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Test beam results of a fluorescence-based monitor for ultra-high dose rates

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Abstract: In recent years, there has been a significant focus on improving the effectiveness of radiotherapy (RT) and particle therapy in treating tumors while minimizing damage to healthy tissue. A promising development is offered by the observation of the so-called FLASH effect, where ultra-high dose rates delivered in a short time have shown to protect healthy tissues while maintaining anti-tumor efficacy. However, conventional detectors face challenges in monitoring charged beams at these ultra-high dose rates due to non-linear effects. To address this challenge, the FlashDC (Flash Detector beam Counter) has been developed. It uses air fluorescence to monitor beam fluence and spatial distribution in real-time with high accuracy and minimal impact on treatment delivery. This innovative

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detector offers a linear response for various charged beams, dose rates, and energies, making it a cost-effective solution. Multiple prototypes have been developed and optimized using Monte Carlo simulations. The analysis of data from recent test beam campaigns with electrons delivered at FLASH intensities has demonstrated a linear correlation between the detector signal and the delivered dose per pulse, confirming that fluorescence can be used for beam monitoring in FLASH-RT studies. This contribution introduces the FlashDC monitor, discusses its expected performance, and presents preliminary test beam results obtained with electron beams in FLASH mode.

Keywords: Beam-line instrumentation (beam position and profile monitors, beam-intensity monitors, bunch length monitors); Instrumentation for particle-beam therapy; X-ray fluorescence (XRF) systems

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1 Introduction

External Beam Radiotherapy (EBRT) stands out as a pivotal tool in cancer therapeutics, significantly impacting patient life expectancy across a wide spectrum of pathologies, constituting over 50% of global cases as of 2021 [1]; used independently or in conjunction with chemotherapy and surgery, EBRT strategically administers ionizing particles (mainly photons and electrons in the MeV energy range), following an optimized treatment protocol to eradicate malignancies while mitigating collateral damage to adjacent healthy tissues. Advancements in early diagnostic modalities and sophisticated imaging techniques play a crucial role in increasing the annual rate of successfully treated patients; however, radiation-induced toxicity on healthy tissues, though subject to control and reduction, imposes stringent constraints on the maximum deliverable dose, both within a singular therapeutic session and throughout the total treatment. While this approach safeguards patients against severe side effects, it concurrently limits the efficacy in tumor control during therapy, particularly in cases featuring radio-resistant tumors of heightened clinical significance.

Over the years, efforts to enhance the Therapeutic Index (TI) have been centered on achieving heightened spatial conformity, strongly concentrating DNA damage to the tumor volume. A notable example is provided by techniques involving multiple fields, where the total dose is dispensed through a sophisticated overlapping of beams featuring diverse energies and directions within intensity-modulated radiation therapy. Furthermore, the escalating adoption of particle therapy leverages the intrinsic precision of proton or heavy ion beams, complemented by their superior relative biological effectiveness compared to photons and electrons.

In recent years, a novel field of investigation has emerged as a potential alternative to conventional approaches in radiotherapy. Experimental evidences from multiple in vivo studies [2] indicate a significant and distinct response when subjecting tissues to therapy irradiation with beams at a mean dose-rate (D_m) exceeding 40 Gy/s, placing it within the Ultra-High Dose Rate (UHDR) range. This phenomenon, termed the FLASH effect [3], consists in a probability of cell killing in tumors strongly comparable to conventional irradiation ($D_m \sim 0.1$ Gy/s), while exhibiting heightened radio-resistance (reduced radiation-induced damage) in healthy tissues. The FLASH effect is currently under investigation as a potential change-of-paradigm in radiotherapy, offering the prospect of elevated allowable doses with diminished side effects on healthy tissues, thereby enabling superior dose delivery to radio-resistant tumors, both with pre-clinical experiments and envisioning advanced treatment planning systems capable of exploiting its beneficial effect following an optimized beam configuration [4].

