



## Original paper

# Dosimetric and temporal beam characterization of individual pulses in FLASH radiotherapy using Timepix3 pixelated detector placed out-of-field

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## ABSTRACT

**Background:** FLASH radiotherapy necessitates the development of advanced Quality Assurance methods and detectors for accurate monitoring of the radiation field. This study introduces enhanced time-resolution detection systems and methods used to measure the delivered number of pulses, investigate temporal structure of individual pulses and dose-per-pulse (DPP) based on secondary radiation particles produced in the experimental room.

**Methods:** A 20 MeV electron beam generated from a linear accelerator (LINAC) was delivered to a water phantom. Ultra-high dose-per-pulse electron beams were used with a dose-per-pulse ranging from 1 Gy to over 7 Gy. The pulse lengths ranged from 1.18  $\mu$ s to 2.88  $\mu$ s at a pulse rate frequency of 5 Hz. A semiconductor pixel detector Timepix3 was used to track single secondary particles. Measurements were performed in the air, while the detector was positioned out-of-field at a lateral distance of 200 cm parallel with the LINAC exit window. The dose deposited was measured along with the pulse length and the nanostructure of the pulse.

**Results:** The time of arrival (ToA) of single particles was measured with a resolution of 1.56 ns, while the deposited energy was measured with a resolution of several keV based on the Time over Threshold (ToT) value. The pulse count measured by the Timepix3 detector corresponded with the delivered values, which were measured using an in-flange integrating current transformer (ICT). A linear response ( $R^2 = 0.999$ ) was established between the delivered beam current and the measured dose at the detector position (orders of nGy). The difference between the average measured and delivered pulse length was  $\sim 0.003(30)$   $\mu$ s.

**Conclusion:** This simple non-invasive method exhibits no limitations on the delivered DPP within the range used during this investigation.

## 1. Introduction and goals

FLASH radiation therapy, a novel cancer radiotherapy technique, has emerged as a promising modality for achieving enhanced tumour control, while minimizing damage to normal tissue, [1]. This innovative approach maintains the total prescribed dose typical of conventional radiation therapy but it is delivered at ultra-high dose rates, exceeding  $40 \text{ Gy}\cdot\text{s}^{-1}$  two orders of magnitude higher than the  $<0.1 \text{ Gy}\cdot\text{s}^{-1}$  dose rate typical for conventional methods. The effectiveness of the FLASH effect has been validated across various particle types, including electrons, protons, and photons [2–4].

In the context of FLASH radiotherapy, where irradiation times are remarkably short—often less than 100 ms, and frequently within the range of a few  $\mu$ s—precise characterization of the irradiation time becomes crucial for accurately defining dose and rate. The necessity for such precision underscores the importance of the quantification of the number of pulses delivered and the dose delivered by each pulse. Factors such as instantaneous dose rate, dose-per-pulse, and the number of pulses delivered have been identified as critical determinants impacting cellular exposure to free radicals [5–7].

Existing techniques for pulse duration measurements, reliant on prompt  $\gamma$ -rays, secondary thermal neutrons, or scattered photons,

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exhibit limitations, including restricted time resolution (on the order of 100 ns or even up to a few  $\mu$ s for scintillator-based methods due to photomultiplier tube limitations) [8]. Pulse length measurements based on thermal neutrons reported delays [9], but the irradiation plan in UHDR proton therapy was measured successfully based on secondary radiation created distal to the Bragg peak [9]. Compared to Charyyev et al. 2023, the novelty of this study consists in proving suitability for single pulse characterization of electron beams using both dosimetric and temporal information. Kanouta et al. [10] utilized an inorganic scintillating crystal-based detector to assess irradiation time in FLASH proton beams. They compared their measurements with output from log files, focusing on irradiation times larger than the millisecond level. The detector was positioned 1 cm downstream of the irradiated volume. However, achieving the necessary time resolution for ultra-high dose-per-pulse (UHDPP) beams, particularly when employing DPP techniques to achieve the FLASH effect, requires resolutions on the order of nanoseconds. In contrast, Kleczek et al. [11] employed long silicon strip detectors based on CMOS technology, offering a time resolution of approximately 80 ns.

In FLASH electron beams, several groups used various detection systems for beam characterization and monitoring of single pulses such as: metal–oxide–semiconductor cameras, ionization chambers, diamond detectors, scintillator detectors, and others [12–14]. Ionization chambers are widely used for reference dosimetry in radiation therapy. As outlined by McManus et al. [15], ionization chambers face substantial inefficiencies when exposed to ultra-high dose rates. In UHDPP conditions, such as those encountered in FLASH-RT, they suffer from significant charge collection efficiency (CCE) degradation due to high dose rates, leading to severe saturation and ion recombination. Recent studies have focused on optimizing ion chamber design to address these limitations. Liu et al. [16] have shown that reducing electrode spacing and increasing electric field strength significantly improve CCE under UHDPP conditions. Their prototype ion chambers demonstrated a CCE of  $\geq 95\%$  for doses per pulse up to 5 Gy, making them more suitable for FLASH dosimetry compared to conventional ion chambers. Recent advancements in ionization chamber design, such as those described by [49], propose the use of a gas-filled chamber with variable pressure (ALLS chamber). This approach, which utilizes a noble gas like argon to prevent recombination, allows for dose-per-pulse measurements of up to 40 Gy with an accuracy of 1 %. The adjustable pressure inside the chamber ensures minimal perturbation of the electric field, thereby avoiding recombination and discharge issues, which have been significant obstacles in conventional setups. Other promising devices have been recently developed and tested, such as the ultra-thin ionization chamber studied by Gomez Rodriguez et al. [17], which offers improved charge collection efficiency by minimizing recombination effects.

Semiconductor-based detectors, including silicon carbide (SiC) and diamond detectors, have also been investigated for FLASH-RT applications due to their high temporal resolution and robustness against recombination effects. These detectors exhibit a linear dose response and are capable of providing real-time measurements, even under high-dose-rate conditions. Silicon carbide detectors, for example, have shown great potential in handling ultra-high dose-rate conditions. According to Milluzzo et al. [18], these detectors exhibit a linear response up to 21 Gy per pulse and can withstand instantaneous dose rates of up to 5.5 MGy/s, making them suitable for both dose-per-pulse and instantaneous dose rate measurements in FLASH radiotherapy. SiC detectors can achieve time resolutions comparable to those of silicon-based detectors, with resolutions on the order of nanoseconds [19]; [48] successfully utilized SiC diode dosimeters for in-beam measurements of dose and time structure. Notably, the temporal response of SiC detectors exhibits some anomalous features for time measurements. The FLASH diamond detector, developed by Marinelli and Verona Rinati et al. [20], was specifically designed for high-dose-rate environments in FLASH radiotherapy. Scintillator-based systems have been proposed for FLASH dosimetry, offering high temporal resolution and the ability to

reconstruct the temporal shape of pulses in UHDPP beams. Scintillators, coupled with fast photodetectors such as silicon photomultipliers (SiPMs), have shown promise in resolving the pulse structure of UHDPP beams, providing real-time dosimetric information. Poirier et al. [21] demonstrated the successful use of plastic scintillators for online dosimetry in FLASH-RT, showing their potential for precise time-resolved measurements in clinical applications. Medina et al. successfully used silicon sensor as possible candidates for UHDR beam monitoring [43].

The abovementioned detection systems are used for in beam measurements. Ideally non-invasive beam monitoring systems should be used in UHDPP beam delivery for FLASH radiotherapy, where accurate real-time monitoring is essential while avoiding perturbation of the primary radiation field. Beam Current Transformers (BCTs) have been successfully implemented in this context to monitor beam current without direct interaction with the radiation. Oesterle et al. [22] demonstrated the successful use of a BCT on a medical pulsed electron beam LINAC for FLASH-RT. This system provided reliable, real-time monitoring of key beam parameters, including pulse width, pulse repetition frequency, and total charge. The BCT avoided the saturation effects commonly encountered with conventional transmission chambers. Despite these advantages, our recent experience has shown limitations in the use of ACCTs systems, particularly in dose accuracy, where beam characteristics within the accelerator may lead to non-linearities in the detected signal. We propose incorporating the Timepix3 detector as a complementary system for beam monitoring. The Timepix3 detector offers high temporal resolution and the capability to measure individual particle events, providing enhanced precision in dose measurements.

