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Prompt Gamma Energy Integration : a new method for online-range verification in proton therapy with pulsed-beams

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2 ABSTRACT

3 We propose a method for prompt-gamma verification of proton range during particle therapy.
4 This method, called Prompt-Gamma Energy Integration (PGEI), is based on the measurement
5 of the total energy deposited in a set of detectors located around a patient. It is particularly
6 suited in the case of high-instantaneous beam intensities, like for pulsed beams extracted from
7 a synchro-cyclotron. GATE simulations show that millimetric range shifts can be measured at
8 a beam-spot scale. The sensitivity is slightly degraded as compared to the Prompt-Gamma
9 Peak Integration Method, for which Time-of-Flight can be employed to reduce the background
10 in single-photon detection conditions at cyclotron accelerators. Experimentally, lead tungstate
11 scintillators have shown to cope with the high instantaneous gamma count rates for PGEI at
12 synchro-cyclotrons.

13 **Keywords:** Prompt-gamma, particle therapy, range verification, Monte Carlo simulations

1 INTRODUCTION

14 In the field of cancer treatment using particle therapy, a crucial asset consists in the ballistic precision,
15 associated to the energy concentration deposited by light ions at the end of their path (Bragg peak),
16 with small lateral and longitudinal dispersions. This feature offers the advantage of fine-tuning treatment
17 precision to the tumor while limiting the impact on surrounding healthy tissues. This can minimize the
18 number of radiation fields needed, a particularly important factor when dealing with tumors close to
19 vital organs [1]. However, various factors have an impact on the location of the Bragg peak, leading
20 to potential sources of errors that might result in under-dosing the tumor or, conversely, overdosing

21 the healthy neighboring tissues. Therefore, additional safety margins are usually applied to account for
22 range uncertainties, and treatment plannings are performed with multi-field plans without organ-at-risk
23 downstream the Bragg peak [2, 3]. As a consequence, the online monitoring of ion ranges inside the patient
24 is highly desirable in order to fully benefit from the ballistic properties of ions. Indeed, better confidence in
25 ion ranges could allow the medical physicists to improve the treatment plans, with less irradiation fields,
26 and possibly organs-at-risk downstream the tumor volume, hence reducing the volume of irradiated healthy
27 tissue [2]. Currently, no method has been widespread in clinical routine, since it would require online
28 imaging, that has to comply with the patient workflow, and be adapted to the accelerator and beam-delivery
29 system.

30 Positron Emission Tomography (PET) is based on the detection of nuclear collision-induced positron
31 annihilation. It has been widely investigated and tested in clinics [4, 5, 6, 7, 8]. However, this technique is
32 limited by the lifetime of radioisotopes, the biological washout, and the available statistics. Therefore, it
33 requires either dedicated online imaging systems, or long data acquisitions offline. In any case, real-time
34 information on a spot-by-spot basis is not feasible. Since the early 2000s, other approaches have been
35 investigated, with a focus on the detection of prompt-secondary particles, particularly the prompt gamma
36 rays (PG), to set up real-time control [9]. The high correlation between the emission points of PG and
37 the trajectories of primary ions has been demonstrated [10, 11]. Furthermore, the vast majority of PG are
38 emitted within a few picoseconds after the interaction, with a roughly isotropic angular distribution, and
39 PG energy spectra strongly depend on the target chemical composition [12, 13]. Various techniques for PG
40 detection have been considered. These encompass imaging systems that use mechanical [14, 15, 16] or
41 electronic collimation (such as Compton cameras [17, 18, 19, 20, 21, 22], or high-resolution Time-of-Flight
42 collimation, as seen in Prompt-Gamma Time Imaging [23, 24]). Non-imaging setups (Prompt-Gamma
43 Timing [25], Prompt-Gamma Spectroscopy [12], Prompt-Gamma Peak Integration (PGPI) [26] and Coaxial
44 Prompt Gamma-ray Monitoring (CPGM) [27]) have been also investigated. These techniques need to be
45 compliant with the beam intensities in order to provide photon-per-photon detection and proton range
46 information. In particular, high-resolution Time-of-Flight (ToF) measurements (projectile-per-projectile)
47 requires reduced intensities with respect to clinical ones [28]. The challenge of adapting the PG detection
48 system with clinical beam delivery has become very complex with the rise of synchrocyclotron accelerators
49 (e.g., IBA-S2C2), with low duty cycle and high instantaneous intensities (from 100 nA to 1 μ A) compared to
50 cyclotrons which usually operate in the nanoampere range, although their average intensities are somewhat
51 similar [29]. Moreover, recent developments in the FLASH therapy field underscore the shift toward
52 higher-intensity treatments doled out over shorter time spans to amplify therapeutic advantages [30, 31].

53 Some techniques of ion-range verification based on the measurements of electric and magnetic fields
54 induced by the beam particles [32, 33] and the secondary particles [34] could benefit from these high
55 intensity beams. This is also the case for the detection of ionoacoustic waves generated when the ion
56 bunches interact with the medium [35, 36]. To alleviate the instrumentation constraints of the event-by-
57 event detection in the context of high-intensity pulsed-beams, the present paper proposes a new method,
58 named Prompt-Gamma Energy Integration (PGEI), derived from the PGPI. It consists in detecting all
59 secondary radiation (mainly PG) with a set of a few detectors in “integration mode” (to cope with high
60 particle fluxes). The information collected is the energy deposition of secondary particles during a beam
61 pulse (integration mode obviously prevents ToF and PG energy measurements). This work consists of
62 two independent and complementary simulation and experimental studies. In a first step, Monte Carlo
63 simulations based on the open-source GATE software [37] are used to evaluate the potential of the method
64 at spot scale. In a second step, we present preliminary measurements showing the feasibility to use fast-
65 and low-luminosity scintillators in order to cope with high PG instantaneous fluxes.

2 MATERIALS AND METHODS

66 2.1 Simulations

67 2.1.1 Mean number of PG detected per HF period from a cyclotron and a synchrocyclotron

68 The PGPI method, proposed in [26], aims at providing ion-range verification from the PG count rates
69 measured by a set of detectors placed around the patient. The count rates of each detector and their ratios,
70 provide information on the beam range, that can be compared quantitatively to simulations. The number of
71 secondary particles induced by nuclear collisions in the patient material is directly related to the intensity
72 of the incident beam. Thus, when several PG interact in a single detector during the same incident particle
73 bunch, there is a risk of information loss. Therefore, the PGPI method is effective when detection units
74 present a compromise between detection efficiency (solid angle) and the probability to avoid pile-up. This
75 compromise is optimum for a maximum duty cycle of the accelerator, e.g with cyclotron-type accelerators
76 that deliver a continuous beam with a current of the order of a few nA (example: IBA C230, average
77 current 3 nA, HF period 10 ns [29]). However, in the context of using synchrocyclotron accelerators and
78 their pulsed mode, a strong issue arises due to the peak intensity during beam delivery. For example, the
79 IBA-S2C2 accelerator emits pulses with a duration of approximately 10 μ s, spaced by about 1 ms, i.e
80 with a duty-cycle of 1%. These pulses themselves consist of a substructure with a period of 16 ns at the
81 extraction, including 8 ns “on” periods delivering particle bunches and 8 ns “off” periods. Therefore, peak
82 intensities may vary between 100 nA and 1 μ A for averaged intensities of a few nA [29].