From a clinical perspective, the FLASH effect has been observed across various irradiation modalities, including electrons, photons, and protons, at different energy levels and for diverse pathologies [5]. However, a comprehensive quantitative characterization in terms of fundamental beam parameters remains lacking, and its underlying mechanisms are yet to be fully elucidated. Existing hypotheses propose a dependence on the temporal structure of the beam, which at the moment is dependent on the existing technology of clinical linear accelerators (linacs), which commonly deliver particle beams in pulses lasting 1 to 10 µs, with a Pulse Repetition Frequency (PRF) ranging from 100 to 1000 Hz. Among the important parameters currently investigated with regard to their roles in triggering the FLASH effect, the most frequently cited [6] are: the *dose per pulse*, representing the dose within a single particle bunch delivered to the patient; the *instantaneous dose-rate*, obtained by dividing the dose per pulse by the pulse duration; and the *mean dose-rate*, derived from the total dose administered during the entire treatment divided by the overall treatment time.

To date, achieving the UHDR regime has primarily involved elevating the dose per pulse to values ranging from 0.1 to 10 Gy, resulting in an instantaneous dose-rate ranging from 10^6 to 10^7 Gy/s. This is at least four orders of magnitude higher than the conventional radiotherapy dose rate, typically around 100 Gy/s. This approach enables the delivery of substantial doses (tens of Gy) within a few ms using the PRF of standard linacs, that typically sits at 10 to 1000 Hz. Alternatively, achieving the UHDR regime could involve reducing the time between pulses while maintaining dose per pulse levels consistent with conventional radiotherapy. Deciphering the distinct contributions of dose per pulse and the temporal structure of dose delivery is anticipated to be a pivotal step in fully characterizing the FLASH effect in the near future. This presents a challenge to a fundamental aspect of clinical machine commissioning and experimental precision: beam monitoring.

Broadly, a beam monitor is a device employed for real-time assessment of characteristics relevant to irradiation quality and safety, such as beam instantaneous rate and spatial distribution [6]. It is distinguished by high spatial and temporal resolution, a broad response dynamic range, radiation hardness, and high beam transparency, typically positioned at the exit of the acceleration system to minimize impact on the transport line. Progress in FLASH effect experimentation necessitates a reliable beam monitoring system for characterizing dose release over time and, from a clinical perspective, monitoring treatments to ensure safety and repeatability in FLASH modality. Essential requirements in this context include linearity of response with dose rate, extending to extreme values encountered in UHDR modality, and optimal temporal resolution to discern the temporal structure down to individual pulses.

Meeting these requirements presents a non-trivial challenge. Conventional radiotherapy devices, such as standard transmission ionization chambers, exhibit sub-optimal performance in the UHDR regime due to the exceedingly high particle flux, leading to reduced ion collection efficiency attributed to volume recombination. Consequently, novel devices and technologies are under investigation as potential candidates to overcome current limitations and achieve the necessary performance (accuracy and precision) for beam monitoring at UHDR. The FlashDC (Flash Detector Counter) project aims to address this need by developing a monitor specifically designed for FLASH radiotherapy. This monitor is intended to measure the number of beam particles per pulse in real time, offering high spatial and temporal resolution, a broad dynamic range, and delivering a linear output signal with respect to the beam current up to values of instantaneous dose-rate of 10^7 Gy/s, avoiding saturation usually associated with the UHDR regime.

2 Materials and methods

2.1 Fluorescence

Several authors [7] have proposed the use of luminescence-based detectors to address the challenges of beam monitoring in the UHDR range of intensities, employing established techniques such as scintillation and Cherenkov light production and detection. Notably, these detectors are advantageous due to their ability to emit light proportionally to beam intensity, providing prompt emissions with a mean time of photon release on the order of a few ns or less. However, they present certain drawbacks: scintillators require construction from complex materials to ensure radiation hardness, leading to increased costs and reduced availability; on the other hand, Cherenkov light is energy-dependent and emitted in a cone, introducing complexity in the geometry of light detection.

A viable solution to overcome these limitations involves the use of an *air detector*, exploiting the phenomenon of fluorescence, which entails the emission of optical photons (wavelengths from 290 to 430 nm [8]) due to the molecular excitation of nitrogen following the passage of a charged particle. While fluorescence in air has been extensively studied in the context of electron passage through air, particularly in extensive air showers from cosmic rays in the atmosphere, it offers a convenient solution for UHDR beam monitoring; given that low-energy electrons are commonly used in pre-clinical studies of FLASH-RT, existing data can be leveraged to make a preliminary investigation on the feasibility of a fluorescence-based beam monitor for UHDR.