In this article, a novel technique for pulse count measurements based on the generation of secondary radiation particles during UHDPP pulses beam inside the experimental room was developed. Leveraging the high time resolution of the AdvaPIX Timepix3 detector (from Advacam s.r.o.) set at 1.56 ns for single particle detection, our method enables online, non-invasive, non-destructive characterization of beam time structure. The detection principle involves tracking [23] secondary radiation in the silicon sensor of the detector [24], allowing precise quantification of both the number of pulses delivered and the dose delivered. Importantly, the detector's placement at a distance of 2 m outside the beam path mitigates saturation effects which is a common issue in FLASH environments and circumvents limitations inherent in alternative techniques.

Experimental validations were conducted at the Metrological Electron Accelerator Facility (MELAF) of the Physikalisch-Technische Bundesanstalt (PTB) using the research linear accelerator (LINAC) [25]. This accelerator is capable of delivering electron beams at 20 MeV at a pulse rate frequency of 5 Hz at a range of instantaneous dose rates and offers the possibility to vary the pulse length. The goal of this investigation was to measure the number of delivered pulses, their corresponding pulse length and pulse structure, and to demonstrate a linear response between the detector dose delivered to silicon and the delivered beam current measured using in-flange integrating current transformer. The number of pulses was measured correctly using the AdvaPIX Timepix3 detector and a clear linear trend between delivered beam current and measured dose to silicon was observed. No significant discrepancy between the measured and delivered pulse lengths was observed. The nanostructure of the pulse, measured using the AdvaPIX Timepix3 detector, was consistent with the expected shape from another publication [26]. This demonstrates the efficacy of our proposed technique for out-of-field monitoring in the context of FLASH electron fields.

## 2. Materials, methods, and measurements

### 2.1. AdvaPIX Timepix3 detector

The AdvaPIX Timepix3 detectors, shorted to TPX3 detector in this

manuscript [27], used in this study were provided by ADVACAM whereas the Timepix3 chip was developed within the Medipix Collaboration at CERN. The detector's sensors were manufactured from silicon (Si). The ASIC read-out chip contains a matrix of  $256 \times 256$  pixels (total 65,536 independent channels, where one-pixel size corresponds to  $55 \times 55 \mu\text{m}^2$ ) and an active sensor area of  $14.08 \times 14.08 \text{ mm}^2$  for a total sensitive area of  $1.98 \text{ cm}^2$  [27]. Timepix3 provides two signal channels per pixel which can be set in various modes such as energy and counting, or energy and time of interaction at the pixel level. For this experiment, the detector's operation mode was set to data-driven to measure simultaneously the *time of arrival* and *deposited energy* of individual particles reaching the sensor. The time of arrival (ToA) can be identified with a resolution of 1.56 ns, whereas the Time over Threshold (ToT) of the respective pixel, and consequently the deposited energy, can be measured with energy resolution in orders of several keV [28].

For this study, the Si sensors had a thickness of  $1000 \mu\text{m}$  and it was calibrated to a minimum threshold of 5 keV and the bias was set to maximum to have a fully depleted volume (+350 V for the  $1000 \mu\text{m}$  Si sensor). The per-pixel threshold calibration and per-pixel energy calibration were performed at Advacam Laboratory [29]. The per-pixel calibration procedure [29] relies on measurements of X-ray fluorescence photons resulting from excitation of  $^{111}\text{In}$  (24.7 keV),  $^{55}\text{Fe}$  (5.9 keV), low-energy gamma rays from radionuclide source of  $^{241}\text{Am}$  (59.5 keV). These measurements serve as the basis for the subsequent derivation of calibration function parameters through the fitting of the ToT spectral peaks that have been measured. By deriving the appropriate calibration matrices and applying them to the measured data, one can obtain the per-pixel energy deposited by each detected particle ranging, in this case, from 5 keV to over 200 keV. As the dimensions of each pixel are known, therefore, the dose delivered to silicon can be determined.

## 2.2. Radiation beam and detector setup

The investigation was carried out at PTB using the research LINAC of MELAF which is described in detail by Schüller et al. [25]. The research LINAC is capable of delivering ultra-high dose-per-pulse electron beams [30]. A primary 20 MeV electron beam passed through a 0.1 mm Cu exit window before being intercepted by the water tank ( $30 \times 30 \times 30 \text{ cm}^3$ ) positioned 50.0(3) cm downstream as illustrated in Fig. 1a. The polymethylmethacrylate (PMMA) water tank front wall was 9.98 mm thick.

The LINAC output was monitored by an in-flange ICT (Bergoz, Saint-Genis-Pouilly, France). The ICT's signal can measure the total charge of individual beam pulses [31], which was measured to be between 15 nC and 108 nC during this investigation. Two LINAC configurations of the beam were used: namely "0" and "2", corresponding to an approximate delivered mean instantaneous dose rate, average dose rate within the pulse, of  $0.8 \text{ Gy}\cdot\mu\text{s}^{-1}$  and  $2.6 \text{ Gy}\cdot\mu\text{s}^{-1}$  respectively [30]. The dose-per-pulse (DPP) used during this investigation corresponds to a macroscopic dose rate between  $5 \text{ Gy}\cdot\text{s}^{-1}$  to  $32 \text{ Gy}\cdot\text{s}^{-1}$  at a constant pulse rate frequency of 5 Hz. A voltage-controlled monostable multivibrator was introduced between the LINAC gun's original triggering circuit and the steering grid to modulate pulse length [32]. The pulse length was varied between  $1.18(4) \mu\text{s}$  to  $2.88(19) \mu\text{s}$  during this investigation by step of  $0.28(5) \mu\text{s}$  for both LINAC configurations, leading to a total of 14 measurement campaigns.

It is important to note that the operational mode of the Timepix3 detector is constrained by a limit of  $40 \times 10^6$  pixel hits per second, corresponding to a maximum flux per pulse of  $2 \times 10^6$  particles·cm $^{-2}$  to  $10 \times 10^6$  particles·cm $^{-2}$  depending on the given type and size of the detected particles. Therefore, the particle flux at the detector level must be neither too small to obtain sufficient data, nor too large to distinguish individual particle tracks. Thus, in this investigation, the Timepix3 detector was positioned 200 cm laterally (parallel) from the beam exit window, as shown in Fig. 1. The detector was housed within a lead bunker with a 5 cm wall thickness as illustrated in Fig. 1e). A 2 cm wide window was set up in the bunker facing the primary beam.

Despite the delivery of a dose rate exceeding the order of a few Gy per pulse to the water phantom at the reference point of measurement [30], the scattered dose at the detector level remained within the order of nGy per pulse, facilitating the detection of individual particles. The out-of-field setup was designed to correlate out-of-field dose measurements from the TPX3 detectors with the in-beam line primary beam current measured using the ICT. In the experimental setup, the beam was directed at a water phantom as shown in Fig. 1a). Comprehensive descriptions of the beam parameters for each setup are presented in Supplementary Data.

## 2.3. Pulse time structure and absorbed dose measurements in silicon

The incident primary beam, upon exiting the beam pipe, interacts with its surrounding material and the experimental room itself (walls, flooring, etc.), thus producing secondary radiation that scatters from diverse directions [33]. Given the sensitivity of the semiconductor Timepix3 chip and its temporal resolution, individual tracks of the secondarily generated particles can be recorded and discriminated in time on the order of nanoseconds. This capability persists even when the detector is positioned at 2 m from the LINAC exit window, where the flux of scattered particles significantly diminishes compared to the primary beam. This unique feature facilitates the investigation of the primary beam time structure. A series of measurements were conducted with both LINAC configurations "0" and "2" for a range of pulse lengths as outlined in Table 1 in Supplementary Data. For each measurement, the number of pulses delivered was compared with the number of pulses measured using the ICT, which was on average 20(2) pulses. In addition, a 100 s beam delivery was measured with the aim of determining the pulse rate frequency to compare it with the nominal value of 5 Hz.

The secondary radiation detection under study enables not only the discrimination and quantification of individual pulses but also the measurement of the pulse temporal duration. Finally, the measured dose-per-pulse can be related to the delivered beam current. As mentioned above, the energy deposited in the silicon sensor can be determined from the particle tracks. Since the silicon mass of the sensor is known, the absorbed dose (D) in silicon can be determined using the following formula:

$$D = \frac{dE}{dm}$$

expressed in gray [Gy], where  $dE$  represents the sum of deposited energy (integrated energy deposited by a single pulse) in the selected area of the sensor and  $dm$  is the mass of the selected area of the sensor (the sensitive volume). The uncertainty of the absorbed dose in silicon measurement includes the uncertainty of the deposited energy measurement and the mass (from sensor thickness and area).