83 In order to determine the number of PG events detected per accelerator period (i.e. particle bunch), Monte
84 Carlo simulations were performed with GATE (version 9.0) [37], a open-source software which is based
85 on the Geant4 toolkit [38]. We used the QGSP_BIC_HP_EMZ physics list recognized as a reference in this
86 field [39], since it includes both electro-magnetic physics (EMZ is a combination of the most accurate
87 EM models) and hadronic physics. The simulation setup consisted in the 160 MeV proton irradiation
88 of a spherical PMMA phantom target (density 1.2 g/cm³) with a radius of 10 cm. Figure 1 shows the
89 the number of PG events detected per accelerator period as a function of the geometric efficiency of the
90 detector. The values for both the IBA-S2C2 synchro-cyclotron and the IBA-C230 cyclotron, with similar
91 average beam current (3 nA) are depicted on this graph. It is observed that the continuous beam of the
92 C230 has the advantage of generating a low number of PG events per particle bunch. Therefore, it is
93 possible to keep the geometric efficiency of the detector at the level of 10^{-3} while maintaining acceptable
94 counting rates (around 1 MHz). In contrast, the low duty cycle, and thus the high intensities achieved by the
95 S2C2, generate a much higher number of PG events per particle bunch, requiring a significantly reduced
96 geometric detection efficiency (at the level of 10^{-5}) for a single-photon detection regime. This limitation
97 would result in a reduction of the size of the detection units, and then to a large increase of the number of
98 detectors in order to preserve the statistical precision of the measurement.

99 2.1.2 Simulations of the PGPI and PGEI techniques

100 In order to address this issue and preserve the concept of a low-cost, simple arrangement of a few
101 detection units, the proposed PGEI method relies on integral measurement of the energy deposited by
102 secondary particles during the beam pulse in each detector placed around the patient. To determine the
103 precision of this method and compare it with the PGPI method, GATE simulations were performed. A
104 sketch of the simulations is shown in Figure 2. A spherical PMMA target with a 10-cm radius was placed
105 at the center of the geometry, surrounded by 8 or 16 LaBr₃ crystals with their entrance face at 20 cm from
106 the target center. The choice of the LaBr₃ scintillation material has minor importance at this stage, since it

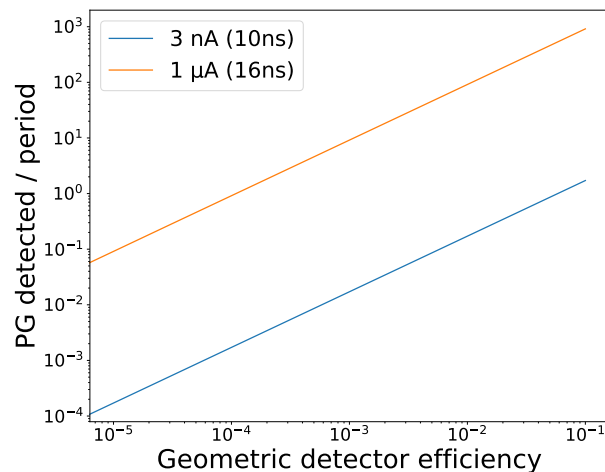


Figure 1. Mean number of PG detected per HF period (i.e. particle bunch) as a function of detector geometric efficiency during beam extraction of two accelerators: 1 μA peak current of a the IBA-S2C2 synchro-cyclotron with 16 ns period, and 3 nA average current of a the IBA-C230 cyclotron, with 10 ns period.

107 is considered only as a calorimeter. Each of these crystals is a cylinder with a radius of 5 cm and a depth of
 108 2.5 cm, corresponding to a geometric efficiency of approximately 1.5 % relative to the simulation center.
 109 For each primary particle, the number of particles and the deposited energy in each detector (“sensitive
 110 detectors” in GATE) are recorded. The target was irradiated by a beam of 10⁹ protons with an energy of
 111 160 MeV. The beam-time structure was modeled in post-processing. Statistical fluctuations on the number
 112 of protons per bunch were applied following the Poisson distribution.

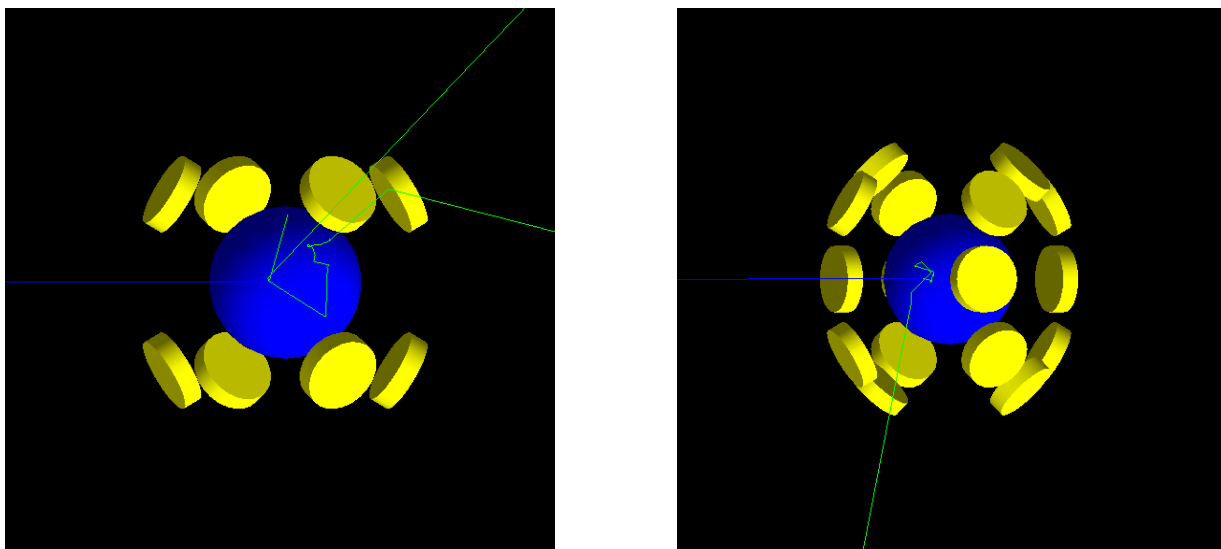


Figure 2. Geometries simulated in GATE: a spherical PMMA target (10-cm radius) placed at the center of the geometry surrounded by 8 (left) or 16 (right) LaBr₃ crystals with their entrance face at 20 cm from the target center.

