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To cite this article: Paulina Stasica-Dudek *et al* 2025 *Phys. Med. Biol.* **70** 095007

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RECEIVED

18 December 2024

REVISED

28 March 2025

ACCEPTED FOR PUBLICATION

9 April 2025

PUBLISHED

29 April 2025

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Experimental validation of LET in intensity-modulated proton therapy with a miniaturized pixel detector

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Keywords: intensity-modulated proton therapy, linear energy transfer, semiconductor pixel detector

Abstract

Objective. Given the increased interest in incorporating linear energy transfer (LET) as an optimization parameter in intensity-modulated proton therapy (IMPT), a solution for experimental validation of simulations and patient-specific quality assurance (PSQA) in terms of proton LET is needed. Here, we present the methodology and results of LET spectra measurements for spread-out Bragg peak (SOBP) and IMPT plans using a miniaturized pixel detector Timepix3. **Approach.** We used a MiniPIX Timepix3 detector that provides single-particle tracking, type-resolving power, and spectral information while allowing measurement in quasi-continuous mode. We performed measurements for SOBP and IMPT plans in homogeneous RW3 and heterogeneous CIRS head phantoms with reduced beam current. An artificial intelligence-based model was applied for proton identification and a GPU-accelerated FRED Monte Carlo (MC) code was applied for corresponding MC simulations. **Main results.** We compared the deposited energy and LET spectra obtained in mixed radiation fields from measurements and MC simulations. The peak positions of deposited energy and LET spectra for the SOBP and IMPT plans agree within the error bars. Discrepancies exceeding the error bars are only visible in the logarithmic scale in high-energy deposition and high-LET tails of the distributions. The mean relative difference of dose-averaged LET values between measurements and MC simulations for individual energy layers is about 5.1%. **Significance.** This study presents a methodology for assessing radiation quality in proton therapy through energy deposition and LET spectra measurements in uniform and clinical IMPT fields. Findings show an agreement between experimental data and MC simulations, validating our approach. The presented results demonstrate the feasibility of a commercially available Timepix3 detector to validate LET computations in IMPT fields and perform PSQA in terms of LET. This will support the implementation of LET in treatment planning, which will ultimately increase the effectiveness of the treatment.

1. Introduction

Proton radiation therapy is increasingly popular worldwide, offering advantageous physical and radiobiological properties in cancer treatment. Contrary to photons applied in conventional radiation therapy, proton, and heavier ion beams are characterized by a finite range and the highest energy deposition at the end of the range, known as a Bragg peak. This enables high conformality of dose distribution, sparing healthy tissue surrounding the tumor and making proton beam therapy widely applied, especially for pediatric patients (Thomas and Timmermann 2019) and patients with tumors located near organs at risk, such as head and neck cancer (Blanchard *et al* 2018).

Pencil beam scanning is a state-of-the-art proton treatment delivery method. In this technique, the scanning magnets direct a narrow pencil beam through a number of positions (spots) at a given depth in a patient's body in a millisecond time scale. This allows adjustment of dose distribution to the tumor's complex shape and modulation of the number of protons delivered to each spot, which is utilized in intensity-modulated proton therapy (IMPT), the proton counterpart to IMRT. The typical IMPT plan consists of several heterogeneous fields, the superposition of which covers the tumor volume homogeneously. In clinical routine, the patient-specific quality assurance (PSQA) procedures include measurements of two-dimensional dose distribution with a matrix of ionization chambers (e.g. MatriXX, IBA) placed in a water phantom for single fields of the treatment plan. The measured dose distributions are compared with the ones recalculated for a homogeneous medium with a treatment planning system.

From the radiobiological point of view, protons, especially at the end of the range, exhibit an increased ionization density correlated with complex lethal DNA damage. In clinical practice, this is considered by weighing the physical dose with a scaling factor—relative biological effectiveness (RBE), which is assumed to be constant and equal to 1.1. In fact, the proton beam, interacting with the patient's body, produces a mixed radiation field comprised of primary and secondary particles (e.g. electrons, secondary protons, deuterium, tritium) and photons of various energies. This results in varying radiation quality that impacts RBE value, which can reach even about 1.7 (Paganetti 2018).

Radiation quality is usually quantified with the linear energy transfer (LET) defined as the mean energy lost by a charged particle in a given material over a given distance (ICRU 2011, chap. 4). In this work, LET refers to unrestricted LET. The information on the radiation quality in a given voxel of a voxelized patient's CT geometry can be provided by a single weighted average value, with frequency or dose as a weighting factor. The most common approach in proton radiotherapy is to apply dose-averaged LET (LET_d) for primary and secondary protons (Kalholm *et al* 2021). The LET_d value depends on several factors, such as the calculation method (Cortes-Giraldo and Carabe 2015, Granville and Sawakuchi 2015) and the geometrical voxel size (Cortes-Giraldo and Carabe 2015). Variable RBE models typically depend on averaged LET_d that impacts radiosensitivity parameters (Wilkens and Oelfke 2004, Alejandro Carabe-Fernandez and Jones 2007, Wedenberg *et al* 2013, McNamara *et al* 2015).

Yet, it has been demonstrated that LET_d alone does not adequately account for radiation effects in complex mixed fields where RBE(LET) relation deviates from linear correlation (Grün *et al* 2019). Also, no consensus has been found on the correlation between elevated LET_d and the risk of necrosis in healthy tissue (Bahn *et al* 2020, Garbacz *et al* 2021, Niemierko *et al* 2021). Lately, Félix-Bautista *et al* (2024) suggested that although the impact of the width of the LET spectrum on RBE value is limited for single proton beams, it will be more significant in complex clinical fields. It is thus noteworthy to consider various approaches for characterizing proton LET for RBE modeling or as an independent plan optimization parameter. Although two different voxels may be represented by a similar average LET value of all protons, the underlying LET spectra of individual protons may differ, resulting in varying levels of radiobiological effect (Guan *et al* 2024). It suggests that the spectrum of protons' LET could provide more comprehensive information in a given voxel compared to average LET values. It is hypothesized that this could offer more nuanced insight into clinical outcomes and be particularly important in scenarios involving broad LET spectra produced by multiple pencil beams of various energies.

Lately, there has been an increased emphasis on incorporating LET into the clinical treatment planning of proton therapy (Deng *et al* 2021, McIntyre *et al* 2023, Paganetti *et al* 2024). This can be accomplished by optimizing the biological dose with variable, LET-dependent RBE or by considering the proton LET distribution alongside the physical dose. Accounting for LET as an optimization parameter enables better utilization of proton radiobiological properties by reducing LET in healthy tissue, particularly in organs at risk, while maintaining the same level of LET or, even more beneficially, enhancing LET in the target volume. There are also efforts to incorporate LET optimization for FLASH proton therapy besides clinical proton therapy (Harrison *et al* 2024b).

Following the recommendations above, the RayStation treatment planning system introduced LET optimization (Janson *et al* 2024). Also, fast, GPU-accelerated Monte Carlo (MC) simulations are available for proton LET spectra scoring in CT patients' geometries within the FRED MC engine (Schiavi *et al* 2017). Despite these advancements on the computational side, there is a need for systematic experimental validation of LET distributions (Harrison *et al* 2024a).

Various passive and active detectors have recently been applied for LET assessment (Christensen *et al* 2024), including optically stimulated luminescence, fluorescent nuclear track detectors (FNTDs), thermoluminescence detectors, and other (Christensen *et al* 2024). In particular, passive detectors including FNTD (Muñoz *et al* 2024) and CR-39 (Kodaira *et al* 2016) are commonly applied. The latter one has a high detection threshold and is insensitive to low LET particles (Yang *et al* 2022). Due to the significant time

required for processing the signal from passive detectors, active detectors hold more potential for application in routine measurements in clinical practice (Christensen *et al* 2024).