## 3. Results

### 3.1. Particle tracking of secondary radiation in silicon

Fig. 2 displays the detection and visualization of single particle tracks, referred to as pixelated clusters, within the detector sensor in the radiation field resulting from the scattered secondary radiation particles in the experimental room, induced by a primary 20 MeV electron beam at UHDP. The figure displays the data from the measurements performed at the low and high DPP regime, using the LINAC configuration "0" and "2" with a pulse length of  $2.88(19) \mu\text{s}$ .

At these LINAC configurations, the DPP of 2.5 Gy and 7.5 Gy, respectively, are expected at the reference depth in the water tank for a pulse length of  $2.88 \mu\text{s}$ . Since the detector was positioned out-of-field, the measured dose rate was nine orders of magnitude smaller, i.e. nGy, and therefore it was possible to distinguish individual particles. Through pattern recognition of the single pixelated tracks utilizing the

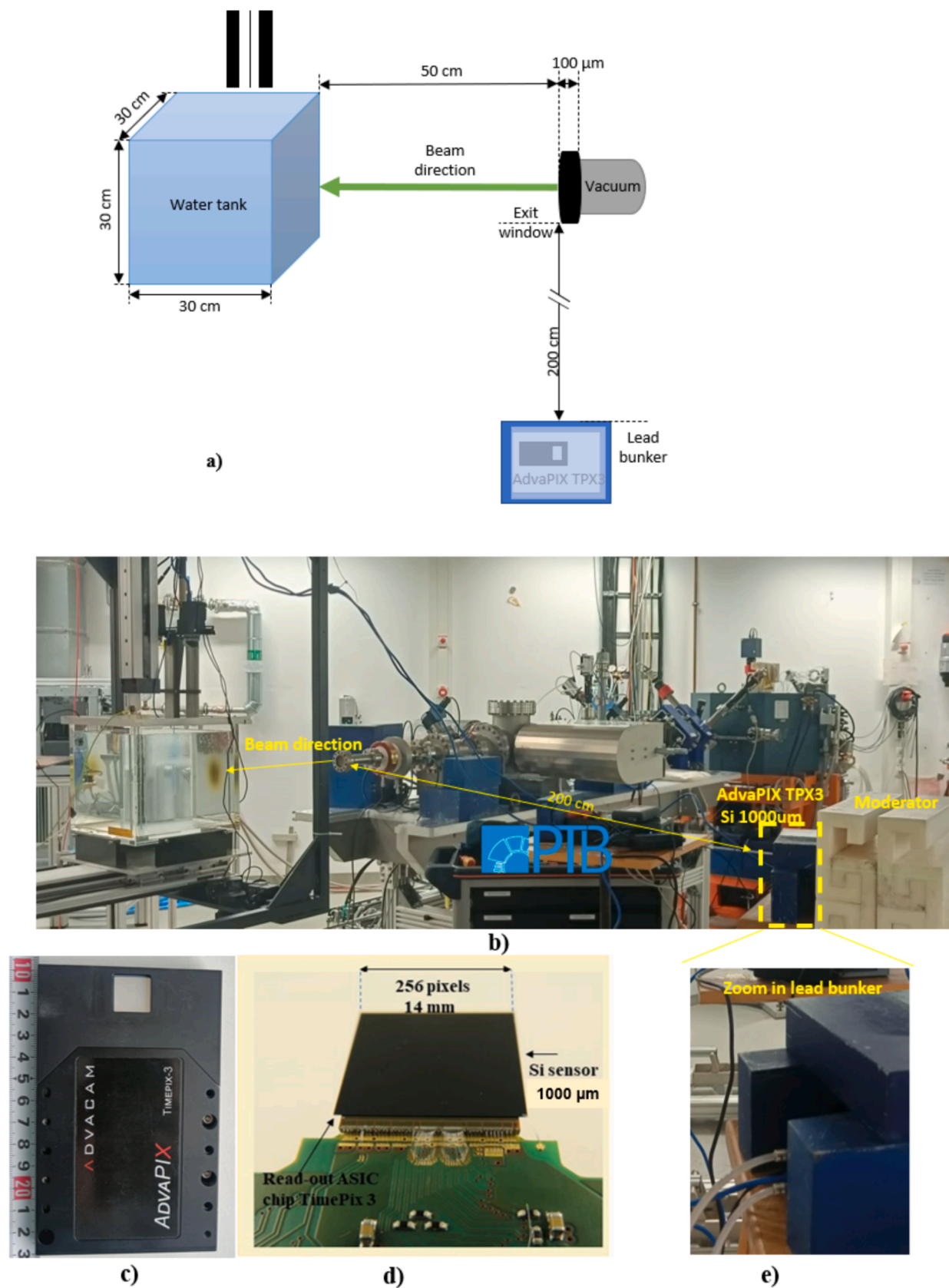


**Fig. 1.** a) schematic representation of the experimental setup b) picture from the experimental room, c) advapix tpx3 detector, d) its asic chip and silicon sensor of 1000  $\mu\text{m}$  thickness, and e) the detector was placed in a lead bunker.

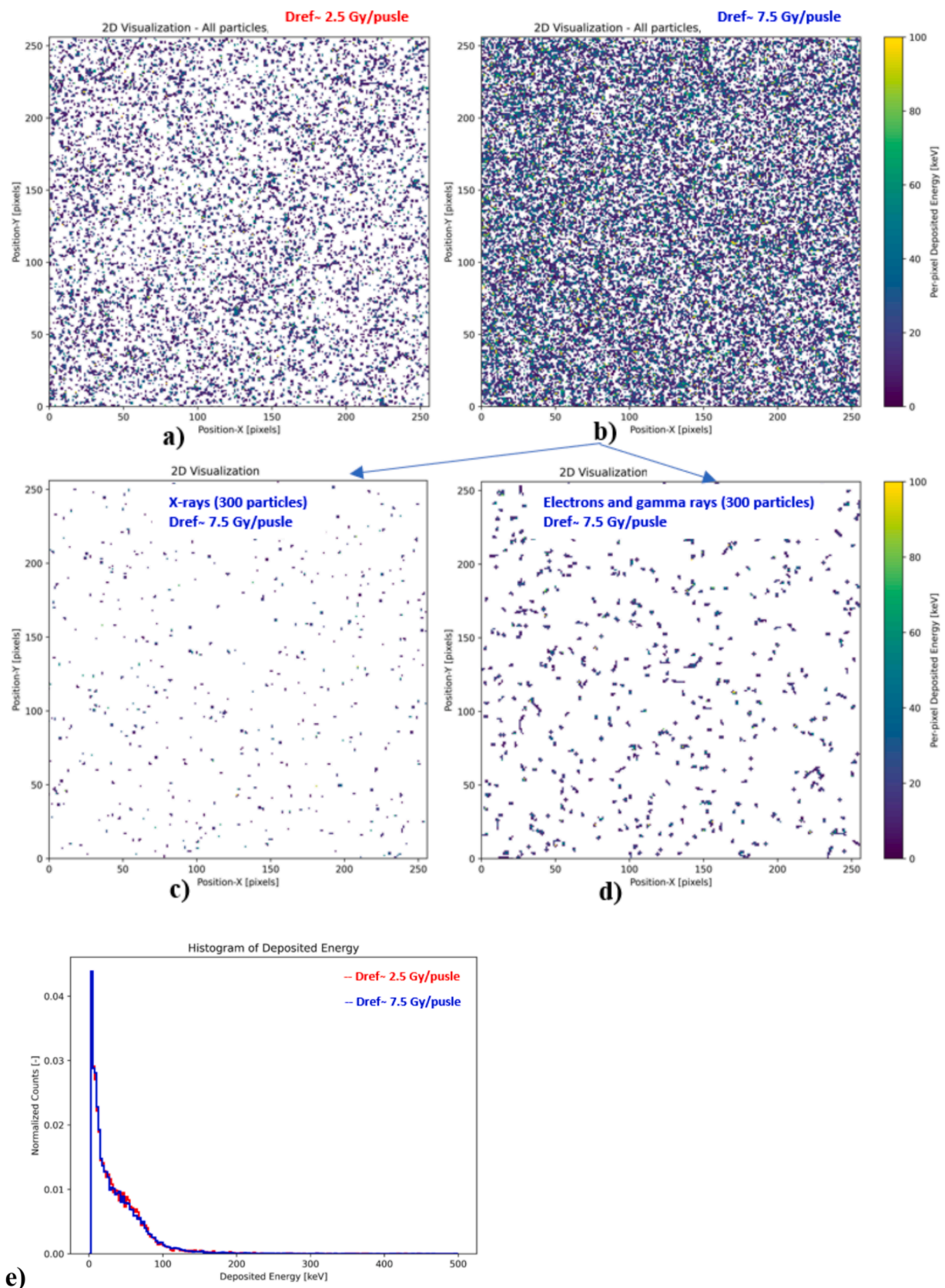


**Fig. 2.** A), b) visualization of the detected secondary radiation particles. integrated deposited energy maps are shown for all delivered 20 pulses measured. radiation field decomposition into two classes of particles for data from figure b): c) low-energy x-rays (below 30 keV) and d) electrons and gamma rays (above 30 keV). e) The normalized histogram of deposited energy spectra of measured single particles from campaigns 14 and 7.