113 Multiple simulations are conducted with lateral (16-detector setup) or longitudinal (8-detector setup)
 114 displacements of the target relative to the proton beam direction, allowing the observation of the evolution

115 of each variable (energy deposited or number of particles) as a function of the target position. A data
 116 analysis is employed to determine the number of particles detected within the detectors as well as their
 117 energy deposition. In the case of PGPI, we did not perform Time-of-Flight discrimination, in order to
 118 have the closest comparison with the PGEI method. However, a threshold of 1 MeV energy deposited
 119 was applied in order to discriminate PG from other secondary particles in the sensitive detectors. This
 120 threshold is the optimal value to reject most of electrons, low energy X-rays and a large fraction of
 121 Compton-scattered gamma, for which the correlation with emission vertex is poor. In practice, to increase
 122 the perceived statistics for an observable and improve the precision of the methods, it is possible to gather
 123 detectors into several groups for longitudinal displacement, thanks to their symmetrical positions relative
 124 to the emission points of secondary particles and the simple geometry used here. The results can then
 125 be compared on a reduced and more clinically relevant sample for 10^6 , 10^7 , and 10^8 incident protons to
 126 determine the sensitivity of the method in real conditions. Moreover, this simulation makes it possible to
 127 estimate the flux of secondary particles and energy deposited in the detectors, providing insights for the
 128 design of a detection system.

129 **2.2 Experiments**

130 The method we used to characterize the detectors under a proton or alpha beam of ~ 70 MeV (total energy)
 131 is presented in Figure 3. These experiments took place at CAL-Nice and at ARRONAX-Saint-Herblain.
 132 Both accelerators are cyclotrons, and ARRONAX is equipped with a pulsation at injection, allowing the
 133 generation of a pulsed beam similar to that of a synchrocyclotron, with adjustable pulse and inter-pulse
 134 durations.

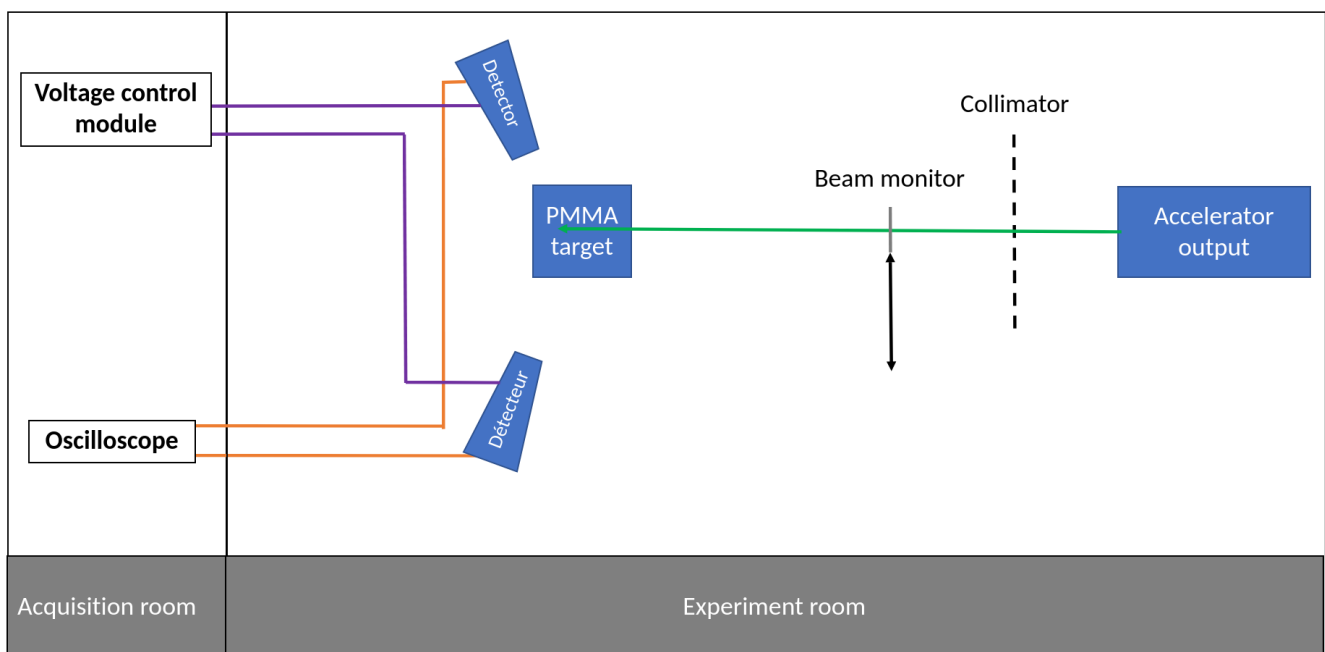


Figure 3. Experimental setup diagram.

135 The detectors used in these experiments are scintillators coupled to photomultiplier tubes. Various
 136 scintillation crystals were employed to determine optimal characteristics based on their luminosity and
 137 scintillation constants.

138 A PMMA target serves as a phantom to stop the proton beam and generate secondary radiation. In
 139 the following, we will focus mainly on the results obtained at ARRONAX with pulsed beams, whereas
 140 experiments at CAL were used to study the behaviour of various detectors with continuous beams. The target
 141 was irradiated with a beam whose intensity could be adjusted up to 20 μA during pulses at ARRONAX.
 142 The measurement of the beam intensity was carried out by an ionization chamber located upstream from
 143 the exit window of the accelerator beamline in vacuum. Detectors are positioned around the target to
 144 detect the secondary radiation or particles produced during irradiation. The signals from the detectors are
 145 recorded using a LeCroy DSO oscilloscope, allowing automatic recording of approximately 100 waveforms
 146 of the characterized detector signals with 20 GHz sampling period. Recording is triggered by the beam
 147 pulse signal. Figure 4 provides an example of waveforms obtained on a PbWO_4 detector at ARRONAX,
 148 illustrating the correlation between the signal of the incident alpha beam pulse from a fast beam monitor
 149 (single diamond used as a solid-state ionization chamber) and the generated secondary particles.