The mean lifetime of the excited states of nitrogen molecules, and consequently, the mean emission interval of optical photons, is approximately 10 ns. This duration is sufficient to capture typical FLASH pulses ranging from 1 to 10 µs, with repetition rates on the order of 1 to 1000 Hz. The isotropic nature of emission facilitates straightforward 3D beam monitoring, enabling the reconstruction of beam position and direction with spatial resolution determined solely by the intrinsic granularity of the light collection system.

The rate of molecular excitation is directly proportional to the deposited energy, establishing a link between the number of photons produced per unit length, referred to as photon yield, and the specific energy loss (dE/dx) of the electron, as described by the Bethe formula. For electrons with kinetic energies above 2 MeV, this photon yield remains approximately constant. Experimental setups [9] have measured this yield to be around 7 photons/m per electron, representing several orders of magnitude less than a typical plastic scintillator and ensuring superior radiation hardness. This constancy is advantageous for beam monitoring since a detector equipped with a suitable photon detection system would yield a signal directly proportional to the instantaneous dose-rate. Importantly, this signal remains unaffected by energy dependence over the wide dynamic range (10 to 1000 MeV) relevant for conventional radiotherapy and potential future applications involving very-high energy electrons.

Moreover, using an active volume of air minimizes detector interference with the beam, preserving expected irradiation conditions. This design choice results in a device that is both simple and cost-effective to produce. The anticipated fluorescence spectrum, along with pressure and temperature dependencies, as well as the impact of quenching elements like oxygen and argon at different concentrations, have been documented in the literature [10]. These factors can be appropriately considered through dedicated detector calibration processes.

2.2 FlashDC detector

In contrast to Cherenkov production and other scintillation processes, air fluorescence has not undergone extensive investigation for its potential application in monitoring UHDR conditions in FLASH radiotherapy. The initial challenge addressed by the FlashDC project involves conducting a proof-of-principle study to assess the accuracy achievable in measuring beam intensity and position using this technique. Previous test beam campaigns [11] with preliminary prototypes successfully confirmed geometry dependence on position relative to the beam and established a linear correlation of the signal with the dose(-rate) per pulse. Qualitative outcomes indicate that a detector with an air-filled active volume and a straightforward readout system employing standard light sensors is a promising candidate for developing a beam monitor based on air fluorescence, although conclusive quantitative evidence for the efficacy of fluorescence in beam calibration regarding spatial distribution and intensity was premature. To increase the level of detail and provide with a more conclusive set of data, recent prototype results presented in this contribution focused on investigating background noise from secondaries and environmental factors, with an appropriate geometry of the sensitive volume implemented to subtract spurious contributions and measure the signal exclusively from fluorescence.

The detector has been specifically designed for installation on the ElectronFlash [12] accelerator, an advanced research linac for pre-clinical studies on the FLASH effect, installed at the Pisan Center for Flash Radiotherapy (CPFR) in Pisa, Italy, and capable of delivering a dose rate for a single pulse up to 10^6 Gy/s, with a nominal beam energy of 9 MeV. Notably, this linac allows for adjusting the triode gun current to modify the charge injected within a single pulse (lasting 4 µs) and thereby vary the dose within each pulse. This feature makes it an ideal testing ground for assessing the linearity of the signal as a function of the dose in the UHDR regime.

The prototype of the air detector, as depicted in figure 1, is contained within a cylindrical structure specifically designed for direct attachment to the ElectronFlash, facilitated by a screw located on the external surface, resulting in an internal diameter of 6.3 cm and an external diameter of 15 cm, matching the dimensions of the Beam Exit Window (BEW). Made of plastic, the structure includes a hollow aperture on the beam line, which can be optionally sealed from the external environment using a thin Tedlar foil. Inside the cylinder, a sliding leaf, also made of plastic, enables the opening or closing of an aperture to control the passage of fluorescence light toward the light collection device, depending on the objective of the acquisition. Complete closure of the aperture allows measurement of only the contribution from the background, generated from the large number of secondary photons and electrons scattered inside the room, which is in turn dependent from the fluence of primary particles, as confirmed by preliminary Monte Carlo simulations.

The optical photons generated at this stage traverse an additional cylindrical pipe made of plastic, attached to the external layer of the container, with black internal walls to prevent photon reflection. This pipe has a length of 1.2 m, allowing the optical photons to freely drift. At its end, the optical photons are converted into an output current signal by a photomultiplier tube (PMT). The PMT is enclosed by a hollow cylinder made of PMMA with a thickness of 1.5 cm, serving to shield against secondary electrons entering the photocathode region. The overall spatial configuration and the resulting distance of the PMT from the BEW of 1.2 m have been determined based on mechanical

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constraints and the available space within the facility. It is worth emphasizing that it is necessary to distance the PMT from the beam line in order to reduce the number of particles reaching the PMT by means of the solid angle [11], avoiding saturation of signal.