Active detectors are generally applied in microdosimetry, which plays a fundamental role in radiobiological studies and provides insight into the effects of radiation on the micrometer scale (Griffiths 1985). It examines a stochastic counterpart of LET, lineal energy, and has been applied before for proton lineal energy measurements, predominantly in laboratory settings (Parisi *et al* 2022a, Magrin *et al* 2023). The measurements were performed also for uniform irradiation plans (Rosenfeld 2016, Wagenaar *et al* 2020). The most popular microdosimetric technologies include tissue-equivalent proportional counter (Conte *et al* 2019, Missiaggia *et al* 2020) and silicon-on-insulator detectors (Petringa *et al* 2020, Lee *et al* 2021, Braby *et al* 2023).

Among active detectors, Timepix MiniPIX has been applied for the LET characterization for single proton pencil beams (Granja *et al* 2021, Nabha *et al* 2022, Stasica *et al* 2023), as well as collimated and uncollimated fields (Charyyev *et al* 2021, Nabha *et al* 2023). Timepix3 has been applied for LET assessment in monoenergetic ion beams (Félix-Bautista *et al* 2024), and a silicon carbide-based dosimeter was used for single beam and spread-out Bragg peak (SOBP) characterization in carbon beam (Yamaguchi *et al* 2022). While great advancement has been achieved in microdosimeter development (Parisi *et al* 2022b), this work focuses on the Timepix3 (Poikela *et al* 2014) detector as a potential commercially available and miniaturized instrumentation to verify LET spectra scored with MC-based treatment planning systems.

Previously, proof-of-concept measurements were performed with single proton pencil beams in a water phantom using Timepix MiniPIX enclosed in a waterproof holder (Stasica *et al* 2023). The main limitations of applying Timepix in scanning beam measurements are due to the frame-based mode of measurement, which means the detector is not operating continuously with a significant dead time and signal overlapping (see section 2.3). The newer generation of Timepix, Timepix3, allows quasi-continuous operation suitable for scanning beam measurement. This work aims to perform single-proton LET characterization for scanning beam (the SOBP, and IMPT fields) in phantoms by applying the MiniPIX Timepix3 Flex detector.

2. Materials and methods

2.1. Proton therapy facility

The Cyclotron Center Bronowice at the Institute of Nuclear Physics of the Polish Academy of Sciences (CCB IFJ PAN) is a proton therapy facility that has been operating since 2016. Two treatment rooms are equipped with rotational gantries and pencil beam scanning, providing IMPT for oncological patients. Currently, up to 50 patients are treated per day in the center. Isochronous cyclotron C-235 (IBA, Belgium) accelerates protons up to 235 MeV. The beam is available within the energy range from 70 to 226 MeV. This corresponds to a depth in water (similar in tissue) of 4.2–31.8 cm. A 4.2 cm thick PMMA range shifter can be inserted in the gantry nozzle to decrease the beam energy for irradiating shallowly located tumors. The lateral beam size (σ) ranges from 2 to 15 mm depending on the beam energy and application of the range shifter. In the standard cyclotron operation mode (Treatment Control Diagnostics), the beam current can be modulated from 1 to 600 nA. Treatment planning is performed with the Eclipse v. 16.1 (Varian Medical Systems, USA) treatment planning system, equipped with an analytical algorithm and commissioned against experimental data.

2.2. Pencil beam scanning with reduced beam current

The clinically used proton beam current in the order of nA is too high for tracking single protons with the Timepix3 detector during irradiation, causing signal overlap and detector saturation. Thus, a methodology of pencil beam scanning with the beam current reduced to a single pA was developed.

The cyclotron was operating in a service mode, controlled with scanning controller diagnostics software, and the duants' voltage was set to slightly different values, manually reducing the efficiency of proton extraction from the source. The exact value was selected during the experiments based on the analysis of the Timepix online response. The beam current was constant within 15% during the irradiation of all layers of a given field, as measured in the preliminary tests performed with the Timepix3 detector.

Each layer of a given plan was irradiated and measured separately. The modulation of the proton number delivered to each spot was controlled by aligning the irradiation time of each spot proportionally to the total monitor units (MUs) to be delivered. The irradiation time in the experimental mode is limited to about one minute in the cyclotron operation system. Therefore, to ensure the best possible statistics, the irradiation time of each spot was optimized so that the irradiation of each layer with constant current lasts for one minute. Simultaneously, the ratio of the irradiation durations for individual spots was preserved and corresponded to the number of MU to be delivered with each beam in clinical settings. The difference between the prescribed spot irradiation time and the time registered in irradiation logs was less than 0.1%.

2.3. Spectral-sensitive single particle tracking with MiniPIX Timepix3 detector

Timepix semiconductor pixel detector was developed at CERN within the Medipix collaboration (Llopart *et al* 2007). It serves a broad spectrum of applications, including imaging, space dosimetry, physics, and radiation therapy (Ruqaya Al Darwish and Bezak 2020). Timepix and its successor, the Timepix3 detector, have been applied in hadron therapy, e.g. for the characterization of dose, flux, composition, and LET (Rosenfeld *et al* 2020, Stasica *et al* 2020, 2023, Nabha *et al* 2023, Oancea *et al* 2023), as well as for treatment monitoring (Charyyev *et al* 2023, Kelleter *et al* 2024). Depending on the purpose, it can be equipped with a sensitive volume of various thicknesses, from 100 to 1000 μm , and materials, i.e. Si, GaAs, CdTe, SiC. The semiconductor sensor is bump-bonded to the ASIC chip and divided into a grid of 256×256 pixels, with a separate signal readout each. The pixel pitch is 55 μm , and the resulting sensitive area is about 2 cm^2 .

An ionizing particle traversing the semiconductor volume produces electric carriers collected by the pixels' electrodes. In the data-driven (self-triggered) mode available with the Timepix3 detector (Poikela *et al* 2014), the time-of-arrival (ToA) and time-over-threshold (ToT) can be registered simultaneously in each pixel. This provides information on the signal time and deposited energy, respectively. When the signal exceeds the threshold, the ToA value is recorded, and the ToT counter starts and continues until the signal drops below the threshold. The signal from a hit pixel is read out immediately after the event and independently from other pixels, providing a quasi-continuous operation of the detector contrary to the frame-based mode of Timepix. In this data-driven mode, the detector operates with minimum dead time (high duty factor operation), which increases with the occupancy of the pixels (Poikela *et al* 2014). The detector is per-pixel energy calibrated, i.e. parameters of the ToT function of deposited energy are provided for each pixel.

A single particle usually produces a trace of multiple adjacent pixels in which the signal surpasses the threshold. In data-driven (self-triggered) mode, 18 bits can be used for precise signal time registration with 40 MHz reference clock (14 bits, ToA) and voltage-controlled-oscillators (4 bits, fToA). This allows for a precise clusterization of the signal from a single particle. The remaining 10 bits can be used for ToT registration. Thus, the ToT range that can be measured is limited to 1022 (the largest number that can be encoded). For standard readout settings digital-to-analog converters (DACs), this corresponds to approximately 400 keV per pixel, above which signal saturation will occur.

In this work, we used a Timepix3 (TPX3) operated with the miniaturized and low-power MiniPIX TPX3 (Advacam, Prague) readout that does not require a complex and heavy active liquid cooling system—see figure 1(a). The detector is equipped with a 300 μm -thick silicon sensor. In the flex configuration (Oancea *et al* 2023), the chip is supported on a graphite plate and connected to the readout electronics with a 10 cm-long cable. The detector readout settings were customized for proton therapy applications. To address the issue of signal saturation caused by limited ToT range, the I_{Krum} current, which controls the signal decay time, was increased from 5 to 30. This allowed mitigation of the signal saturation effect by reducing the signal duration. The energy threshold was increased from 3 keV to 12 keV to reduce the number of occupied pixels. The threshold value was determined as a compromise between low-signal sensitivity and trace size reduction as well as a reduction of signal from electrons and photons (Stasica-Dudek *et al* 2025). It has also been demonstrated that following the calibration with three radiation sources (Am-241 59.5 keV photons, Indium K-line at 24 keV, and Zirconium K-line at 15.775 keV) (Jakubek 2011), the relatively high threshold does not impact the measurement of energy deposition from protons (Stasica-Dudek *et al* 2025).