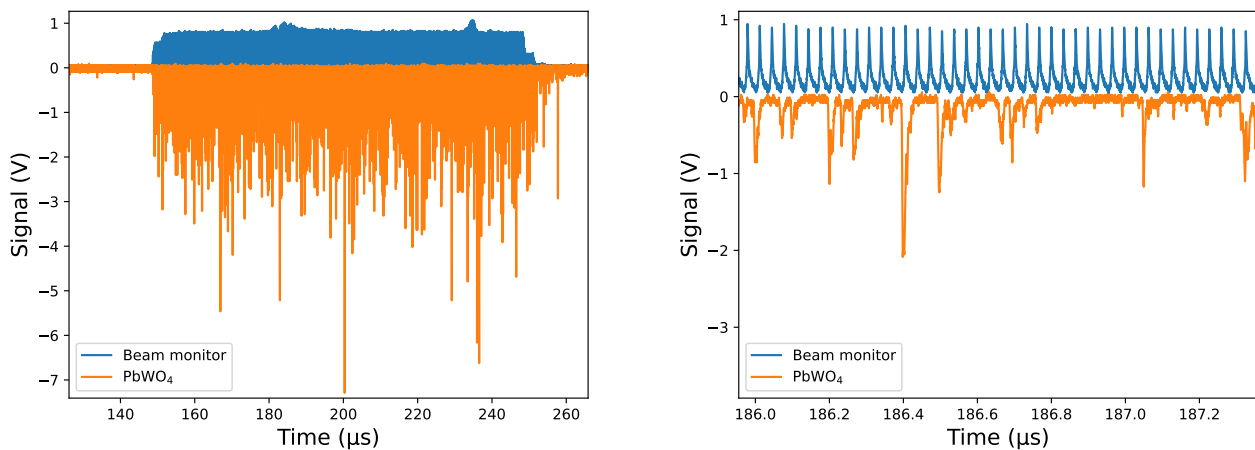


Figure 4. Waveforms recorded on the PbWO_4 detector and on the fast beam monitor (whose maximum has been normalized to 1 V) for an intensity of 2 μA of the 70 MeV (total energy) alpha particle beam in ARRONAX and a bias voltage of 2500 V. The figure on the right is an enlarged local view.

150 The recorded waveforms are then analyzed by a Python script, which initially corrects slight fluctuations
 151 in the detectors' baseline (average value subtraction, calculated from the start of the waveform that
 152 corresponds to 50 ns without signal). Subsequently, the script performs the integration of the detector
 153 signal over the duration of the beam pulse. Various parameters will be explored, such as the evolution of
 154 the integral with respect to the incident beam intensity, PMT bias (detector gain), and the distance from the
 155 impact point on the target (15 or 25 cm). Moreover, this Python script is able to detect each individual signal
 156 within the pulse (Figure 5) to enable correlation between the amplitudes of these signals and their integrals.
 157 The detection of individual signals occurs with the following conditions: a threshold value corresponding
 158 to 6 times the standard deviation of the points used for determining the baseline value, a time duration of
 159 2.5 ns above this threshold, and a minimal time separation of 2.5 ns between two consecutive signals. The
 160 integral of an individual signal is calculated over a duration of 32.5 ns, 7.5 ns before the local maximum,
 161 and the subsequent 25 ns.

162 The first experiments at CAL and ARRONAX demonstrated a rapid saturation of detectors with high
 163 luminosity (NaI and BaF_2), when count rates are no longer small compared to the accelerator frequency, as
 164 illustrated in Figure 6. In order to avoid detector saturation, a reduction of the PMT bias is necessary to

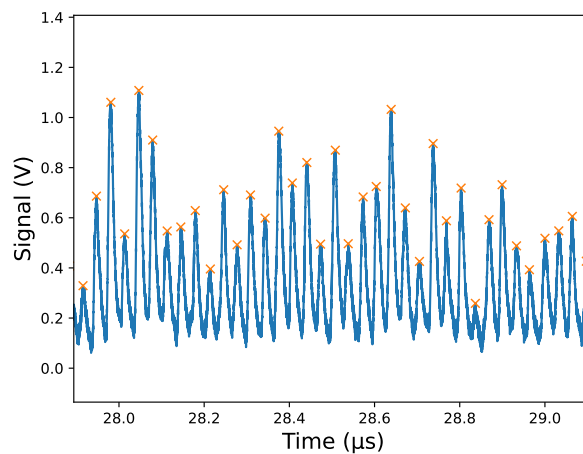


Figure 5. Waveforms recorded on the PbWO_4 detector for an intensity of 1600 nA of the 70 MeV (total energy) alpha particle beam in ARRONAX and a bias voltage of 1800 V, displaying the markers provided by the analysis program for identifying individual signals. The waveform has been reversed for the analysis.

165 reduce signal amplitudes so that a lower number of PG is expected – with a loss of information – after data
 166 analysis based on individual signal detection.

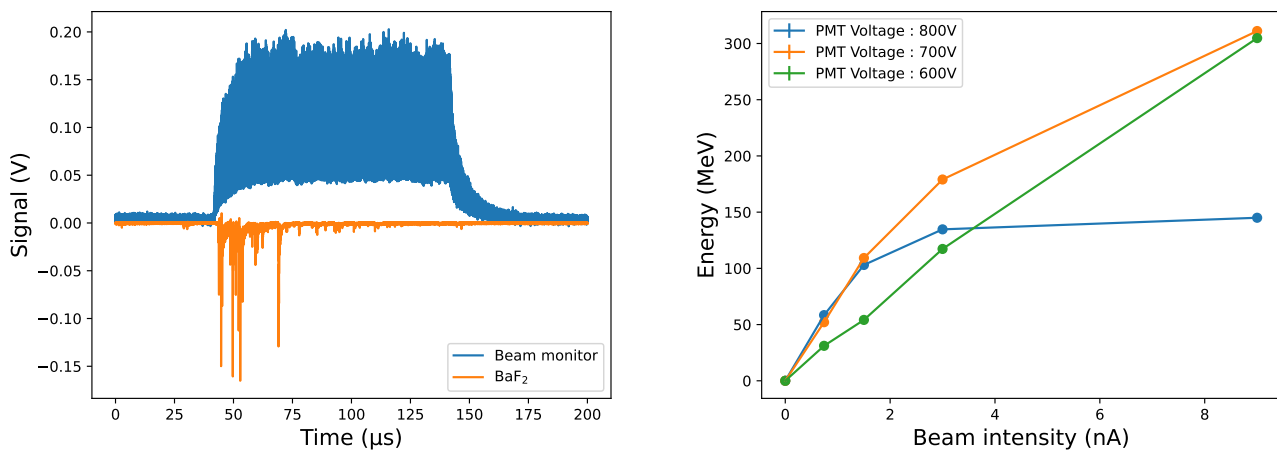


Figure 6. Results obtained with NaI(Tl) and BaF_2 scintillators placed at 45 cm from the target irradiated with the 68 MeV proton beam in ARRONAX. The pulse duration in 100 μs . Left: waveforms of the beam monitor in blue and the scintillator BaF_2 in orange at 3 nA beam intensity; right: evolution of the integral of the waveform during the pulse (expressed in equivalent energy following the detector calibration) on NaI(Tl) versus the intensity of the beam for different biases.

