appears to be slowed down in a radiation dose dependent manner. Protons slowed the migration of A549 cells down by approximately 40% compared to X-rays at high doses. The analyses on the HUVEC migration data are currently being finalized. No significant differences ($p<0.05$) were seen in the invasion of HUVECs after proton and photon exposure. Similarly, minimal apoptotic differences were seen in all three cell types exposed to protons and photons ($p>0.05$). In these instances, RE yielded no greater cell killing or inhibitory benefit on cell invasion. Proliferation assays (MTT) showed a dose dependent decrease in cell proliferation after proton and photon exposure. No significant effect of RE could be observed in all three cell lines. Tubulogenesis data from photon experiments are being finalized, but the tubulogenesis proton data showed a significant effect of RE on HUVEC tube formation ($p=0.00025$). Additionally, protons alone also significantly inhibited tube formation ($p<0.05$) however, this effect is not dose dependent. Protein expression analysis is currently under way and will be presented at the 2nd Workshop "Trento Proton Beam Line Facility".

21

FLASH understanding: the radiobiology program of FRIDA-WP1

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Despite growing and accumulating evidence,the FLASH effect - i.e. the differential sparing of normal tissue versus a same efficacy on the tumor, when radiation is delivered at an ultra-high dose rate, as compared to a conventional way - remains largely unexplained mechanistically, a limit which hinders importantly its potential for a clinical translation. In this context the Workpackage 1 "FLASH understanding" of the FRIDA INFN Call, "Flash Radiotherapy with High dose rate beams" is dedicated to contribute to unravel this issue with a combined modelling and experimental approach. An overview of the experimental ongoing and planned in this framework, in particular, those based at the TPBL, for proton FLASH irradiations of in vitro same at different oxygen concentrations, DNA damage analysis, radiation chemical tests, also in comparison with the same performed at the Pisa Electron FLASH facility will be reported and critically discussed, in connection with the parallel modelling activities.

22

Welcome

23

Detectors - First Session

24

Detectors - Second Session

25

Radiation Hardness

26

Invited Speakers Round Table

27

Radiation Biology - First Session

28

Radiation Biology - Second Session

29

Closing Remarks

30

Radiation damage and mitigation strategies for the SiPM of the ePIC-dRICH detector at the EIC

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The dual-radiator (dRICH) detector of the ePIC experiment at the Electron-Ion Collider (EIC) will be equipped with silicon photomultipliers (SiPM) sensors. SiPMs have excellent performance for efficient photodetection in high-magnetic field environments, but they are very sensitive to radiation damage. Rigorous testing is needed to ensure that their dark count rates (DCR) are kept under control over the years of running. The DCR can be maintained to an acceptable rate by reducing the SiPM operating temperature and by recovering the radiation damage with high-temperature annealing cycles. We present an overview of the current status of the R&D performed on significant samples of SiPM sensors. Proton and neutron irradiation tests have been performed at the Trento Proton Beamline Facility and at the INFN LNL-CN accelerator, respectively. The goal was to study the performance of the devices with increasing non-ionising energy loss (NIEL) doses up to 10^{11} 1-MeV neq/cm^2, the device recovery with long high-temperature annealing cycles and the reproducibility of the performance in repeated irradiation-annealing cycles. We also studied the use of the self-heating capabilities of the SiPM to exploit the Joule effect as an effective way to perform the high-temperature annealing "in-situ".

Facilities / 31

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Detectors / 32

CCharacterization of thin silicon detectors for applications in conventional and flash irradiations

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Detectors / **33**

Dosimetric characterization of ultra-high dose rate proton beams for FLASH radiotherapy using calorimetry

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Detectors / **34**

Beam and treatment monitoring in FLASH and CONV regimes for PT applications

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Detectors / **35**

Towards real-time dose control during cancer radiation therapies based on full-organic wearable dosimeter

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Detectors / **36**

Microdosimetry at the proton therapy facility of Trento

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Radiation Hardness / **37**

Proton-induced Radiation Damage Effects on Silicon Photomultipliers for HEP and space experiments

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Radiation Hardness / **38**

xRadiation damage and mitigation strategies for the SiPM of the ePIC-dRICH detector at the EIC

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Radiation Hardness / 39

Study of SEU effects in readout circuits of silicon micro-strips detectors developed in 110 nm UMC technology.

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Radiobiology / 40

p21: a new player in colon cancer cell radioresistance.

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Radiobiology / 41

Activation of the p53 pathway in combination with photon or proton irradiation for the treatment of brain tumours

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Radiobiology / 42

The effect of particle therapy on tumour angiogenesis

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Radiobiology / 43

Microtubules as IR target

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Radiobiology / 44

FLASH understanding: the radiobiology program of FRIDA-WP1

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Radiobiology / 45

Validation of Trento's Proton Centre for FLASH Radiotherapy: A Comparative Analysis, Insight from Zebrafish

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Radiobiology / 46

Comparative study of the effects induced by innovative radiotherapy treatments in zebrafish

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Radiobiology / 47

MGM: development and validation of a microdosimetric genomic model to predict radiation-induced mutation in space

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Detectors / 48

The Proton Radiography experiment

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Detectors / 49

Characterization of FOOT silicon microstrip detectors with protons.

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Detectors / 50

Test of amorphous silicon detectors on the Trento Proton Beam Line

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Detectors / 51

The beam test journey of the HEPD-02 detector at Trento Proton therapy center

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