Figure 1. The prototype of the FlashDC experiment, unmounted from the linac BEW.

The initial segment of the detector installed on the ElectronFlash machine is depicted in figure 2. The current output from the PMT undergoes analysis using a digital oscilloscope, wherein the signal is integrated across the pulse duration to obtain a charge value. The linac current was set, based on guidance from local operators, at 9 different presets, corresponding to the following values of dose per pulse D_p (Gy): 0.4, 0.7, 3, 6, 9, 12, 15, 18, and 23, with pulse duration t_p equal to 4 µs and a PRF of 100 Hz. For each data point, measurements were acquired for the *total signal* (comprising fluorescence and background) with the leaf open and for the *background* with the pipe closed at the BEW entrance. Due to radiation protection considerations and machine heating concerns, the ElectronFlash could deliver only 30 pulses for each current, resulting in relatively low statistics.

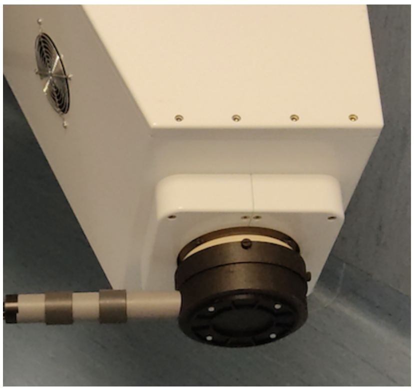

Figure 2. Portion of the experimental setup at CPFR with the detector mounted on the BEW.

Throughout the entire data acquisition process, the response quality of the air volume, which is not insulated from the external environment, remained unaffected by volume saturation thanks to constant renewal of the molecules. However, due to the substantial quantity of fluorescence photons generated, taking into account also the geometric acceptance, it became imperative to reduce the gain of the PMT to 4×10^3 photoelectrons/photon; this adjustment was necessary to sustain a consistent signal throughout the pulse, preventing saturation. Nonetheless, this reduction in gain resulted in a deterioration of the signal-to-noise ratio, placing the sensor in a sub-optimal operating region. This necessitated careful consideration in subsequent analyses, introducing additional systematic uncertainties to account for these non-ideal operating conditions.

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3 Results

The initial examination of the comprehensive signal, corresponding to the opening of the leaf, resulting from individual pulses administered at varying values of D_p, is depicted in figure 3. This analysis was conducted through the post-processing of data files recorded by the oscilloscope. The findings confirm the anticipated correlation between the charge observed by the PMT and the beam current, demonstrating a progressively escalating amplitude with increasing doses per pulse. The acquisition time window was meticulously set at 10 μs, and the presented plot has been magnified to emphasize the pertinent segment of the signal. The integration process, aimed at determining the cumulative charge collected over the pulse, was executed within the time interval spanning from 2.9 to 6.5 μs. This interval was chosen to ensure the constancy of the waveform, thereby ensuring a conservative assessment of the resulting charge.