167 Subsequently, the results will pertain to a scintillator crystal, PbWO_4 , with a surface area of 4 cm^2 and a
 168 thickness of 3 cm, coupled with a PMT Photonis-XP2020. PbWO_4 was chosen due to its low luminosity
 169 (100 to 300 photons/MeV compared to approximately 38,000 for NaI(Tl)) and rapid scintillation decay
 170 constant (6 ns compared to 250 ns for NaI(Tl)), making it an ideal candidate for such applications. Indeed
 171 its fast decay time allows it, in principle, to return to its baseline between two consecutive proton pulses
 172 separated by 30 ns. However, this low luminosity induces a degraded energy resolution.

3 RESULTS

173 3.1 Simulations

174 The simulations allowed for the determination of the evolution of deposited energy based on longitudinal
175 displacements (with 8 detectors in operation) and lateral displacements (with 16 detectors) of the PMMA
176 target. Figure 7 illustrates the obtained results. In each case, a correlation between the target displacement
177 and the energy deposited per incident particle can be observed. In the longitudinal case, two groups of
178 detectors are noticeable — those located upstream from the target (backward) and those located downstream
179 (forward). Within one group, each detector exhibits the same behavior as the others, due to the geometry
180 and symmetry of the setup. Forward detectors (numbered from 0 to 3) experience an increase in deposited
181 energy as the target approaches them, due to the increase of their solid angle relative to the PG emission
182 points. The situation is reversed for backward detectors.

183 Similarly, the observed variation during lateral displacement is attributed to the variation in the solid angle
184 of the detectors relative to the emission points. However, other effects contribute to this variation, including
185 the thickness in materials that secondary particles must traverse to reach the detectors. Additionally, the
186 target displacement leads to a modification of the beam entry point and thus the depth of the Bragg peak,
187 resulting in a parabolic evolution of the detected energy in forward detectors for large target displacements.
188 Similar to the longitudinal displacement, symmetries are also clearly seen, explaining the similar evolution
189 of detector pairs, for example, [0,4], [1,3], and [5,7] for forward detectors.

190 The relatively large number of simulated incident ions (10^9) allows for the modeling of a certain number
191 of beam pulses containing a specific quantity of protons. One may add the responses of backward detectors
192 on one hand, and those located forward on the other hand, to detect longitudinal displacement. This
193 increases the perceived statistics as well as precision by a factor \sqrt{N} , with N being the number of detectors
194 in the group. Figure 8 illustrates the evolution of the total number of detected particles (left) and the total
195 energy deposition (right) in all detectors of each group for one given pulse of 1.5×10^7 incident protons.

196 A quasi-linear behaviour is observed (mainly due to the observation angle). The sensitivity of each
197 method is obtained by the ratio between the standard deviation of the simulated statistics and the slope of
198 the linear adjustment function. In this way, the sensitivity to displacement along the beam axis using the
199 PGPI method was calculated to be 1.3 mm at 1σ , while that of the PGEI is 3 mm at 1σ .

200 3.2 Experiments

201 The experiments carried out at ARRONAX allowed us to obtain the evolution of the response of a PbWO_4
202 scintillator coupled with a PMT XP2020 (from Photonis) as a function of the incident beam intensity
203 and the PMT bias, for two distances between the entry point of the target and the detector: 15 and 25 cm
204 (Figure 9). First, these experiments show that for each bias value, the integral evolves linearly with the
205 beam intensity until reaching a saturation value (close to 5×10^7 pV·s), at which loss of linearity is
206 seen; the loading charge of the PMT becomes too high. Lowering the bias voltage, and thus reducing the
207 PMT gain, helps to overcome this saturation. Second, as expected, increasing the distance between the
208 detector and the source reduces the detector counting rate, and thus increases the usable range of beam
209 intensity. This is due to the decrease of the detector solid angle: we could check that the count rate ratios
210 are approximately equal to $(15/25)^2$ (the square of the ratio of “target center-detectors” distances) for a
211 given bias in the linear response regime.