Clusterer software [34,35], detailed spectral and tracking information is derived with high resolution. The 2D integrated deposited energy maps in Fig. 2a) and b) contain data corresponding to all 20 pulses delivered. As seen in Fig. 2e), energy spectra exhibit the same shape for both LINAC configurations. Furthermore, deposited energy in silicon can be converted into dose [36].

Based on pattern recognition algorithms and the track morphology [37,38], a mixed field of particles is observed as shown in Fig. 2, and it can be decomposed into two classes: x-rays with energy roughly below 30 keV (cluster size < 5 pixels, see Fig. 3d) and a mix of electrons and  $\gamma$ -rays with energy roughly above 30 keV (cluster size  $\geq 5$ , see Fig. 3e). The cluster size interval which separates x-rays from other particles was determined based on measurements using an x-ray tube. The 300 pixelated clusters are displayed in each of Fig. 2c) and 2d) to visualize radiation field components. Note that the latter class presented in Fig. 2e) also contains both electrons and gamma rays resulting from neutron interactions inside the experimental room or in the silicon sensor. In Fig. 2e is shown the deposited energy spectra of detected particles at the detector's position for two different delivered doses, exhibiting the same shape. The ability to detect and analyze these spectra provides an additional layer of quality assurance, particularly important in UHDP beams, where energy spectrum instabilities may occur.

Fig. 3 shows the time evolution of both the measured flux and DPP of the scattered radiation field at the out-of-field position of the Timepix3 detector for the same LINAC configuration as in Fig. 2. The results are provided for a sequence of 20 pulses, representing 4 s of beam-on time. At the detector level, a particle flux per pulse of 191(11) particles·cm<sup>-2</sup>·s<sup>-1</sup> and a dose-per-pulse of 4.961(15) nGy were measured for the LINAC configuration "0". With the LINAC configuration "2", i.e. for a beam current three times greater, a flux of 621(25) particles·cm<sup>-2</sup>·s<sup>-1</sup> and a dose-per-pulse of 15.373(35) nGy were measured at the detector level.

### 3.2. Out-of-field dose response in UHDP beams

To examine the TPX3 detector dose response, the total number of primary electrons accelerated was gradually increased for both LINAC configurations, namely "0" and "2", by increasing the pulse length from 1.18(4)  $\mu$ s to 2.88(19)  $\mu$ s. In Fig. 4, the DPP measured by the TPX3 detector in the Silicon sensor as a function of the total charge accelerated measured by the ICT is presented. A linear relationship with  $R^2 \sim 1$  between the delivered beam and the corresponding measured DPP at the detector's location, i.e. 200 cm lateral to the beam exit window, is found.

As shown in the lower panel of Fig. 4, no particular trends are

observed between the DPP measured from the TPX3 detector and the number of charges accelerated in the beam line. All 14 measurement points are within  $k = 3$  from the linear fit as shown in the lower panel. Here, a linear relationship was expected between the out-of-field dose measurement and the number of particles accelerated since it is the secondary radiation that is measured rather than the primary beam. Therefore, minor beam divergence change [39] wouldn't affect the linear relationship between the number of particles accelerated and the out-of-field dose measured. In addition, the beam intensity was changed mainly by modifying the pulse length and not the instantaneous dose rate, which is known to exhibit a linear behaviour between charge accelerated and dose delivered [32].

### 3.3. Pulse count and pulse rate frequency

In the designed setup and method, the high-time resolution of the TPX3 detector was utilized to count the delivered pulses. For all the measurement campaigns, the number of pulses measured by the TPX3 detector was exactly the same as measured with the ICT. The pulse frequency for the 14 measurement campaigns was determined to be 4.9996(4) Hz.

Fig. 5 illustrates the particle counts as a function of time for the 100 s long measurements campaign with a delivered pulse length of 2.39(12)  $\mu$ s. The acquired particle count was binned into equal time intervals, each having a length of 1.56 ns corresponding to the time resolution of the detector. Throughout the entire measurement, individual pulses were distinctly identified, as shown by the selection of two 5-second zoomed-in windows situated near the beginning and the end of the campaign measurement. For every campaign, including the 100 s long one, the pulse frequency was calculated by dividing the measured number of pulses by the time difference between the initiation of the first and the last recorded pulse.

### 3.4. Pulse length measurement

For each pulse, the pulse length was determined from the measured data, which, although measured continuously over time, is binned into time intervals of 100 ns to ensure at least several tens of counts per bin. The pulse length was defined as the time elapsed between the two points where the number of counts reached 50 % of the average pulse intensity, see illustration in Fig. 6 for one selected pulse. Observe that the tail at the end of the pulse is longer than at the beginning, possibly due to a delayed neutron signal.

Measured pulse lengths for all measurement campaigns, 14 in total, as a function of delivered pulse lengths are shown in Fig. 7. The

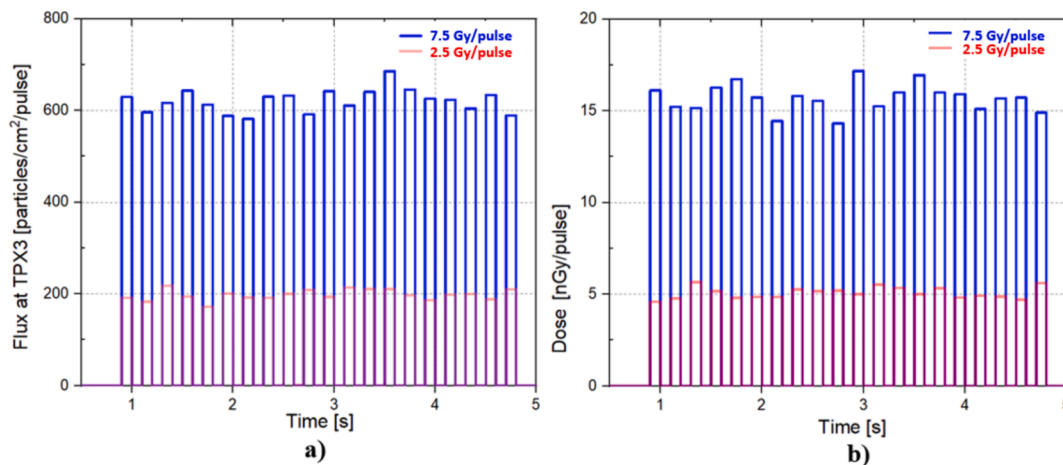


Fig. 3. Evaluation of scattered radiation field at the TPX3 detector out-of-field position. Measured (a) particle flux and (b) DPP in the TPX3 detector are shown for the same LINAC configurations as in Fig. 2. Results are given for 20 pulses (corresponding to 4 s of beam-on irradiation).