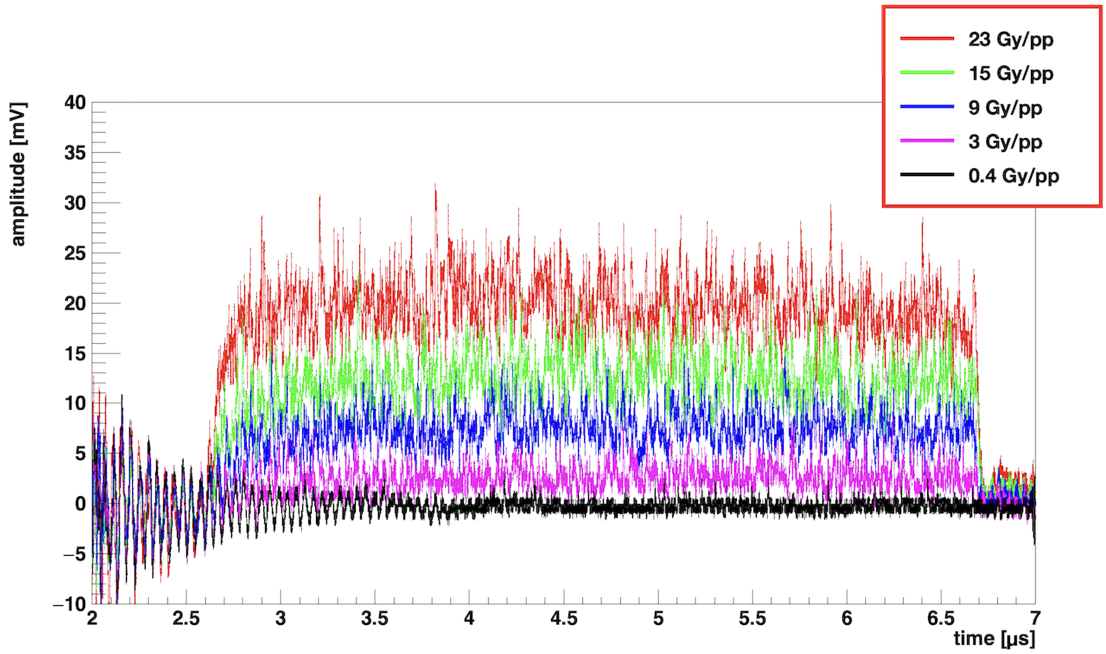

Figure 3. Examples of a single pulse event, at different values of D_p (representing a sample of the complete set of values explored) as seen post-processing the wave-form file saved by the oscilloscope. The amplitude increases with D_p as expected.

Figure 4 illustrates an instance of waveforms captured at a consistent D_p value delivered by the ElectronFlash, specifically at 23 Gy/pulse. This example pertains to a single pulse and serves to contrast signals obtained from the two configurations employed for the initial background subtraction in the FlashDC experiment. In this context, the red curve represents the overall signal, encompassing both fluorescence and background components, while the black curve is derived solely from the measurement of the background. An observation that emerges is the relatively modest signal-to-noise ratio, attributable to the necessity for a low gain setting, essential to discern the uniformity of the readout response across t_p while preventing signal saturation.

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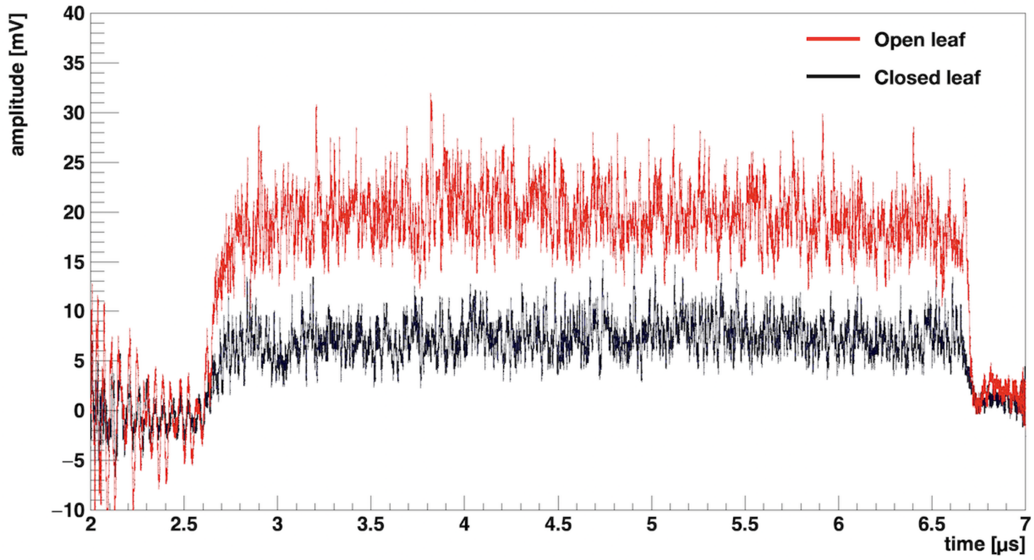

Figure 4. Examples of a single pulse event as seen post-processing the wave-form file saved by the oscilloscope. The two curves highlight the difference between the signal amplitude seen in the different configurations of total signal vs. background only acquisition.