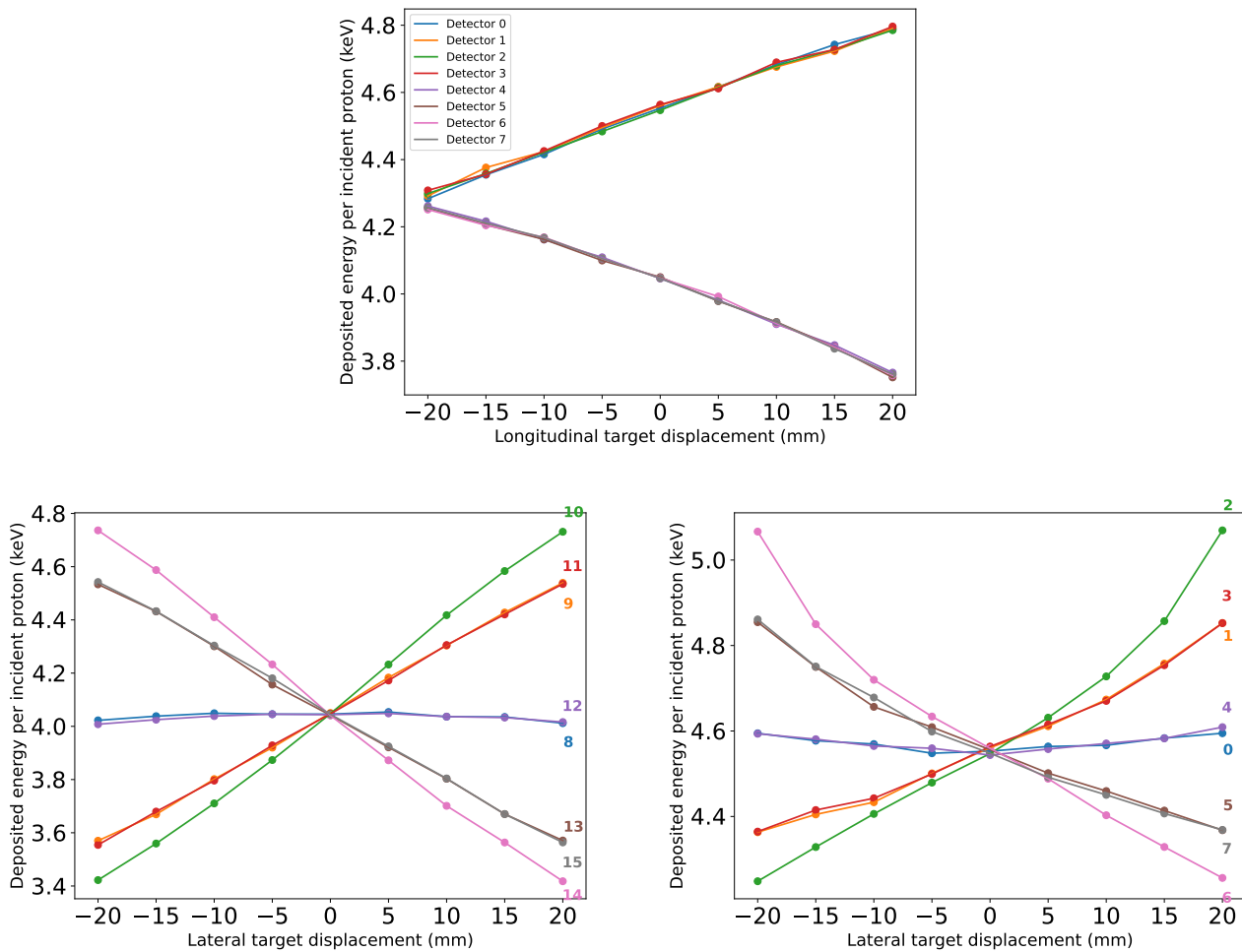


Figure 7. Deposited energy (keV) per incident particle (for 10^9 simulated protons) as a function of target displacement in mm. The first figure shows the evolution for longitudinal displacements, the second and the third ones for lateral displacements, with backward and forward detectors, respectively.

212 These results can also be compared to the documentation from the manufacturer of the PMT XP2020,
 213 which provides the characteristic evolution of gain as a function of the bias voltage. By plotting the
 214 evolution of the integral of signals against the applied bias, as shown in Figure 10, lines with the same
 215 slopes as those in the literature are obtained. The saturation configurations of the detector also appear in
 216 these figures; indeed, there is a noticeable inflection in all curves beyond an integral value of approximately
 217 2×10^7 pV·s.

218 An example of correlating the amplitudes of individual signals with their integrals is illustrated with
 219 density maps shown in Figure 11. These results correspond to a PMT bias of 2000 V for a distance of
 220 25 cm between the target and the detector and a beam intensity of 380 nA (left) and 3200 nA (right). These
 221 results reveal a clear correlation between the signal amplitudes and their integrals. At 380 nA (left figure),
 222 saturation is observed for signals above 1.6 V, which is due to the oscilloscope’s acquisition window and
 223 pertains to only a small number of signals. Moreover, although the two acquisitions presented in Figure 11
 224 correspond to beam intensities different by almost one order of magnitude, there is no indication for detector
 225 saturation, as the correlation is maintained. Furthermore, it can be observed that the increase in intensity
 226 leads to both an increase in the amplitude of each signal and its integral. In this experimental configuration,

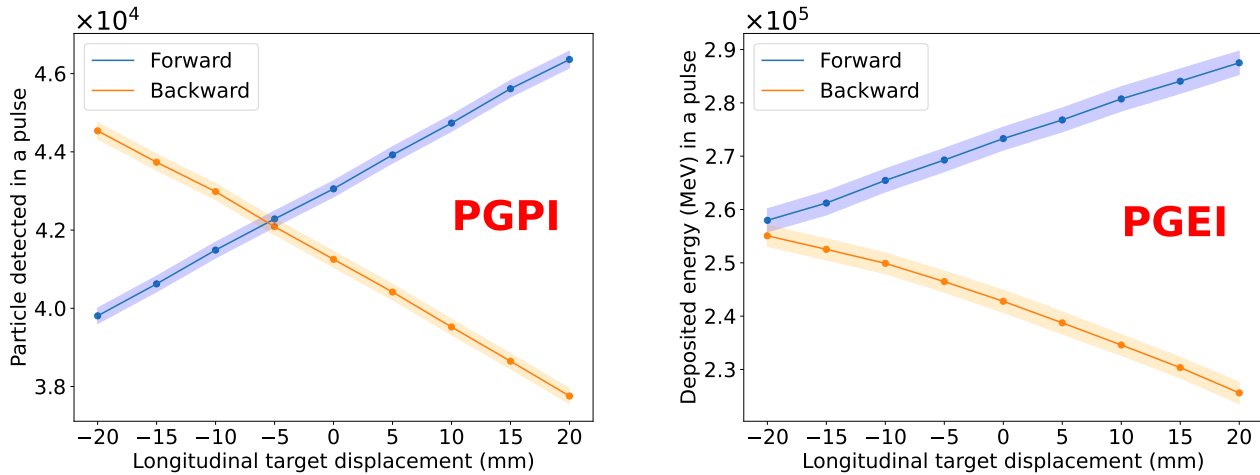


Figure 8. Expected number of particle detection (PGPI, left) or deposited energy in MeV (PGEI, right) within a group of detectors (forward or backward) for a beam pulse of 1.5×10^7 protons as a function of the target displacement along the incident beam direction. A 1 MeV threshold is applied on particle detection in order discriminate PG that did not interact in the target from background (Compton-scattered PG, electrons, neutrons...). The coloured zones correspond to the 1-sigma statistical uncertainty for one measurement.

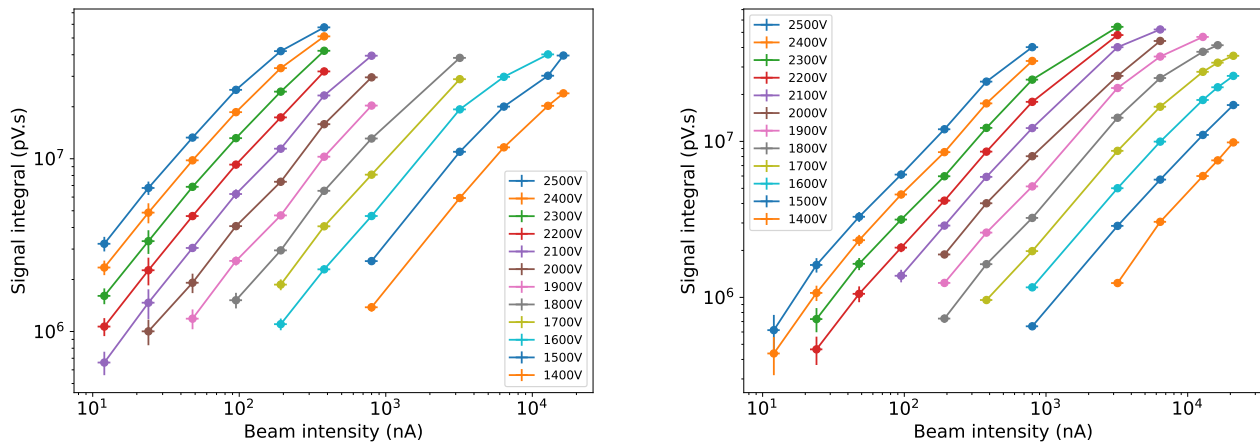


Figure 9. Integrals per beam pulse of the ARRONAX accelerator obtained with the $PbWO_4$ detector as a function of 70 MeV proton beam intensity (from 12 nA to almost 21 μA), for the various PMT bias values and 2 distances between the target entrance and the detectors: 15 cm (left) and 25 cm (right).