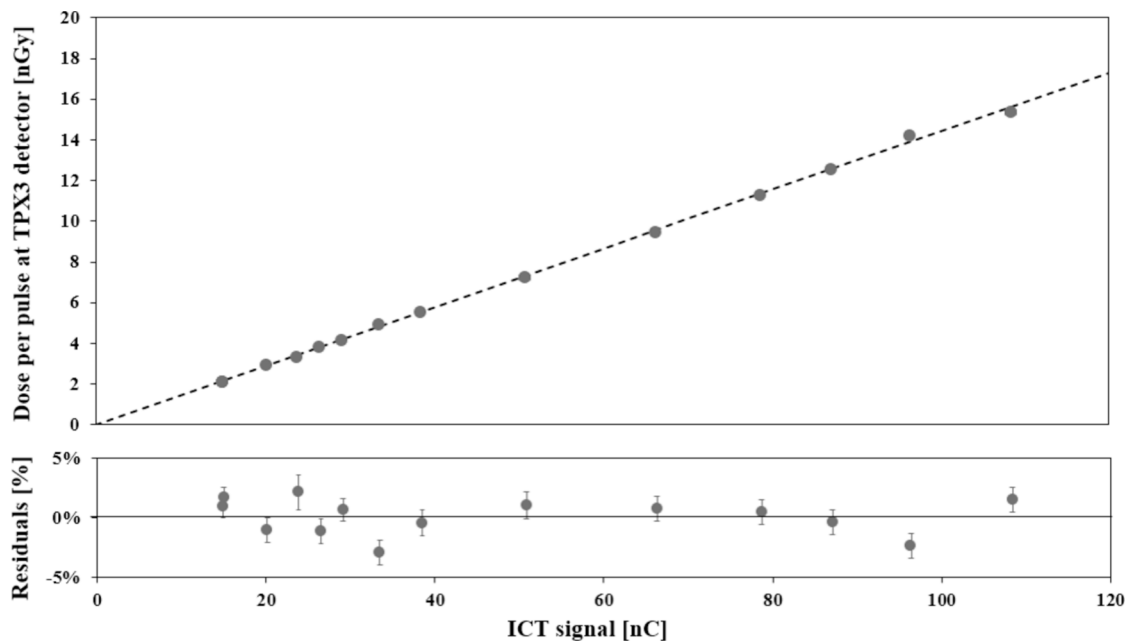


**Fig. 4.** DPP measurement with TPX3 detector as a function of the beam delivered monitored by the ICT. The linear regression coefficient of determination is calculated to be  $R^2 \sim 1$ . The lower graph shows the residual from the linear fit. The error bar represents  $k = 1$ .

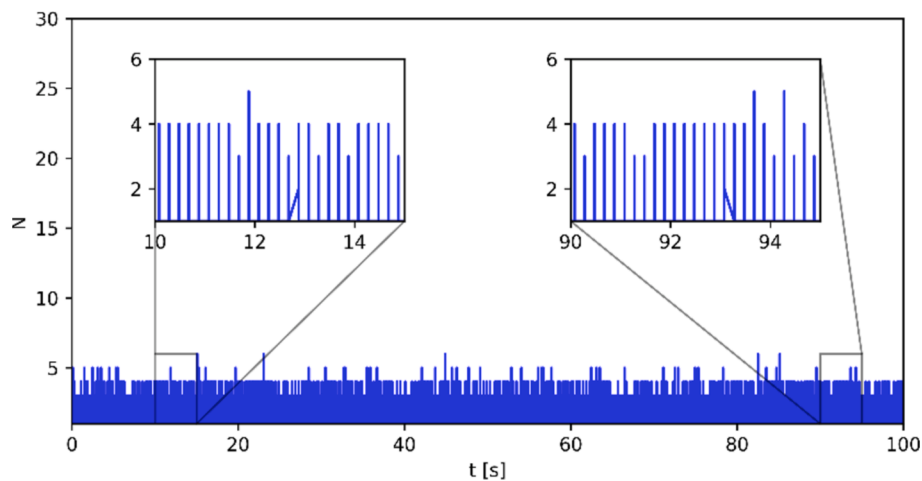


**Fig. 5.** Out-of-field scattered particle count generated by UHDP electron beams as measured by the TPX3 detector. The zoomed-in windows with 5 s time intervals allow for visualization of individual pulses.

measured pulse lengths from the Timepix3 detector are consistent with the expected value from the LINAC configuration used during the 14 different measurement campaigns. A non-significant difference of 0.003 (30)  $\mu$ s between the measured and expected pulse length was observed.

### 3.5. Pulse nanostructure measurement

Utilizing the TPX3 high-time resolution, it was possible to observe the pulse shape time resolution in the nanostructure scale. In Fig. 8, the measured average temporal pulse structure across various pulse lengths is presented for both LINAC configurations. The nanostructure of the pulse was determined using binned time intervals of 200 ns and 100 ns, for LINAC configuration “0” and “2” respectively, to ensure a minimum of tens counts per bin. As shown in Fig. 8, the delivered pulses do not maintain a constant count rate but rather possess a distinct temporal structure. This behaviour was also observed during another investigation, Fig. 6 of Paz-Martin et al. [26]. Despite variations in pulse length, the temporal structure remains remarkably consistent throughout, albeit

interrupted at the demarcation of each pulse length. Such consistency between varying pulse lengths is more pronounced for the LINAC configuration “2” due to the better stability of the measured pulses from a higher dose rate.

## 4. Discussions

### 4.1. Establishment of QA methods

When looking for a robust non-invasive quality assurance (QA) method for UHDP, three key parameters were systematically investigated: dose per-pulse measurements, number of delivered pulses, and pulse length duration. The detailed examination of such quantities involved measurements using a single high-sensitivity semiconductor detector with a Timepix3 chip without collimators, which facilitated precise measurements even positioned at 200 cm lateral distances parallel from the primary beam.

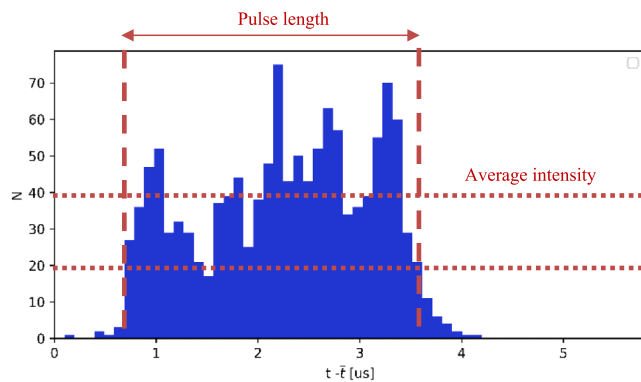


**Fig. 6.** The measured particle count for one selected pulse from campaign number 7 as a function of time is shown with the pulse's initiation at  $\bar{t}$  4s. The measured data were binned into time intervals of 100 ns. The dotted horizontal lines mark average pulse intensity and 50 % of average pulse intensity. Vertical dashed lines indicate the start and the end of a pulse.

#### 4.1.1. Dose-per-pulse measurements

The linear response of the TPX3 detector was demonstrated by comparing the dose delivered to the silicon-sensitive volume with the number of charges accelerated which was measured using an in-beam-line monitor, an ICT. It can be therefore argued that the TPX3 detector can be used as a non-invasive real-time dose-monitoring system since the number of secondary particles generated is in direct correlation with the beam intensity, and consequently, the dose delivered at the reference position of measurement. The presented method for dose-per-pulse measurements is suitable for quality assurance. However, since the detector measures scattered radiation, it is sensitive to changes in the experimental setup, and in the case of treatment monitoring, to patient-related variations. Thus it cannot be applied for treatment monitoring with the current setup. To apply this method for purposes beyond pre-experiment beam QA—such as during experiments or treatments—the

detector's geometry would need to be adjusted. Specifically, positioning the detector to capture scattered particles directly from the beam exit window would enhance its reliability and accuracy under dynamic conditions.

The developed method for DPP and dose-rate measurements can be applied in other types of radiotherapy beams including conventional or FLASH proton therapy or ion therapy.

#### 4.1.2. Number of delivered pulses

The high time resolution of the TPX3 detector enabled continuous pulse count monitoring during prolonged irradiations. Even with acquisition times extending 100 s, individual pulses at a frequency of 5 Hz were reliably identified. This robust counting capability was validated through detailed analyses, ensuring the accurate determination of the number of delivered pulses. Counting of number of pulses is straightforward as the background radiation at the detector's position was practically 0 when the beam was turned off and the accelerator frequency is rather low. Further work should include measurement at higher pulse rate frequency. Our findings underscore the robust capability of the TPX3 detector to reliably and accurately quantify the number of pulses delivered by UHDP electron beams.

#### 4.1.3. Pulse length and temporal structure

The pulse length and temporal structure of the beam can be obtained with 100 ns–200 ns resolution using the presented non-invasive method based on the correlation of the primary beam with scattered radiation inside the experimental room. A very good agreement was found with the delivered pulse length; hence the TPX3 detector has shown that it is capable of determining pulse time nanostructure via measuring out-of-field scattered radiation. Thus, the method can be further integrated for FLASH radiotherapy beam monitoring. The requirements to replicate this method in a treatment room are a low flux to distinguish individual particles and integration of the pulse length definition detailed in [Section 3.4](#) into data processing.