2.4. Experimental setup and irradiation plans

The measurements were performed in one of the treatment rooms equipped with a rotational gantry at CCB IFJ PAN. Three experiments have been conducted measuring the radiation quality in homogeneous and heterogeneous phantoms for homogeneous and heterogeneous irradiation plans corresponding to the standard dose distribution quality assurance and control procedures in proton radiotherapy facilities. The measurements were performed behind a solid RW3 phantom (PTW, Freiburg, Germany) (Hill *et al* 2008) for (i) an SOBP plan (section 2.4.1) and (ii) a single field of an IMPT plan of a patient with a pituitary gland tumor treated in CCB IFJ PAN (section 2.4.2) as well as (iii) behind half head of a heterogeneous CIRS phantom (model 731-HN) (Albertini *et al* 2011) for a single field of an artificially created IMPT plan (section 2.4.3).

In all the experiments, the detector was enclosed in a protective PMMA holder with a 1 mm-thick window in front of the sensor. The detector was operated remotely from the control room, and the data acquisition was controlled using PixetPro software v. 1.7.8 (Advacam, Prague). Measurements were performed with the detector operated in a data-driven (ToT + ToA) mode. The bias was set to 80 V to ensure full depletion of the sensor. The measurements were performed separately for each layer of irradiation plans introduced below.

2.4.1. Measurements in a homogeneous phantom for SOBP plan

For the first two experiments with the solid RW3 phantom, the gantry was rotated to achieve a horizontal beam, and the experimental setup, consisting of the phantom and the Timepix detector, was positioned on the patient table (see figure 1(b)). The middle of the sensor was positioned in the room isocenter at 45° to the beam axis. Rotating the sensor by 45° allowed to distribute the energy deposited by the protons through more pixels and thus to reduce very high per-pixel signals. Also, elongating the proton track in the sensor aims to increase the accuracy of the track length estimation.

The SOBP plan with a 20 cm range in water, 4 cm modulation, and $5 \times 5 \text{ cm}^2$ lateral size consists of 8 energy layers (153.87–172.76 MeV) and 81 spots per layer. The RW3 phantom (water equivalent ratio of 1.035) was 17.4 cm thick, corresponding to 18 cm of depth in water, hence the measurement was performed in the middle of the cubic dose distribution, as presented in figure 2(a).

2.4.2. Measurements in a homogeneous phantom for the IMPT plan

With a similar experimental setup, measurements were performed for the IMPT plan. The single field of the IMPT patient treatment plan consists of 23 energy layers (79.29–123.09 MeV) and 587 spots in total. The measurements were repeated at two positions with the middle of the sensor positioned at 8 cm depth (7.7 cm of RW3) at $Y = 1.79 \text{ cm}$, and $Z = 0.2 \text{ cm}$ (IMPT-A, see figure 3(a) and at 9 cm depth (8.7 cm of RW3) at $Y = 0.79 \text{ cm}$, and $Z = -0.6 \text{ cm}$ (IMPT-B, see figure 4(a)). The points were selected according to the PSQA protocol used at CCB IFJ PAN for dose measurement. The lateral detector position was adjusted using the table positioning system.

2.4.3. Measurements in a heterogeneous phantom for the IMPT plan

The IMPT plan for the experiment in a heterogeneous phantom was prepared for an artificially contoured, round PTV structure with 4 cm diameter, located in the CIRS head center (IMPT-C, see figure 1(c)—left panel). To achieve IMPT dose distribution, the plan was prepared with two fields, vertical and horizontal, irradiating from the head side at 45° and the head top, respectively. The measurements were performed for the first field only, consisting of 13 energy layers (96.57–140.31 MeV) and 315 spots. The field was recalculated for half of the head, and the middle of the Timepix sensor was positioned behind the heterogeneous structure in the room isocenter (see figure 1(c)—middle and right panel).

2.5. MC simulations and analysis

In this work, a fast, GPU-accelerated MC code FRED v. 3.70.0 (Schiavi *et al* 2017) was used to simulate the energy deposition and LET spectra for each experimental scenario. In this code, primary and secondary protons, deuterons, and tritons are transported, while the energy from heavier ions, gammas, and delta-electrons is deposited locally. The simulations were performed using an experimentally validated clinical beam model for a scanning proton gantry room at CCB IFJ PAN and the HU-to-material lookup table (Gajewski *et al* 2021).

The geometry consisted of the detector and RW3 phantom of an appropriate thickness or CT of half of the CIRS phantom. The detector geometry included graphite support, a silicon chip, bump-bonding made of Sn–Pb alloy, a silicon sensor, an aluminum electrode, and a PMMA holder. From the phase space files, several physical quantities for each proton traversing the sensor volume were scored, including hitting position, incident angle, energy deposition, and step length. The simulations were repeated for the sensor lateral shift of 1 mm in both directions to account for positioning uncertainty.

As the presented approach aims to validate MC simulations, the analysis of simulation results was performed to correspond to the measurement conditions. The track length of each proton was computed assuming the particle crossed the sensor based on the particle incident angle and the sensor thickness following experimental data analysis. The unrestricted LET value of each proton was calculated as the ratio of its total energy deposition in the sensor and the track length. No electronics-related effects, such as nonlinear detector energy response, electronics saturation, and readout dead time, have been simulated. The spectra of energy deposition and LET of scored protons were produced. The area between the minimum and maximum bin values obtained due to positioning shifts was shaded on the spectra.

2.6. Data analysis and comparison with MC simulations

The raw data registered with PixetPro in T3PA format (Timepix3 Pixels ASCII) contains information on each event (pixel hit), including ToT, ToA, fToA, and the pixel index. The time of registration in ns was computed using the following formula (Ghesquiere-Dierickx and Helene 2022):

$$t = \text{ToA} * t_{\text{slow}} - \text{fToA} * t_{\text{fast}} \quad [\text{ns}], \quad (1)$$

where $t_{\text{slow}} = 25 \text{ ns}$ and $t_{\text{fast}} = 1.5625 \text{ ns}$.