227 the duration of pulses are about 3-4 ns, and they are separated by 33 ns (HF period). Therefore, photons
 228 detected from the same pulse do lead to both added amplitudes and added signal integrals.

229 These results are confirmed by the histograms of the integrals of each of these individual signals, which
 230 are presented in Figure 12. The spread of the spectrum of integrals at high intensity can be seen in
 231 comparison with the lowest intensity.

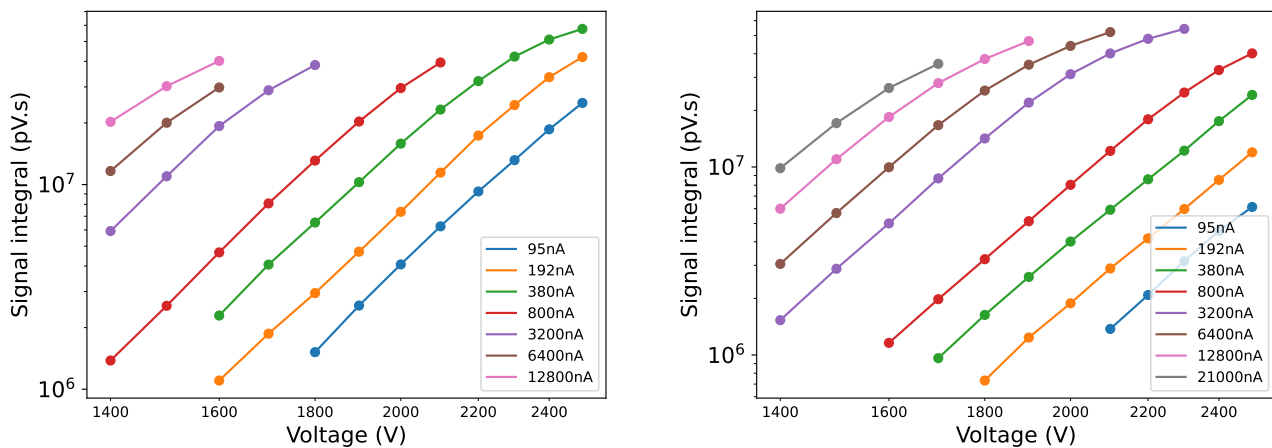


Figure 10. Integrals of the recorded waveforms at ARRONAX, with a proton beam of 68 MeV, as a function of the biases applied to the detector and 2 distances between the target entrance and the detectors: 15 cm (left) and 25 cm (right). The different curves correspond to different chosen intensities.

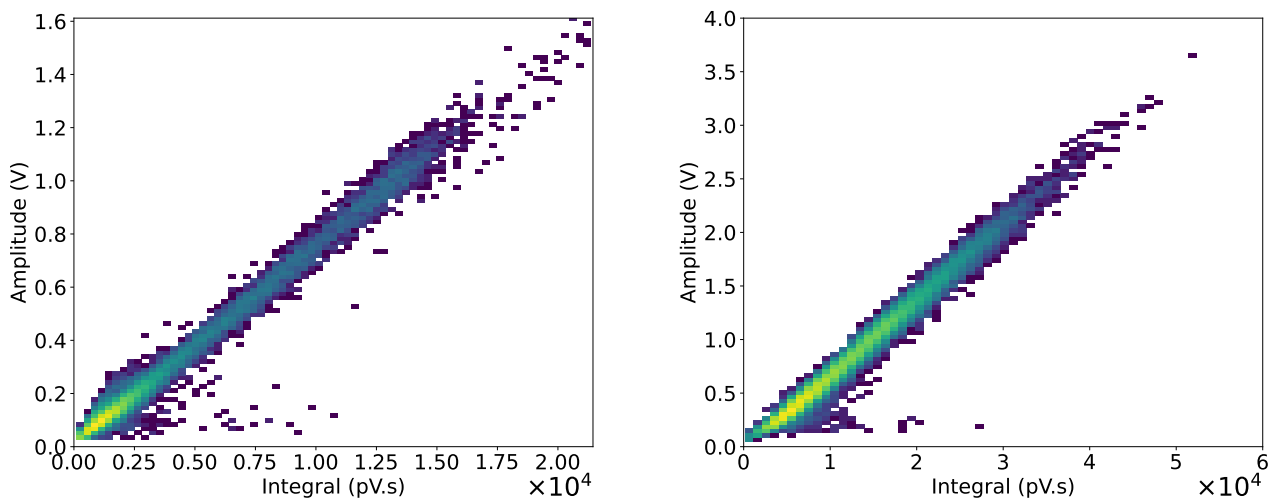


Figure 11. Density map of the amplitudes of the individual signals as a function of their integrals for a bias of 2000 V, with the detector placed at a distance of 25 cm from the target entrance and 68 MeV proton beam intensities of 380 nA (left) and 3200 nA (right).

4 DISCUSSION

232 4.1 Simulations

233 The conducted simulations demonstrated that each of the PGPI and PGEI methods is sensitive to the
 234 displacement of a target along either the incident beam direction or a transverse axis. Furthermore, it
 235 has been shown that the sensitivity obtained from both methods is of the order of a few millimeters with
 236 1.5×10^7 incident protons, positioning these techniques competitively compared to other PG detection
 237 methods in the context of online monitoring in hadron therapy [9]. The degradation observed between
 238 these two methods arises from two factors. First, the absence of any filter for the PGEI method leads
 239 to the necessity of accounting for the contribution induced by neutrons and all other secondaries during

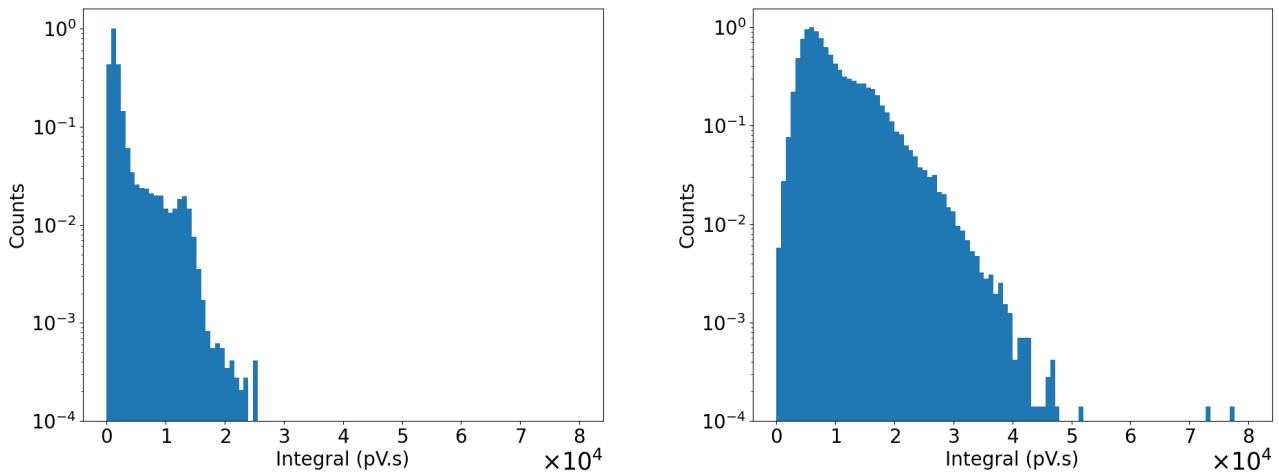


Figure 12. Histograms of individual signal integrals for intensities of 380 nA and 3200 nA with the detector placed at a distance of 25 cm from the target entrance.