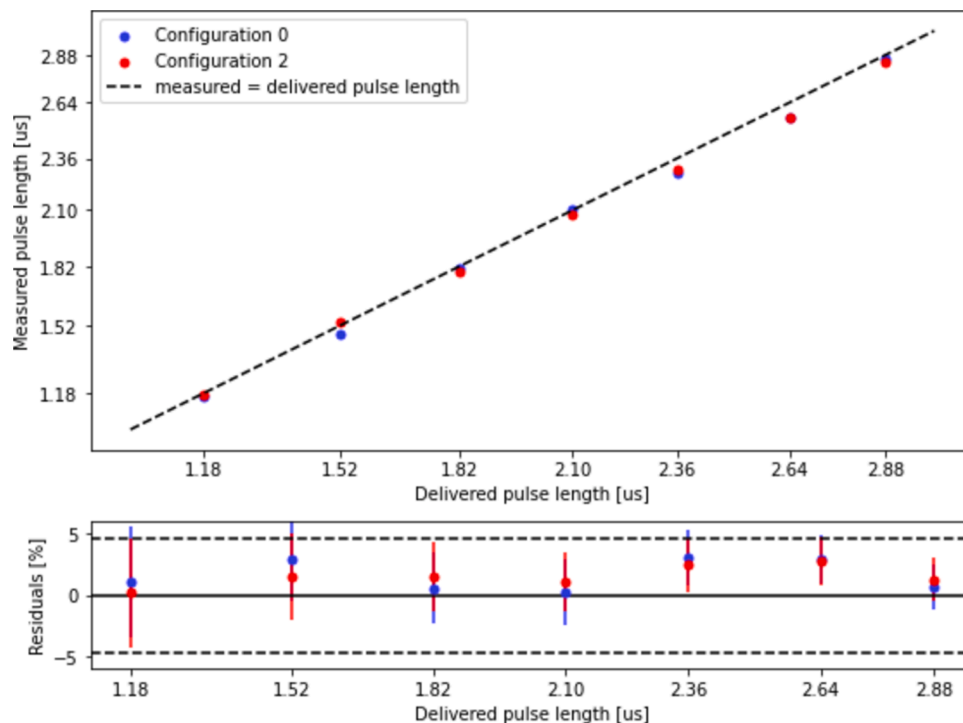


**Fig. 7.** Upper panel: Measured pulse lengths as a function of delivered pulse lengths for campaigns 1–7 and 15–21 for LINACS configurations “2” and “0”, respectively. Lower panel: Residuals of average measured pulse lengths are well within the margin of average relative error of delivered pulse lengths, denoted by dashed lines in the Residuals subplot. Error bars represent type A uncertainty for TPX3 pulse length measurements.

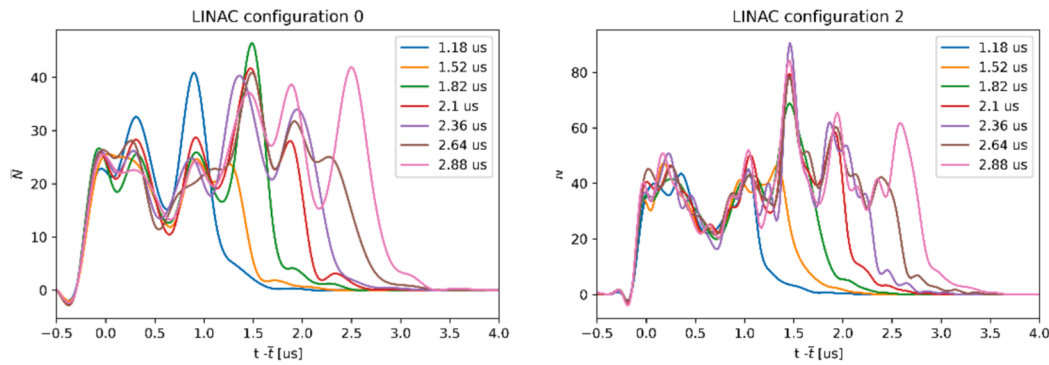


**Fig. 8.** Measured temporal pulse nanostructure across various lengths for the two LINAC configurations. The data were binned into 200 ns and 100 ns time intervals for configurations “2” and “0”, respectively, to ensure sufficient data in a bin. The binned data were smoothed for visual purposes,  $\bar{t}$  denotes the start of a pulse as defined in Section 3.4.

#### 4.2. Suitability of the QA methods for other radiotherapy beams and systems

##### 4.2.1. Adaptation for upgraded LINACs of different energies

The proposed method and system for QA are suitable for a broad range of electron beam energies, including those generated by FLASH-upgraded LINACs operating between 6 and 18 MeV. This adaptability is primarily due to the low energy threshold of the Timepix3 detector, which enables the detection of particles depositing energies as low as 3–5 keV in the silicon sensor. As a result, the system is capable of tracking and measuring secondary particles across a wide spectrum of beam energies, making it adaptable to various FLASH electron beam configurations.

To ensure optimal performance, adjustments to the detector’s position relative to the beam may be necessary when transitioning between different beam energies. Orienting the detector’s field of view towards the beam nozzle improves statistics and enhances secondary particle tracking. Additionally, calibration of the system may be required for beams at the lower (6 MeV) and higher (18 MeV) values of the energy range to ensure accurate dosimetric and temporal characterization.

The system is designed to handle variations in dose rate, with the Timepix3 detector capable of processing up to  $10^6$  particles/cm<sup>2</sup>/s in single-particle tracking mode. In the current setup, a maximum particle flux of approximately 650 particles/cm<sup>2</sup>/s was detected, leaving ample capacity to accommodate higher dose rates or different pulse structures, thereby ensuring the system’s suitability for FLASH-upgraded LINAC applications.

##### 4.2.2. Use of the system on FLASH LINAC with PMMA applicators

The proposed system can be applied on FLASH LINAC using PMMA applicators for QA purposes [44–46]. However, its use for patient dosimetry would be limited, as the geometry of the patient introduces complexities that can significantly influence the measurement. While the number of pulses and temporal structure of the beam can be accurately measured regardless of the setup inside the treatment room, the presence of a patient, along with the PMMA applicators, would have a direct impact on the dose recorded by the detector. Thus, the configuration used in this study would no longer be suitable for patient treatment without modifications of the geometry. Adjusting the detector’s position and field of view to align with the beam nozzle and PMMA applicators would be necessary to ensure reliable dose and particle detection.

##### 4.2.3. Adaptations for use in other radiotherapy beams

**4.2.3.1. Proton therapy.** For proton therapy applications, the method presented is used to evaluate the dosimetric and temporal structure of the beam, particularly for QA purposes. To improve detection statistics,

the detector could be positioned towards the beam nozzle to track scattered protons. A similar configuration was successfully implemented in a fixed-beam treatment room for QA purposes [40]. Alternatively, for setups independent of the experimental conditions or patient in proton RT, positioning the detector closer to the beam exit is recommended to enhance the detection of scattered protons [47]. In this scenario, a detector distance of approximately 50 cm from the exit window would be ideal. This distance optimizes scattered proton detection while minimizing delays caused by neutron-induced signals, despite the limited neutron detection efficiency of the system. This independent setup would provide an optimal configuration for both conventional and FLASH proton therapy beam and treatment monitoring.

**4.2.3.2. Carbon ion therapy.** In carbon ion therapy, the primary challenge of using the presented method arises from the relatively low number of scattered particles. However, ion interactions with matter, such as the patient or experimental setup, generate fragments that are temporally correlated with the primary beam. These fragments can be used for real-time monitoring of the beam’s temporal structure and dose rate. By placing the detector at an optimal angle to capture these fragments, this method could be applied for QA in ion therapy. However, positioning the detector behind the patient may introduce significant interference in dose measurements, as the setup and surrounding materials influence the measurement. For example, a system consisting of 28 Timepix3 detectors placed close to the patient’s head has been employed for non-invasive monitoring [41] in conventional carbon ion radiotherapy clinical trials. However, to avoid saturation and overlapping particles in FLASH RT, modifications to the geometry—such as increasing the detector distance/orientation—would be necessary.

To address this challenge related to patient treatment monitoring in FLASH carbon ion RT, an optimal approach would involve positioning the detector in front of the patient or experimental setup with the sensor field of view towards the beam nozzle, similar to the setup proposed for proton RT. This positioning would minimize interference from the surrounding environment and improve dose measurement accuracy while detecting sufficient secondary fragments. These fragments, when detected by the TPX3 system, would enable both temporal and dosimetric characterization of the FLASH ion beam.

## 5. Conclusions

The purpose of this work was to provide a method for temporal characterization of UHDPP beams generated by a research LINAC at PTB. When looking for a robust non-invasive quality assurance method for these types of beams used during FLASH radiotherapy, three key parameters were systematically investigated: dose per-pulse measurements, number of delivered pulses, and pulse length duration at the order of microseconds. The detailed examination involved

measurements using a single high-sensitivity semiconductor Timepix3 chip without collimators, which facilitated precise measurements even at 200 cm lateral distances from the primary beam. In summary, our investigation into new methods and detectors for FLASH radiotherapy QA has yielded promising results. The detector demonstrated precise measurements of DPP, reliable counting of pulses even during prolonged acquisition times, and accurate determination of pulse lengths. Moreover, TPX3 high time resolution allowed for pulse shape time nanostructure investigation. These findings highlight the detector's robust capabilities and its effective utilization in quality assurance of FLASH electron beams particularly when placed out-of-field, being a non-invasive method.