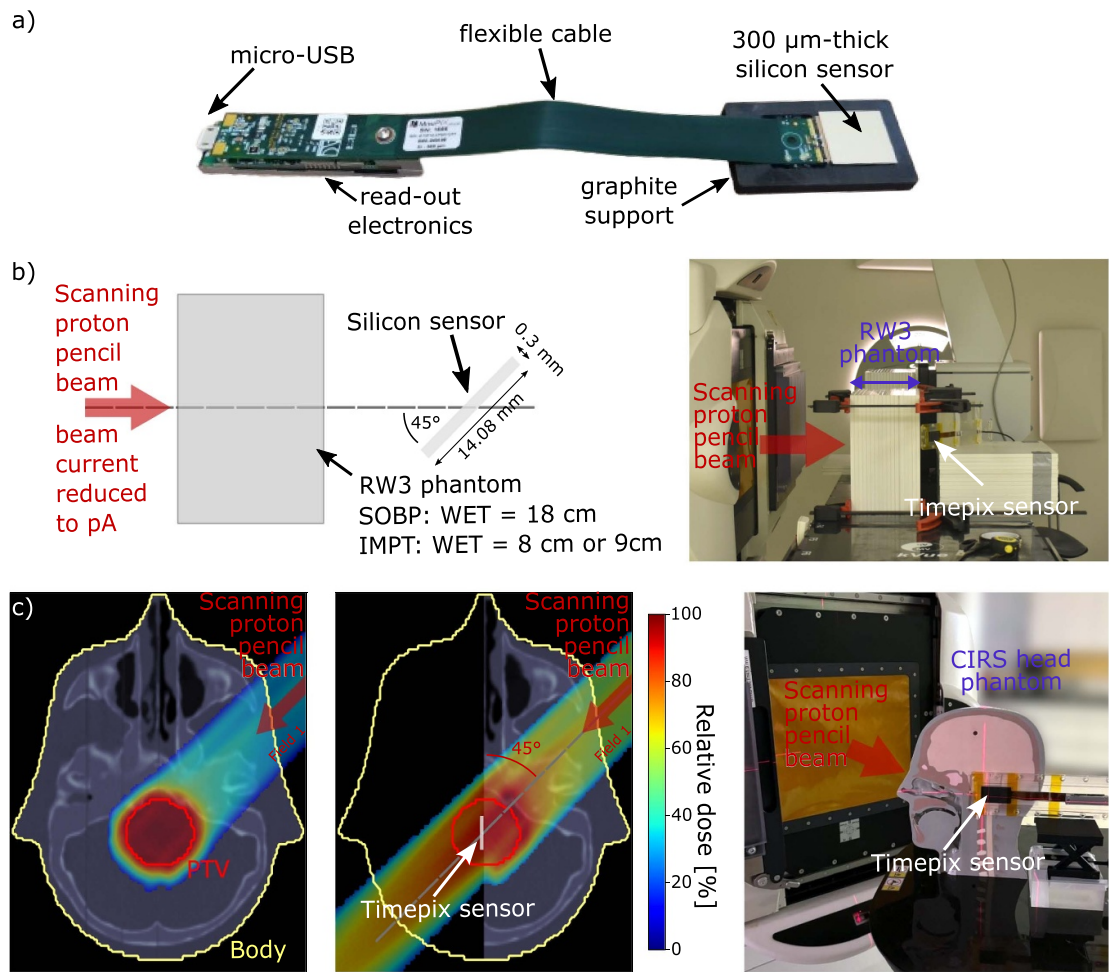


Figure 1. (a) The MiniPIX Timepix3 detector with 300 μm-thick silicon sensor in Flex configuration (Advacam, Prague). Adapted from Stasica-Dudek *et al* (2025). CC BY 4.0. (b) A scheme (left) and a photo (right) of the experimental setup for the SOBP and IMPT field measurements behind a solid RW3 phantom. (c) IMPT treatment plan prepared for the CIRS head phantom (left), one of the fields recalculated for half of the head with indicated sensor position (middle), and a photo of the experimental setup for the measurements behind a heterogeneous phantom (right). The sensor thickness in the middle panel is not to scale.

Next, clusterization was performed with an in-house-implemented script in Python. The code was written based on an algorithm for connected components labeling in sparse matrices (Hennequin *et al* 2019) and expanded to three-dimensional space: the pixel's position in a two-dimensional matrix of pixels and time. The script clusterizes the signal occurring in multiple pixels within a time window of 150 ns.

As 14 bits are used for ToA measurement with 40 MHz clock, the maximum signal registration time equals 409.6 μs before ToA overflow (Poikela 2015). If the signal readout time exceeds this period, some pixelated tracks might occur in fragments separated by 409.6 μs. Thus, in the post-clusterization stage, the data were searched for clusters (pixelated tracks) separated by $409.6 \pm 0.1 \mu\text{s}$, and subsequently, the clusters were merged if they were adjacent.

The energy deposited in a single pixel was computed based on the calibration function (Jakubek 2011):

$$\text{ToT} = aE + b - \frac{c}{E - t} \quad [\text{keV}], \quad (2)$$

where a , b , c , and t are parameters obtained for each pixel in the detector calibration procedure. The standard calibration procedure is performed for low-energy deposition regions, resulting in increasing uncertainty of spectral measurements for higher ToT values. Also, non-linearity of the calibration curve for energy deposition values occurs, leading to an underestimation of deposited energy value (Sommer *et al* 2022). For Timepix3, this occurs for even lower energies than in the case of Timepix, above approximately 120 keV. Thus, to correct the detector response for high-energy depositions, correction functions proposed by Mihai *et al* (2025), derived from a similar Timepix3 detector calibration with monoenergetic low-energy protons and alpha particles, were applied. The first function (a third-degree polynomial fit) was applied to pixels with

energy deposition exceeding 150 keV, and subsequently, the second function (a second-degree polynomial fit) was applied to pixels with energies above 600 keV.

The particle identification model was developed based on the methodology presented in Stasica *et al* (2023). Proton identification was performed using a newer, lighter (lower number of trainable parameters) convolutional neural network-based EfficientNET model (Tan and Le 2019). The model was pretrained with the Image-NET dataset (Deng *et al* 2009) and fine-tuned with reference protons and other types of particles (photons, electrons) data. The model achieved an accuracy, precision, and F1-score of over 99% for both categories of particles.

The cluster length was computed as the maximum distance between pixels in the cluster while ignoring the effect of charge-sharing (Campbell *et al* 2007). Based on the cluster length, the particle track length l_{3D} was calculated assuming the particle crossed the sensor. LET of a single proton n in silicon was computed energy deposited in a single cluster of pixels E_n averaged over the particle track length l_n :

$$\text{LET}_n = \frac{E_n}{l_n}. \quad (3)$$

The conversion of LET from silicon to water was performed based on a fitted function proposed by Benton *et al* (2010) that covers a wide range of energies of charged particles.

The spectra of energy deposition and LET of protons were produced for each layer separately and normalized to the height of spectra obtained with MC simulations providing the weight of each component spectrum. In this approach, the absolute values of the spectra correspond to the actual amount of primary protons to be delivered in the clinical plan. Then, the superposition of spectra from all measured layers was performed for each measurement point.

While beam current variations do not impact the proton energy and LET spectra for measurements with a single beam, this is not the case for more complex irradiation plans composed of multiple spots and energy layers. In the presented approach, we perform a separate measurement for each layer of a given plan. Thus, the spectra shape can be potentially impacted by variations of beam current within individual spots, as well as between the measurements of separate layers. Based on preliminary tests, we assumed the negligible variation of beam current within a single layer and a 15% variation between the irradiation of individual layers. The variation of bin values for measurement data was computed and marked with a shaded area on the spectra.

LET_d value was computed for each layer as a weighted average for all protons with energy deposited by a single proton E_n in the sensor volume based on the following formula:

$$\text{LET}_d = \frac{\sum_n \text{LET}_n * E_n}{E_n}. \quad (4)$$

Then, the weighted average was computed for combined spectra with the same weights obtained based on MC simulations. The relative percentage differences were computed between the LET_d values obtained based on measurement and MC simulation results with simulations as a reference.

The RBE was computed using the Wedenberg model (Wedenberg *et al* 2013) based on average LET_d and single proton LET in water for both MC simulations and measurements. The computations followed the methodology introduced by Muñoz *et al* (2024) and assumed glioblastoma (A-172 cell line) with $\alpha_X = 0.405 \text{ Gy}^{-1}$ and $\beta_X = 0.0588 \text{ Gy}^{-2}$ (Tsuboi *et al* 1998). The α radiosensitivity parameter of the linear-quadratic model was computed for each recognized proton k with the following formula:

$$\alpha_k = \alpha_X \left[1 + c \left(\left[\frac{\alpha}{\beta} \right]_X \right)^{-1} \text{LET}_k \right],$$

where $c = 0.434 \text{ Gy } \mu\text{m keV}^{-1}$ (Wedenberg *et al* 2013). Following the Wedenberg model, the β radiosensitivity parameter was assumed to be constant. Next, a weighted average value of α was computed with LET value for each proton as a weighting factor following the formula (equation (4) in Muñoz *et al* 2024):

$$\alpha_{\text{spect.}} = \frac{\sum_k \alpha_k \text{LET}_k}{\text{LET}_k} \quad (5)$$

Additionally, the α parameter was computed using LET_d (α_{LET_d}). Based on the obtained α values, the RBE was computed using the following formula:

$$\text{RBE} = -\frac{1}{2D} \left[\frac{\alpha}{\beta} \right]_X + \frac{1}{D} \sqrt{\frac{1}{4} \left[\frac{\alpha}{\beta} \right]_X^2 + \frac{\alpha}{\alpha_X} \left[\frac{\alpha}{\beta} \right]_X D + \frac{\beta}{\beta_X} D^2},$$

where D is the dose delivered to the sensor's volume and converted to water. α in this equation refers to $\alpha_{\text{spect.}}$ for computation of RBE with LET spectrum as an input ($\text{RBE}_{\text{spect.}}$) and to α_{LET_d} when using LET_d as an input. The RBE values were computed for each layer of the plan, and the weighted average was computed with the weights obtained based on MC simulations. The relative percentage differences between RBE values obtained based on the averaged LET_d and LET spectra were computed for MC simulations and measurements.