For comprehensive coverage, table 1 presents the outcomes derived from the integration of charge values plotted on histograms. The mean values, along with their associated uncertainties obtained through Gaussian fits, are included. Figure 5 provides a visual representation, exemplifying selected histograms (not comprehensive for clarity purposes) corresponding to the complete set of pulses acquired for the specified D_p values illustrated in a single waveform event in figure 3.

Table 1. Summary of the results of the test beam campaign at CPFR verifying the background subtraction method implemented in the prototype of the FlashDC experiment. Each value has been obtained by fitting a Gaussian histogram of the charge measured within 30 pulses at different values of D_p.

	Total signal		Background	
Dose per pulse (Gy)	Mean charge (pC)	Err.	Mean charge (pC)	Err.
0.4	1.1	0.2	0.3	0.2
0.7	2.7	0.2	0.5	0.1
3	12.5	0.2	4.3	0.2
6	20.4	0.2	7.0	0.1
9	31.6	0.5	11.9	0.1
12	45.8	0.5	16.5	0.2
15	55.8	0.3	20.5	0.2
18	64.5	0.8	24.2	0.1
23	86.4	0.3	34.1	0.5

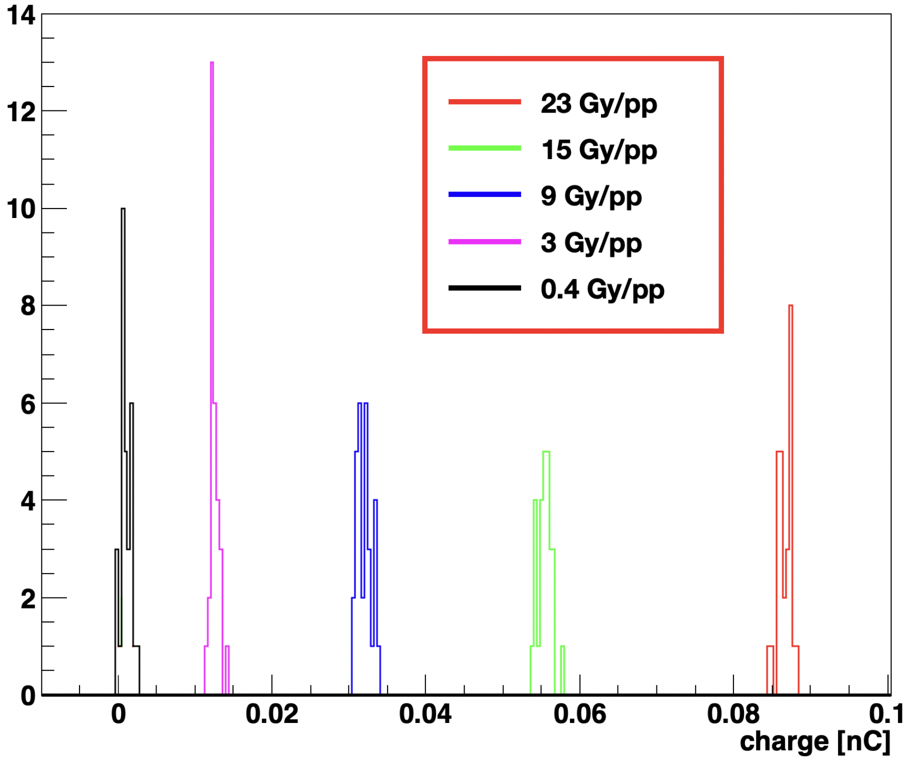

Figure 5. Histograms of the charge obtained by integrating the PMT signal as read from the oscilloscope irradiating the prototype with different dose-rates per pulse. The examples pictured refer to the total signal with opened leaf.

Maintaining consistency, the systematic uncertainty on the dose per pulse is set at 3% of the beam current value, following guidance from CPFR dosimetric personnel. Notably, with this configuration, the background-to-signal ratio ranges substantially between 30% and 40%; it is important to highlight that, despite the error on the fit parameter being on the order of 0.2 pC, the subsequent analysis of the anticipated linear trend incorporates an additional systematic uncertainty of 3% on the charge value. This precautionary measure is motivated by low statistical counts and pronounced fluctuations in waveform amplitude resulting from the PMT low gain. It is essential to note that this qualitative consideration does not compromise the validity of the drawn conclusions.