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## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Cristina Oancea, Katerina Sykorova, Jan Jakubek, and Jiri Pivec are employees of ADVACAM and they are involved in the manufacture of the TPX3 detectors. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejmp.2024.104872>.

## References

- [1] Favaudon V, Caplier L, Monceau V, Pouzoulet F, Sayarath M, Fouillade C, et al. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. *Sci Transl Med* 2014;6(245). [https://doi.org/10.1126/SCITRANSLMED.3008973/SUPPL\\_FILE/6-245RA93\\_SM.PDF](https://doi.org/10.1126/SCITRANSLMED.3008973/SUPPL_FILE/6-245RA93_SM.PDF).
- [2] Montay-Gruel P, Petersson K, Jaccard M, Boivin G, Germond JF, Petit B, et al. Irradiation in a flash: unique sparing of memory in mice after whole brain irradiation with dose rates above 100 Gy/s. *Radiation Oncol* 2017;12(4):365–9. <https://doi.org/10.1016/j.radonc.2017.05.003>.
- [3] Abel E, Girdhani S, Jackson I, Eley J, Katsis A, Marshall A, et al. Characterization of radiation-induced lung fibrosis and mode of cell death using single and multi-pulsed proton flash irradiation. *Int J Radiat Oncol Biol Phys* 2019;105:E652–3. <https://doi.org/10.1016/j.ijrobp.2019.06.1033>.
- [4] Montay-Gruel P, Bouchet A, Jaccard M, Patin D, Serduc R, Aim W, et al. (2018) X-rays can trigger the FLASH effect: ultra-high dose-rate synchrotron light source prevents normal brain injury after whole brain irradiation in mice. *Radiation Oncol* 2018;129:582–8. <https://doi.org/10.1016/j.radonc.2018.08.016>.
- [5] Friedl AA, Prise KM, Butterworth KT, Montay-Gruel P, Favaudon V. Radiobiology of the FLASH effect. In: Medical Physics. Vol 49, John Wiley and Sons Ltd; 2022: 1993–2013. 10.1002/mp.15184.
- [6] Labarbe R, Hotoiu L, Barbier J, Favaudon V. A physicochemical model of reaction kinetics supports peroxy radical recombination as the main determinant of the FLASH effect. *Radiation Oncol* 2020;153:303–10. <https://doi.org/10.1016/j.radonc.2020.06.001>.
- [7] Jansen J, Beyreuther E, García-Calderón D, et al. Changes in radical levels as a cause for the FLASH effect: impact of beam structure parameters at ultra-high dose rates on oxygen depletion in water. *Radiation Oncol* 2022;175:193–6. <https://doi.org/10.1016/j.radonc.2022.08.024>. Published online August 2022: S0167814022042451.
- [8] García Díez M, Espinosa Rodríguez A, Sánchez Tembleque V, et al. Technical note: measurement of the bunch structure of a clinical proton beam using a SiPM coupled to a plastic scintillator with an optical fiber. *Med Phys* 2023;50:3184–90. <https://doi.org/10.1002/mp.16333>.
- [9] Charyyev S, Liu R, Yang X, Zhou J, Dhabaan A, Dynan WS, Oancea C, Lin L. Measurement of the time structure of FLASH beams using prompt gamma rays and secondary neutrons as surrogates. *Phys Med Biol* 2023;68(14). <https://doi.org/10.1088/1361-6560/acdc7c>. PMID: 37285847.
- [10] Kanouta E, Johansen JG, Kertzscher G, Sitarz MK, Sørensen BS, Poulsen PR. Time structure of pencil beam scanning proton FLASH beams measured with scintillator detectors and compared with log files. *Med Phys* 2022;49(3):1932–43. <https://doi.org/10.1002/MP.15486>.
- [11] Kleczek R, Szczygiel R, Grybos P, Otfinowski P, Kasinski K. Time and energy measuring front-end electronics for long silicon strip detectors readout. *IEEE Nucl Sci Sympos Conf Rec* 2013. <https://doi.org/10.1109/NSSMIC.2013.6829538>.
- [12] Rahman M, Ashraf MR, Zhang R, Gladstone DJ, Cao X, Williams BB, et al. Spatial and temporal dosimetry of individual electron FLASH beam pulses using radioluminescence imaging. *Phys Med Biol* 2021;66(13):135009. <https://doi.org/10.1088/1361-6560/ac0390>.
- [13] Kim H, Hyeok Jeong D, Koo Kang S, Lee M, Lim H, Jin Lee S, Won Jang K. Real-time monitoring of ultra-high dose rate electron beams using bremsstrahlung photons. 10.1016/j.net.2023.05.033. 2023.
- [14] Levin DS, Friedman PS, Ferretti C, Ristow N, Tecchio M, Litzenberg DW, et al. A prototype scintillator real-time beam monitor for ultra-high dose rate radiotherapy. *Med Phys* 2024;51(4). <https://doi.org/10.1002/mp.17018>.
- [15] McManus M, Romano F, Lee N, Billas I, Foster B, Greig L, et al. The challenge of ionisation chamber dosimetry in ultra-short pulsed high dose-rate very high energy electron beams. *Sci Rep* 2020;10(1):9089. <https://doi.org/10.1038/s41598-020-65819-y>.
- [16] Liu K, Holmes S, Hooten B, Schüller E, Beddar S. Evaluation of ion chamber response for applications in electron FLASH radiotherapy. *Med Phys* 2024;51(1): 494–508. <https://doi.org/10.1002/mp.16726>.
- [17] Gomez Rodriguez F, et al. Development of an ultra-thin parallel plate ionization chamber for dosimetry in FLASH radiotherapy. *Med Phys* 2022;1–10. <https://doi.org/10.1002/mp.15668>.
- [18] Milluzzo G, Petasecca M, Arianer J, Martínez-Rovira I, Cutajar D, Rosenfeld AB. Comprehensive dosimetric characterization of novel silicon carbide detectors with UHDR beams for FLASH radiotherapy. *Med Phys* 2024. <https://doi.org/10.1002/mp.17172>.
- [19] de Napoli M. SiC detectors: a review on the use of silicon carbide as radiation detection material. *Front Phys* 2022;10:898833. <https://doi.org/10.3389/fPHY.2022.898833/PDF>.
- [20] Marinelli M, Verona Rinati G, et al. Design, realization, and characterization of a novel diamond detector prototype for FLASH radiotherapy dosimetry. *Med Phys* 2022. <https://doi.org/10.1002/mp.15473>.
- [21] Poirier Y, Boudou C, Haddad F, Le Foulon P, Fuduli I. Scintillator-based detectors for FLASH radiotherapy: development and initial tests. *Radiat Phys Chem* 2022;192: 109827. <https://doi.org/10.1016/j.radphyschem.2022.109827>.
- [22] Oesterle R, Gonçalves Jorge P, Grilj V, et al. Implementation and validation of a beam-current transformer on a medical pulsed electron beam LINAC for FLASH-RT beam monitoring. *J Appl Clin Med Phys* 2021;22(11):165–71. <https://doi.org/10.1002/acm2.13433>.
- [23] Bergmann B, Pichotka M, Pospisil S, Vycpalek J, Burian P, Broulim P, Jakubek J. 3D track reconstruction capability of a silicon hybrid active pixel detector. *Eur Phys J C* 2017;77(6):1–9. <https://doi.org/10.1140/EPJC/S10052-017-4993-4>.
- [24] Stasica P, Baran J, Granja C, Krah N, Korcyl G, Oancea C, et al. A simple approach for experimental characterization and validation of proton pencil beam profiles. *Front Phys* 2020;346. <https://doi.org/10.3389/fPHY.2020.00346>.
- [25] Schüller A, Pojtinger S, Meier M, Makowski C, Kapsch RP. The metrological electron accelerator facility (MELAF) for research in dosimetry for radiotherapy. *IFMBE Proc* 2019;68:589–93.
- [26] Paz-Martín J, Schüller A, Bourgouin A, González-Castaño DM, Gómez-Fernández N, Pardo-Montero J, et al. Numerical modeling of air-vented parallel plate ionization chambers for ultra-high dose rate applications. *Phys Med* 2022; 103:147–56. <https://doi.org/10.1016/j.ejmp.2022.10.006>.
- [27] Poikela T, Plosila J, Westerlund T, Campbell M, de Gaspari M, Llopart X, et al. Timepix3: a 65K channel hybrid pixel readout chip with simultaneous ToA/ToT and sparse readout. *J Instrum* 2014;9(05):C05013. <https://doi.org/10.1088/1748-0221/9/05/C05013>.
- [28] Turecek D, Jakubek J, Soukup P. USB 3.0 readout and time-walk correction method for Timepix3 detector. *J Instrum* 2016;11(12):C12065. <https://doi.org/10.1088/1748-0221/11/12/C12065>.
- [29] Jakubek J. Precise energy calibration of pixel detector working in time-over-threshold mode. *Nucl Instrum Methods Phys Res, Sect A* 2011;633(SUPPL. 1): S262–6. <https://doi.org/10.1016/J.NIMA.2010.06.183>.
- [30] Bourgouin A, Knyziak A, Marinelli M, Kranzer R, Schüller A, Kapsch RP. Characterization of the PTB ultra-high pulse dose rate reference electron beam. *Phys Med Biol* 2022;67(8). <https://doi.org/10.1088/1361-6560/AC5DE8>.
- [31] Schüller A, Illemaann J, Renner F, Makowski C, Kapsch RP. Traceable charge measurement of the pulses of a 27 MeV electron beam from a linear accelerator *JINST* 12 P03003. 10.1088/1748-0221/12/03/P03003. 2017.
- [32] Bourgouin A, Hackel T, Kapsch RP. The PTB water calorimeter for determining the absolute absorbed dose to water in ultra-high pulse dose rate electron beams. *Phys Med Biol* 2023;68(11). <https://doi.org/10.1088/1361-6560/acce1d>.
- [33] Oancea C, Bălan C, Pivec J, Granja C, Jakubek J, Chvatil D, et al. Stray radiation produced in FLASH electron beams characterized by the MiniPIX Timepix3 Flex detector. *J Instrum* 2022;17(1):C01003. <https://doi.org/10.1088/1748-0221/17/01/C01003>.