3. Results

3.1. Deposited energy spectra, LET spectra, and LET_d values for SOBP in homogeneous phantom

In figure 2(b), the spectra of deposited energy and LET in water for individual energy layers of the SOBP plan are depicted in various colors, with the combined spectra of all weighted layers displayed in black. The range of beams from the two layers of the lowest energy was too short for protons to reach the sensor, and thus, the spectra for these layers were not reported in the figure. The high-deposited energy (high-LET) tails were smoothed, applying a moving average only for visualization purposes (no impact on LET_d values). The peak positions of the deposited energy and LET spectra, derived from measurements and MC simulations, show good agreement for individual layers.

For the measured energy deposition spectra, the proton number is overestimated in the high-energy region above approximately 7000 keV, as observed in the logarithmic scale. Regarding LET spectra, the underestimation of the proton number for the spectra obtained based on measurement occurs in the high LET region above $8 \text{ keV } \mu\text{m}^{-1}$, also visible only in the logarithmic scale. There is up to about one order of magnitude relative difference (with respect to simulations) in the tail regions for energy and LET spectra. However, this difference occurs for the number of protons about three orders of magnitude lower than in the peak position, and thus, it has a limited impact on LET_d and RBE, as presented in tables 1 and 2 (section 3.4). The relative differences of LET_d values computed for measurements and simulation for individual layers range from 1.7% to 4.9%.

Figure 2(c) presents a comparison of energy deposition and LET spectra combined for all relevant monoenergetic layers. The 1 mm positioning error bars are negligible due to the size of the homogeneous SOBP field, which is much larger than the sensor. The measured and simulated deposited energy and LET spectra align well within the measurement error bars in the linear scale. The LET_d values obtained for the combined spectra were $1.62 \text{ keV } \mu\text{m}^{-1}$, and $1.56 \text{ keV } \mu\text{m}^{-1}$ for experimental and simulation results, respectively. The relative difference is about 3.8%.

3.2. Deposited energy spectra, LET spectra, and LET_d values for IMPT plan in homogeneous phantom

Figure 3(b) presents the spectra of deposited energy and LET in water for all layers of the IMPT field at the first measurement location in a homogeneous phantom, as shown in the dose distribution above (IMPT-A). The comparison reveals an excellent agreement of the peak positions for both energy deposition and LET spectra within the bounds of the error margins. The obtained LET_d values are $1.66 \text{ keV } \mu\text{m}^{-1}$ and $1.59 \text{ keV } \mu\text{m}^{-1}$ for experimental and simulation results, respectively. The relative difference is about 4.4%. Figure 4(b) shows similar spectra—deposited energy and LET in water for all layers of the IMPT field at the second measurement position in homogeneous phantom, also marked on the dose distribution above (IMPT-B). Similarly, we obtained agreement in the peak positions of energy deposition and LET spectra within the error bars. The obtained LET_d values are $1.93 \text{ keV } \mu\text{m}^{-1}$ and $1.87 \text{ keV } \mu\text{m}^{-1}$ for experimental and simulation results, respectively. The relative difference is about 3.2%. The relative differences for individual layers ranged from 0.1% to 7.4%.

3.3. Deposited energy spectra, LET spectra, and LET_d values for IMPT plan in heterogeneous phantom

Figure 5 shows deposited energy and LET spectra for protons for IMPT plan in CIRS phantom (IMPT-C). The measurement position is indicated in figure 1(c), middle panel. The peak positions for measurement and simulation results agree within the error bars. The LET_d is about $1.47 \text{ keV } \mu\text{m}^{-1}$ for measurement results and $1.46 \text{ keV } \mu\text{m}^{-1}$ for MC simulation results. The relative difference is about 0.7%. In the case of measurements in a heterogeneous CIRS phantom, the relative differences for individual layers ranged from 0.6% to 17.4%, and the mean value was 8.7%. For the individual energy layers, the mean relative difference between LET_d values derived from MC simulation and measurement results was below 5.1%.

3.4. Variable RBE based on LET spectra and LET_d

Table 1 presents RBE values for individual layers of the SOBP plan calculated using the Wedenberg model (Wedenberg *et al* 2013) based on MC simulation and Timepix measurement results. The values are computed accounting for single-proton LET and are compared with those computed based on the averaged