The conclusive outcome of the test beam campaign investigating the linearity of the fluorescence signal in relation to the dose per pulse is illustrated in figure 6. The plot presents the normalized charge signal relative to its maximum; it can be seen that, as D_p decreases from 20 Gy to 1 Gy, there is a corresponding decline in the charge signal from approximately 100% to approximately 20%. These findings strongly suggest that employing a detector devoid of material (except air) along the beam line enables the differentiation of the signal attributed to the generation of optical photons from fluorescence in air against the background. Furthermore, the discerned variation holds promise for real-time beam monitoring of the dose-rate per pulse.

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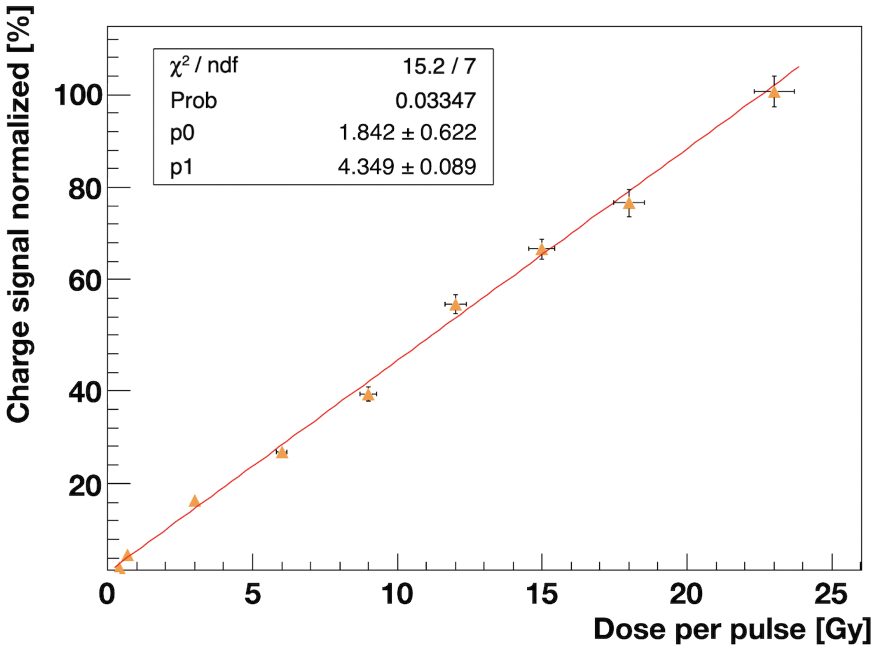

Figure 6. Results of the scan in current of the detector response as a function of the dose per pulse, background subtracted.

4 Conclusions

The comprehensive series of measurements conducted with the FlashDC detector has systematically validated the anticipated geometric dependencies and demonstrated linearity with respect to the dose per pulse, as documented in [11]. The optimal temporal resolution achievable with this technique facilitated a thorough tracking of the beam evolution. With the final prototype, a successful implementation of a background rejection method has been achieved. This method proves effective in discriminating the fundamental signal, and exhibits a robust response across the entire range of intensities explored, without signs of performance degradation over time. This foundational operating principle holds promise for efficient beam monitoring at UHDR, and potentially extends to lower dose rates. Future developments will explore additional applications in medical and fundamental physics, including experimentation with lower dose-rate beams akin to those employed in intra-operative electron radiation therapy treatments — an area of active research.

It is noteworthy that none of the prototypes necessitated methods to enhance signal transmission to the readout system, as the latter tended to saturate due to the high rate of optical photon production. To address this challenge, the acceptance was reduced by distancing the PMT from the beam line, and the gain was adjusted to values considered sub-optimal for sensor functionality. Consequently, efforts are underway to implement alternative readout methods, with preliminary work aligning with the FRIDA[1] project for dosimetry and beam monitoring at UHDR. Furthermore, optimization of the detector geometry is imperative to reduce background and enhance the signal-to-noise ratio. The uncontrolled production of scattered secondaries across the treatment room exacerbates this challenge.

[1] *Flash Radiotherapy with hIgh Dose-rate particle beAms*, a multidisciplinary collaboration funded by the INFN-CSN5 investigating various challenges related to the phenomenological understanding and modeling of the FLASH effect (https://web.infn.it/FRIDA/index.php/it/).

Addressing this issue may involve situating the next prototype beyond the chamber walls, necessitating the development of a new collimation system. These efforts will aim to refine the performance of the detector and broaden its applicability in demanding radiation monitoring scenarios.

Acknowledgments

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