- [34] Oancea C, Granja C, Marek L, Jakubek J, Šolc J, Bodenstein E, et al. Out-of-field measurements and simulations of a proton pencil beam in a wide range of dose rates using a Timepix3 detector: dose rate, flux and LET. *Phys Med* 2023;106: 102529. <https://doi.org/10.1016/J.EJMP.2023.102529>.
- [35] Marek L, Granja C, Jakubek MJ, Ingerle MJ, Turecek MD, Vuolo MM, Oancea C. *Data Processing Engine (DPE): Data Analysis Tool for Particle Tracking and Mixed Radiation Field Characterization with Pixel Detectors Timepix*. JINST, 2024; 19 C04026 10.1088/1748-0221/19/04/C04026. 2023.
- [36] Oancea C, Solc J, Bourgouin A, Granja C, Jakubek J, Pivec J, et al. Thermal neutron detection and track recognition method in reference and out-of-field radiotherapy FLASH electron fields using Timepix3 detectors. *Phys Med Biol* 2023;68(18). <https://doi.org/10.1088/1361-6560/ACF2E1>.
- [37] Granja C, Jakubek J, Polansky S, Zach V, Krist P, Chvatil D, et al. Resolving power of pixel detector Timepix for wide-range electron, proton and ion detection. *NIMPA* 2018;908:60–71. <https://doi.org/10.1016/J.NIMA.2018.08.014>.
- [38] Granja C, Solc J, Gajewski J, Rucinski A, Stasica P, Rydygier M, et al. Composition and spectral characterization of mixed-radiation fields with enhanced discrimination by quantum imaging detection. *IEEE Trans Nucl Sci* 2024. <https://doi.org/10.1109/TNS.2024.3369972>.
- [39] Bourgouin A, Hackel T, Marinelli M, Kranzer R, Schüller A, Kapsch RP. Absorbed-dose-to-water measurement using alanine in ultra-high-pulse-dose-rate electron beams. *Phys Med Biol* 2022;67(20):205011. <https://doi.org/10.1088/1361-6560/AC950B>.
- [40] Granja C, Kurucz S, Solc J, Vondracek V, Pacik J, Oancea C. Non-invasive particle beam tracker for high-resolution radiation quality and dose delivery monitoring in proton radiotherapy. *JINST* 2024. under review.
- [41] Kelleter L, Marek L, Echner G, Ochoa-Parra P, Winter M, Harrabi S, Jakubek J, Jäkel O, Debus J, Martisikova M. An in-vivo treatment monitoring system for ion-beam radiotherapy based on 28 Timepix3 detectors. *Sci Rep* 2024;14(1):1–12. <https://doi.org/10.1038/s41598-024-66266-9>.
- [42] Schüller A, Heinrich S, Fouillade C, Subiel A, De Marzi L, Romano F, et al. The European Joint Research Project UHDPulse – Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates. *Phys Medica: Eur J Med Phys* 2020;80:134–50. <https://doi.org/10.1016/J.EJMP.2020.09.020>.
- [43] Medina E, Ferro A, Abujami M, Camperi A, Centis Vignali M, Data E, del Sarto D, Deut U, di Martino F, Fadavi Mazinani M, Ferrero M, Ferrero V, Giordanengo S, Marti Villarreal, Hosseini MA, Mas Milian F, Masturzo L, Montalvan Olivares, Montefiori M, Vignati A. First experimental validation of silicon-based sensors for monitoring ultra-high dose rate electron beams. *Frontiers in Physics* 2024;12: 1258832. <https://doi.org/10.3389/FPHY.2024.1258832/BIBTEX>.
- [44] Poirier Y, Mossahebi S, Becker SJ, Koger B, Xu J, Lamichhane N, Maxim PG, Sawant A. Radiation shielding and safety implications following linac conversion to an electron FLASH-RT unit. *Medical Physics* 2021;48(9):5396–405. <https://doi.org/10.1002/MP.15105>.
- [45] Dal Bello R, von der Grün J, Fabiano S, Rudolf T, Saltybaeva N, Stark LS, Ahmed M, Bathula M, Kucuker Dogan S, McNeur J, Guckenberger M, Tanadini-Lang S. Enabling ultra-high dose rate electron beams at a clinical linear accelerator for isocentric treatments. *Radiotherapy and Oncology : Journal of the European Society for Therapeutic Radiology and Oncology* 2023;187. <https://doi.org/10.1016/J.RADONC.2023.109822>.
- [46] Deut, U., Camperi, A., Cavicchi, C., Cirio, R., Data, E. M., Durisi, E. A., Ferrero, V., Ferro, A., Giordanengo, S., Villarreal, O. M., Mas Milian, F., Medina, E., Olivares, D. M. M., Mostardi, F., Monti, V., Sacchi, R., Salmeri, E., & Vignati, A. (2024). Characterization of a Modified Clinical Linear Accelerator for Ultra-High Dose Rate Beam Delivery. *Applied Sciences* 2024, Vol. 14, Page 7582, 14(17), 7582. <https://doi.org/10.3390/AP14177582>.
- [47] Shen J, Ding X, Charyyev S, Liang X, Oancea C, Wang P, Rule WG, Liu W, Bues M, Lin L. Time structures of proton pencil beam scanning delivery on a microsecond scale measured with a pixelated semiconductor detector Timepix3. *Journal of Applied Clinical Medical Physics* 2024;25(9):e14486. <https://doi.org/10.1002/ACM2.14486>.
- [48] Fleta C, Pellegrini G, Godignon P, Rodríguez FG, Paz-Martín J, Kranzer R, Schüller A. State-of-the-art silicon carbide diode dosimeters for ultra-high dose-per-pulse radiation at FLASH radiotherapy. *Physics in Medicine & Biology* 2024;69(9): 095013. <https://doi.org/10.1088/1361-6560/AD37EB>.
- [49] Di Martino, F., del Sarto, D., Giuseppina Bisogni, M., Capaccioli, S., Galante, F., Gasperini, A., Linsalata, S., Mariani, G., Pacitti, M., Paiar, F., Ursino, S., Vanreusel, V., Verellen, D., & Felici, G. (2022). A new solution for UHDP and UHDR (Flash) measurements: Theory and conceptual design of ALLS chamber. *Physica Medica : PM : An International Journal Devoted to the Applications of Physics to Medicine and Biology : Official Journal of the Italian Association of Biomedical Physics (AIFB)*, 102, 9–18. <https://doi.org/10.1016/J.EJMP.2022.08.010>.