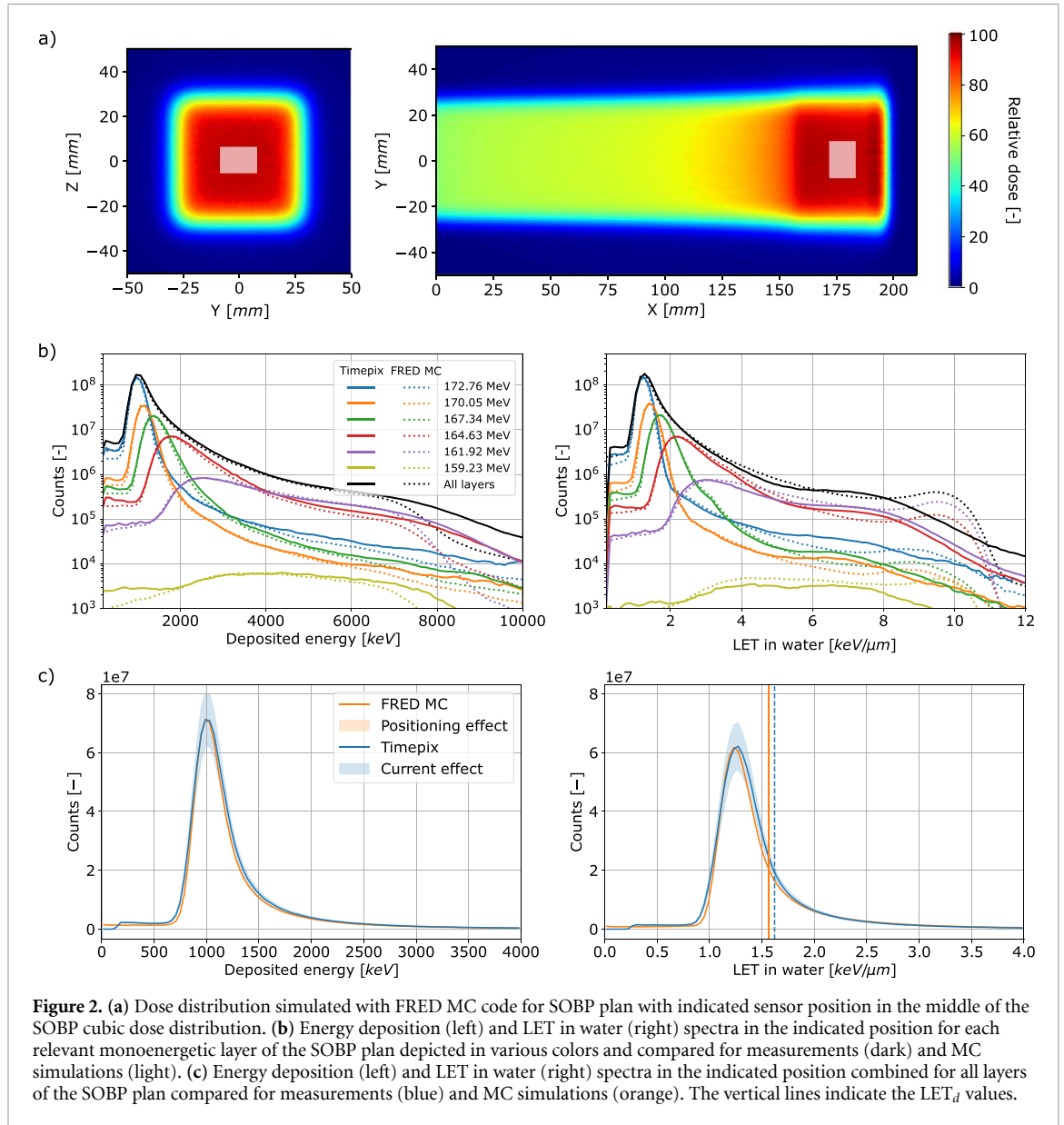


Figure 2. (a) Dose distribution simulated with FRED MC code for SOBP plan with indicated sensor position in the middle of the SOBP cubic dose distribution. (b) Energy deposition (left) and LET in water (right) spectra in the indicated position for each relevant monoenergetic layer of the SOBP plan depicted in various colors and compared for measurements (dark) and MC simulations (light). (c) Energy deposition (left) and LET in water (right) spectra in the indicated position combined for all layers of the SOBP plan compared for measurements (blue) and MC simulations (orange). The vertical lines indicate the LET_d values.

Table 1. RBE values computed based on LET spectra (RBE_{spect.}) and LET_d values (RBE_{LET_d}) with relative differences for MC simulations (FRED MC) and experimental results (Timepix) for individual energy layers of SOBP field.

Layer (MeV)	FRED MC			Timepix		
	RBE _{spect.}	RBE _{LET_d}	Rel. diff (%)	RBE _{spect.}	RBE _{LET_d}	Rel. diff (%)
172.76	1.07	1.07	0.02	1.09	1.09	0.22
170.05	1.09	1.09	0.02	1.10	1.10	0.18
167.34	1.12	1.12	0.04	1.12	1.13	0.22
164.63	1.21	1.21	0.38	1.23	1.23	0.10
161.92	1.37	1.36	0.64	1.37	1.37	0.16
159.23	1.45	1.45	0.18	1.42	1.43	0.26

LET_d. For measurement results, the relative differences between the values computed based on LET spectra and LET_d are below 0.26%. For MC simulation results, the differences are below 0.64%. Table 2 presents RBE values calculated for whole irradiation plans (SOBP, IMPT-A, IMPT-B, IMPT-C). For measurement results, the relative differences between the values computed based on LET spectra and LET_d are below 0.32%. For MC simulation results, the difference is even more minor (up to 0.05%).

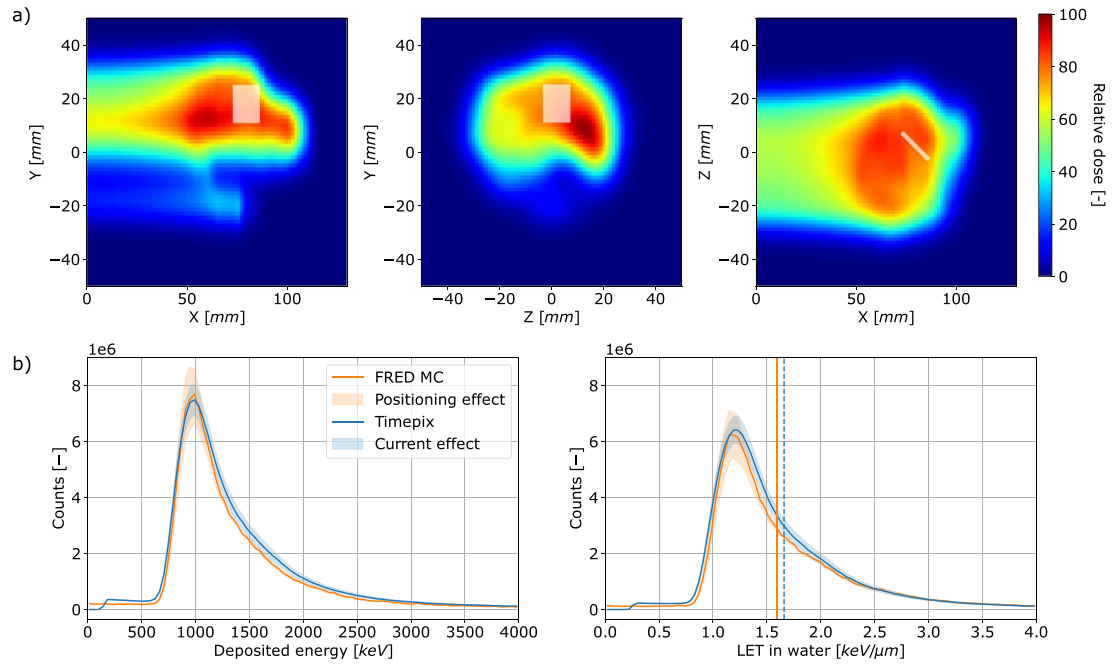


Figure 3. (a) Dose distribution simulated with FRED MC code for a selected field of IMPT plan with indicated sensor location (IMPT-A). The sensor thickness on the right panel is not to scale. (b) Energy deposition (left) and LET in water (right) spectra in the indicated position obtained based on measurements (blue) and MC simulations (orange). The vertical lines indicate the LET_d values.

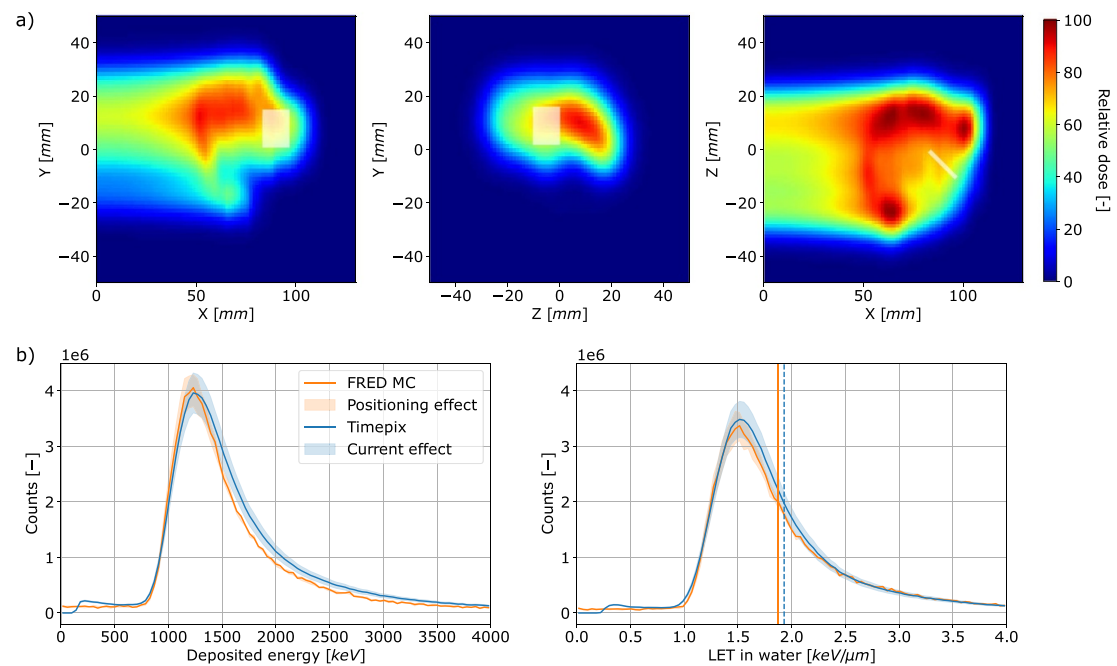


Figure 4. (a) Dose distribution simulated with FRED MC code for a selected field of IMPT plan with indicated sensor location (IMPT-B). The sensor thickness on the right panel is not to scale. (b) Energy deposition (left) and LET in water (right) spectra in the indicated point obtained based on measurements (blue) and MC simulations (orange). The vertical lines indicate the LET_d values.