240 irradiation, which carries less precise information about the ion path. Second, even if one considers only
 241 prompt-gamma rays, the PGEI method undergoes degradation compared to the PGPI method due to the
 242 wide energy spectrum of prompt-gamma rays, ranging from 1 to 10 MeV with an average located at 2 MeV.
 243 This leads to a broad dispersion of the averaged sums when multiple photons are detected during a beam
 244 pulse (total energies are of the order of 10^5 MeV in figure 8). Additionally, the sensitivity of each of these
 245 two methods increases with the expansion of the detection zones or the number of detectors around the
 246 target.

247 **4.2 Experiments**

248 This experiment demonstrated that the PbWO_4 crystal used, with a surface area of 4 cm^2 and a thickness
 249 of 3 cm, coupled with an XP2020 PMT, is capable, in certain configurations, to withstand a significant
 250 deposited energy flux without saturating the readout system. Thanks to the system performance, we
 251 were able to use the same peak intensities as those employed in clinical settings with pulsed beams from
 252 clinical synchro-cyclotron accelerators, or even much higher intensities, making the use of the PGEI
 253 method feasible for online monitoring in hadron therapy. The crystal used in these characterizations has
 254 an equivalent depth but a much smaller surface area than those used in the simulations. In the best case,
 255 this detector represents a solid angle about 10 times smaller than that of a detector used in simulations.
 256 However, this detector keeps a linear response at high beam intensities, well above the maximum intensity
 257 of the considered synchro-cyclotron. It may therefore be possible to increase its solid angle, with a limit
 258 of detector saturation at $1 \mu\text{A}$. This increase could be accompanied by an expansion of the solid angle by
 259 increasing the detection surface. Nevertheless, it is worth noting that a technological constraint on the size
 260 of PbWO_4 crystals may arise, requiring an increase in the number of detectors in the device to enhance its
 261 solid angle.

262 Furthermore, the development of this method will make use of a dedicated electronic system capable
 263 of integrating the signal from each detector. In practice, these signals will be compared to predictions by
 264 simulations associated to treatment plans to deduce any potential discrepancies.

265 4.3 Towards clinical implementation

266 The simulations were performed with large-sized detectors (cylindrical with a radius of 5 cm). These
267 surface areas are exaggerated but can partly be compensated by increasing the depth of the crystals, which
268 has been set here at 2.5 cm. Indeed, this depth corresponds to a 35% probability of absorption of a 4 MeV
269 photon for LaBr₃. Increasing this depth could be a way to compensate for the reduction in surface area.
270 Finally, the application context of these techniques, particularly the PGEI, with pulsed and high-intensity
271 beams offered by synchro-cyclotrons, leads to large loading charge to each detection channel. Therefore,
272 the choice of the scintillation crystal is of crucial importance. The sensitivity of the technique must be
273 studied with realistic simulation of patient treatments. Since MC simulations are not able to thoroughly
274 model all background sources, an additional background level based on experimental measurements can
275 be a posteriori added as proposed in [40, 41]. These realistic simulations will allow us to estimate false
276 negatives due to a compensation of different variations (eg combined variation in tissue composition and in
277 beam energy) and false positives due to wrong or outdated calibrations (geometry, radiation damage).

278 The proposed PGEI method has some pros and cons with respect to other range verification methods
279 envisaged for pulsed-particle beam therapy. The detection setup should be compact, like for iono-
280 acoustic [35, 36], electric-field [32] and magnetic field [33, 34] detection. The short-lived beta+ emission
281 detection [6] is less compact, but corresponds to a more mature technology. Iono-acoustic detection is an
282 integral method, restricted to soft tissues (without bone barrier). Electric field measurement is an integral
283 method that faces the issue of very low signal, and its feasibility has not been demonstrated yet. Magnetic
284 field measurements are also an integral method, the expected signals are very low and may be perturbed by
285 the environment (beam HF, magnets). The short-lived beta+ annihilation detection faces the issue of low
286 statistics at the spot scale for real time verification, and, relative to in-beam PET, the long positron range of
287 beta+ emitters like ¹²N blurs the signal.

288 Last, the present feasibility study has been intentionally performed using a phantom target with simple
289 geometry, and homogeneous chemical composition. The next step will consist of more realistic studies
290 using several real-size detectors and more complex (anthropomorphic) phantoms irradiated under clinical
291 conditions, in order to compare PGEI measurements with corresponding Monte Carlo simulations. Ideally,
292 a clinical-routine system should be compliant with the (possibly rotating) nozzle and the patient positioning
293 couch. Therefore, a flexible design should be envisaged, depending on the treatment type.

5 CONCLUSION

294 This simulation and experimental work brings together the preliminary bricks showing the feasibility of
295 a new prompt-gamma detection technique for particle therapy, adapted to the particular beam delivery
296 conditions of synchro-cyclotrons. The Prompt Gamma Energy Integration (PGEI) is designed to withstand
297 the high counting rates of secondary particles from such accelerators, due to their low duty cycle, and
298 therefore very high peak intensity. Simulations have demonstrated the feasibility of this technique by
299 showing millimetric sensitivity to the displacement of a target along a longitudinal axis for 10⁷ protons,
300 corresponding to a single spot of a pencil-beam scanning treatment. Although the background source from
301 scattered particles like neutrons cannot be filtered, unlike PGPI when ToF is measured, the integral energy
302 information makes it possible to reach this performance also with a reduced number of detectors located
303 around the patient. To withstand these high counting rates, it is crucial to choose an appropriate detection
304 system. Characterizations performed on a PbWO₄ scintillator have shown a large dynamic range of linear
305 response. This dynamic range extends from the lowest beam intensities to intensities higher than those

306 currently used in clinical practice. This confirms the choice of this detection system and opens up the
307 possibility of monitoring for FLASH-type particle therapy.

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