4. Discussion

In this study, we developed a methodology for the experimental characterization of radiation quality in clinical proton therapy treatment plans. We analyzed and compared the energy deposition and LET spectra at selected measurement positions within the SOBP and IMPT fields against predictions of MC simulations.

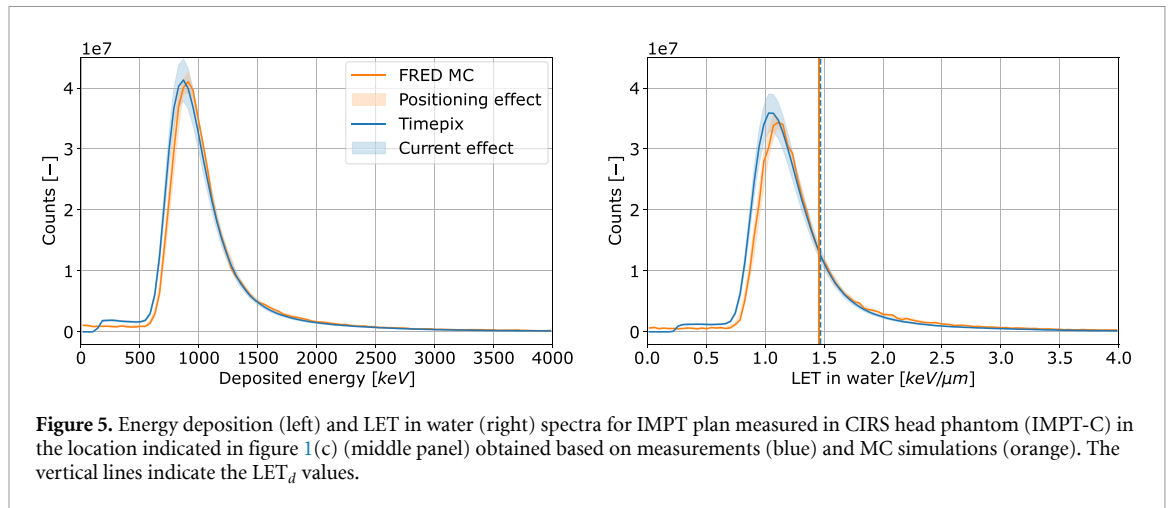


Table 2. RBE values computed based on LET spectra ($RBE_{spect.}$) and LET_d values (RBE_{LET_d}) with relative differences for MC simulations (FRED MC) and experimental results (Timepix) in SOBP and IMPT fields.

	FRED MC			Timepix		
	$RBE_{spect.}$	RBE_{LET_d}	Rel. diff (%)	$RBE_{spect.}$	RBE_{LET_d}	Rel. diff (%)
SOBP	1.08	1.08	0.00	1.10	1.10	0.21
IMPT-A	1.10	1.10	0.03	1.10	1.10	0.20
IMPT-B	1.12	1.12	0.04	1.12	1.12	0.18
IMPT-C	1.09	1.09	0.05	1.09	1.09	0.32

We considered the sensor positioning and stability of beam current, the source of the most significant uncertainty of energy, and LET spectra characterization (1 mm and 15% respectively). To evaluate the reliability of positioning, we conducted a robustness verification by simulating sensor lateral position shifts. The variable RBE values were computed using the Wedenberg model (Wedenberg *et al* 2013) based on LET spectra and LET_d for SOBP and IMPT plans.

In the presented measurement methodology, the spectra for individual layers were measured separately, providing the best single-particle statistics for a given layer, and then relatively normalized. The splitting of measurement for separate layers allowed presenting spectra for individual layers of the SOBP plan, including the low-energy ones in the distal fall-off of the Bragg Peak, and their impact on LET spectra in figure 2. For the SOBP plan, the peaks of measured and simulated energy deposition and LET spectra were found to be in excellent agreement. Likewise, in the case of the IMPT field, an agreement within the error bars was observed at the peak position of deposited energy and LET spectra. In a heterogeneous CIRS phantom, higher differences between LET_d values were observed for individual layers obtained based on measurements and simulations.

The mean relative difference between measurements and simulations for all single layers of SOBP and IMPT plans is about 5.1%. This marks a significant improvement compared to the study, where Timepix Minipix was applied to characterize single pencil beams, and the mean difference in LET_d was 17% (Stasica *et al* 2023). Despite generally superior detectable energy response, Timepix, operated in frame mode, is prone to signal overlaps that disturb the energy spectra, LET spectra, and average LET values. Another study found an agreement within 12% between frequency-averaged LET obtained based on Timepix measurements and TOPAS MC simulations for protons (Nabha *et al* 2022). In Félix-Bautista *et al* (2024), deviations below 7% were observed across a wide range of track-averaged LET values for single proton, helium, carbon, and oxygen beams obtained based on Timepix3 measurements and FLUKA MC simulations.

The energy correction functions proposed by Mihai *et al* (2025) allowed for reducing the nonlinear energy response of the detector that causes the energy underestimation in the high energy tail of the spectrum. For the SOBP plan, the energy correction resulted in the agreement in the tail region up to about 7000 keV, as visible in figure 2(b). Multiple factors, including temperature, aging of the detector, DACs settings, and the cross-talk effect, may influence the correction parameters, especially for the second correction function (see section 2.6), which has also been noted by Mihai *et al* (2025). Therefore, the discrepancies observed in the energy spectra, LET spectra, and thus LET_d values could be minimized even further by employing energy correction functions tailored specifically from measurements conducted with the exact detector and DACs settings utilized in this study.

The differences observed in LET spectra in the logarithmic scale may also be attributed to the charge-sharing effect caused by the lateral spread of charge carriers in the sensor (Campbell *et al* 2007). This effect becomes more pronounced with higher energy depositions. Currently, cluster morphology determined by the charge-sharing effect is not reflected in MC simulations. This effect can lead to the apparent elongation of the measured track for high-LET protons, resulting in an underestimation of the measured LET value compared to MC simulations. However, the impact of this effect on the track length is reduced in this work by utilizing a high threshold of 12 keV. Future efforts to address this problem could involve implementing a correction function for track estimation similar to the approach suggested by Granja *et al* (2021), but adapted for applied sensor and read-out settings, or by implementing charge-sharing in MC simulation utilizing the Allpix Squared package (Spannagel *et al* 2018), which will be explored in future work.

The larger relative differences were observed for the measurements in heterogeneous phantom compared to those in homogeneous ones. This can result from simplification related to representing the medium properties with a CT calibration curve. Also, the yields of nuclear reactions may not be reflected accurately enough in the MC simulations. Although there are significant differences in individual layers, the best agreement of LET_d for the combined spectra was achieved in this setup.

The comparison of RBE values derived using LET spectra and LET_d values in SOBP and IMPT conditions showed that the relative differences are less than 1% for both experimental and simulation results. Differences below 1% were also observed for single beams of various ions in Félix-Bautista *et al* (2024). Determining whether it has a clinical impact is out of the scope of this work. Currently, given the generally significant uncertainties related to experimental radiobiology and RBE modeling, direct incorporation of LET in treatment plan optimization in proton therapy is suggested (Paganetti and Giantsoudi 2018, Paganetti *et al* 2024). Thus, most of all, fine validation of LET values is desirable.

In this work, LET was assessed as the ratio of the energy deposited by a given proton to the track length for both measurements and simulations. While traversed distance in ICRU reports no 16 (ICRU 1970) and 85 (ICRU 2011) refers to the infinitesimal value, the track length measured and computed in this work is at a level of hundreds of micrometers. Also, while LET is fundamentally a deterministic (non-stochastic) quantity for a given material, particle type, and particle energy, as indicated in ICRU report no 98 (Braby *et al* 2023), LET determined in our work becomes a stochastic quantity characterized by a spectrum. This is because of the stochastic nature of radiation interactions (energy straggling) in the medium that leads to variations in the deposited energy and particle track length (Kolata *et al* 1968, Janni 1982, Selau *et al* 2021).

The primary limitation of the discussed methodology relates to the irradiation of IMPT plans with reduced beam current at the pA level required for the Timepix3 application. The current restrictions of the beam delivery system limit the irradiation time to one minute in the scanning controller diagnostics mode, which reduces the ability to extend the irradiation time for each spot. This restriction forces separate irradiation for each layer. Performing measurements for IMPT plans exhibiting substantial MU value variation across different spots can also be challenging. As the approach utilizes a constant beam current and varies the irradiation time instead of intensity modulation across spots, one must find a fair compromise between the desired measurement time and the statistical representation needed for spots with lower MU values. As the beam current level does not influence the LET spectra's shape, a software update enabling continuous irradiation with low beam current without the time constraints imposed by the beam delivery system would effectively facilitate the adoption of the proposed methodology.

Challenges in accurately evaluating the track length in the case of protons that stop in the sensor lead to overestimating the track length and underestimating the LET for these protons. Based on PSTAR data (Berger *et al* 2005), the maximum LET that can be measured with this methodology within 5% accuracy (relative difference) is about $18 \text{ keV } \mu\text{m}^{-1}$ in silicon ($10 \text{ keV } \mu\text{m}^{-1}$ in water), assuming CSDA, a proton's incident angle of 45° and correct energy measurement. For the incident angle of 45° protons of the energy below about $7.5 \text{ keV } \mu\text{m}^{-1}$ will stop in the sensor. For a 7 MeV proton at 45° LET obtained based on measurement (assuming the proton crossed the sensor) is $17.3 \text{ keV } \mu\text{m}^{-1}$ in silicon ($9.5 \text{ keV } \mu\text{m}^{-1}$ in water), and LET computed for true track length is $18.1 \text{ keV } \mu\text{m}^{-1}$ ($10.0 \text{ keV } \mu\text{m}^{-1}$ in water). Then, the relative difference with respect to the computations with the true track length is about 5%.

Non-tissue-equivalent sensitive volume of the Timepix detector and sensitive volume-based measurement (or voxel-based computation) are fundamental limitations for assessing LET and characterizing the radiation quality at a micro-scale level. The radiobiological effects that occur on a scale corresponding to the size of the cell nucleus (from a few to dozens of micrometers) will be better reflected by the lineal energy y measured with silicon or tissue-equivalent microdosimeters (Rosenfeld 2016, Parisi *et al* 2022a, Magrin *et al* 2023). Nevertheless, Timepix is the only commercially available active detector that provides an estimate of LET spectra and average LET values at a voxel size scale in silicon (Christensen *et al* 2024) that can be converted to water (Benton *et al* 2010).

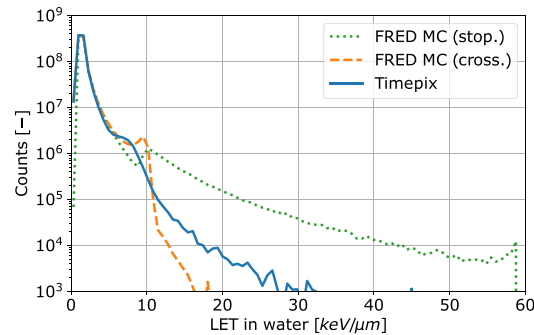


Figure 6. LET in water spectra for SOBP plan in a homogeneous phantom in the location indicated in figure 2(a) obtained based on measurements (solid blue line), and MC simulations with the track length computed mimicking the experimental approach (dashed orange line) and by taking into account stopping of the protons in the sensor (dotted green line).

We performed additional analysis of MC simulation results for SOBP to verify the impact of stoppers on LET spectra and average LET. Figure 6 presents a comparison of the LET spectrum for SOBP. The spectrum obtained based on MC simulation was computed taking into account the true track length, even if the proton stopped in the sensor. As predicted, there is a larger number of protons in the high-LET region. However, the differences occur in the region of a very low number of protons (more than two orders of magnitude lower than in the peak position). The spectra are presented without smoothing the tails, to better visualize the level of statistics in this region. For two layers of the lowest energy in the spectra, the relative differences in LET_d were at a level of 20%–30%, while for the layer of higher energies, the differences were lower than when assuming that the proton crosses the sensor. As a result, for the weighted average of LET_d for the combined spectra, the resulting difference between measurements and simulations (0.65%) is even lower than when assuming that the proton crosses the sensor (3.95%).

This introduces a need for developing post-processing techniques to identify stopping particles and accurately determine their actual track lengths. Addressing this in the future could involve advanced cluster morphology simulations using, e.g. the Allpix Squared package (Spannagel *et al* 2018) combined with AI-driven recognition methods. Nevertheless, as the presented approach aims to validate MC simulations, the analysis of simulation results was performed to correspond to the measurement conditions. In MC simulation analysis, it was assumed that the protons were crossing the sensor. Thus, this limitation of Timepix3 does not impact the agreement with simulation results.

Given the compact design and commercial availability of the Timepix3 detector, it holds a promise for broad application across proton therapy centers. Potential implementation of the detector for commissioning quality assurance of treatment plans in terms of LET, or at least in research studies confronting simulations and experimental data, could increase confidence in LET-based treatment planning. In future applications, Timepix2 (Wong *et al* 2020, Bergmann *et al* 2022) or Timepix4 (Llopart *et al* 2022) could also be considered, as both detectors offer adaptive gain, allowing a superior energetic response. Timepix4 offers about ten times higher maximum data rate in data-driven mode, while Timepix2 can potentially operate dead time-free in the frame mode. First measurements utilizing the Timepix2 detector in the clinical beam intensities were performed (Oancea *et al* 2024).

Given current trends toward including LET as a radiation quality factor in treatment planning optimization, there is a need for fast, miniaturized, and commercially available experimental validation solutions. The presented methodology and results demonstrated that the Timepix3 detector can be used for LET verification in IMPT patient treatment plans offering spectra-sensitive single proton tracking, quasi-continuous measurement, and a broad dynamic range.

5. Conclusions

In this study, we introduced a methodology for evaluating radiation quality in proton therapy, focusing on energy deposition and LET spectra analysis within homogeneous and clinical IMPT dose fields in homogeneous and heterogeneous phantoms. Key outcomes include an overall agreement between measurement results and MC simulations, underscoring the validity of the proposed setup. Further accuracy improvements with tailored detector-specific corrections were suggested. The presented approach and analysis results indicate the applicability of Timepix3 for evaluating LET spectra in IMPT fields.

Data availability statement

The data that support the findings of this study are openly available at the following URL/DOI: <https://doi.org/10.48733/ccb.25.017>.

Data will be available from 18 December 2025.

Conflict of interest statement for all authors

Cristina Oancea and Carlos Granja are employed by Advacam. The remaining authors have no conflict of interest to disclose.

Funding statement

The work of PS, DK, AR, MR, and JG was supported by the National Center for Research and Development (NCBiR) within Grant No. LIDER/43/0222/L-12/20/NCBR/2021. PS acknowledges the financial support provided by the Polish National Agency for Academic Exchange NAWA under the Programme STER-Internationalisation of Doctoral Schools, Projects No. PPI/STE/2020/1/00020 and BPI/STE/2023/1/00027/U/00001. DK, AR and MR acknowledge the financial support provided by the Polish Ministry of Education and Science within Grant No. NdS/544748/2021/2021. DK and MR acknowledge the financial support provided by the Polish Ministry of Education and Science within Grant No. NdS-II/SP/0292/2024/01. The work of CG at VSB TU Ostrava was supported by the Project SGS SP 2024/016 at the VSB Ostrava financed by the Ministry of Education, Youth and Sports of the Czech Republic.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used Grammarly in order to verify spelling and improve readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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