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Detection systems for range monitoring in proton therapy: Needs and Challenges

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Abstract

In-vivo range verification has been a hot topic in particle therapy for about two decades. In spite of vast efforts made by research groups all over the world, clinical devices and procedures for routinely monitoring the range of therapeutic particle beams in the patient's body and to ensure their correspondence with the treatment plan are not yet available. The paper reviews recent approaches with focus on prompt-gamma based methods of proton range verification and points to challenges that have not been discussed with the necessary depth and rigor in many (even recent) publications: First, the macro time structure of treatment beams in common proton therapy facilities requires detection systems with extreme load tolerance, throughput capability, and stability against load leaps. Second, the time period available for verifying the range of a single pencil beam spot is of the order of milliseconds, which limits the number of prompt gamma events that can be detected and processed. In view of these constraints it might be favorable to waive tight event selection by collimation or coincidence conditions as applied in most prompt-gamma based range verification techniques considered so far, and to move on to straight detection with uncollimated detectors combined with a multi-feature analysis deploying all pieces of information comprised in a registered event. Energy deposition, timing, and energy sharing between the involved detector segments in case of Compton-scattering or pair production are parameters bearing information on the beam track that could be extracted in a comprehensive analysis. This would maximize the number of valid events on the expense of 'information sharpness', but could eventually increase the total yield of information exploitable for range verification. Some aspects of such a strategy have already been realized with the Prompt Gamma-Ray Timing (PGT) and the Prompt Gamma Peak Integration (PGPI) techniques proposed recently. Data analysis schemes for a more generalized approach have not yet been developed, but the hardware to be used can already be sketched: Prompt gamma rays should be detected with scintillation detector modules consisting of single pixels with individual light readouts and independent electronic channels, similar to those developed for PET-MR. Prompt gamma-ray detection in this context is, however, much more demanding with respect to dynamic range,

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33 energy resolution, load acceptance, and stability. The corresponding requirements represent a challenge for the detector
34 physics community.

35 *Keywords:* Proton therapy; particle therapy; range verification; prompt gamma ray; Compton camera; gamma camera;

36 **1. Introduction**

37 Particle therapy (PT) has become a widely accepted and promising option for tumor treatments,
38 complementing the conventional radiotherapy performed with megavolt X-rays and electrons.
39 Meanwhile, more than 70 facilities all over the world can provide beams of protons, carbon or other
40 ions for clinical treatments [1]. The well-defined range of ions in tissue with the final dose maximum
41 (Bragg peak) followed by a sharp distal dose fall-off allows focusing the dose in the tumor while
42 minimizing the damage of surrounding normal tissue. The accuracy of predicting (i.e., planning) the
43 range in tissue is, however, affected by uncertainties in converting CT images in stopping power maps,
44 by anatomical changes in the patient's body during the treatment, and by other factors that are hard to
45 assess in clinical routine [2]. These uncertainties lead to rather large safety margins in the treatment
46 planning and constrain potential benefits of particle over conventional therapies [3]. The reduction of
47 range uncertainties would improve the precision and reduce the normal-tissue toxicity of particle
48 therapy. In this context, considerable efforts have been made to develop clinically applicable
49 instruments for verifying the particle range in situ, just during dose delivery, ideally with a precision of
50 one or two millimeters [4].

51 In spite of these efforts, commercial instrumentation for range monitoring is not yet available. This
52 seems astonishing in view of the many papers on this topic that have been published since the 1990ies.
53 However, clinical environment and clinical workflow in a particle therapy facility put severe
54 constraints on an instrument design:

- 55 (i) A range verification system (RVS) must neither interfere with the treatment beam nor with
56 the patient who is usually positioned on a robotic couch. In case of a treatment gantry, the
57 RVS should be gantry mountable. This limits the acceptable size and weight.
- 58 (ii) The range verification procedure must not extend the time a patient has to stay in the
59 treatment room. This is a question of resource economy. Clinics have to take care for a high

60 patient throughput in order to justify and to refund considerable investment and operational
61 costs of a PT facility.

62 (iii) Range verification systems must cope with the time structure and intensities of treatment
63 beams as given by the therapy facility and treatment planning rules. Physicians (and,
64 accordingly, manufacturers of PT facilities) try to keep irradiation times as short as possible.
65 This reduces the patient's strain as well as the risk of positioning errors caused by unwanted
66 motions of a patient. It is useless to hope that treatments could be lengthened to relax
67 demanding conditions for an RVS.

68 Unfortunately the latter aspect has been ignored in many (also recent) papers dealing with range
69 verification techniques. Therefore we will exemplify so-called 'treatment conditions' in a common,
70 commercial proton therapy facility, and discuss constraints resulting for the construction of RVS.
71 Finally we justify a generalized concept to overcome load and statistics issues in range verification
72 based on prompt gamma rays, and derive key parameters for corresponding detection systems.

73 **2. State of the art in range monitoring**

74 As a matter of principle, therapeutic particle beams stop in the patient's body. Any non-invasive
75 technique of range monitoring must therefore rely on secondary signatures, namely signals that are
76 generated by the beam, bear information on its location or range, and escape the body.

77 Particle-therapy PET, developed in the 1990ies, was the first method of in-vivo range verification
78 that has ever been successfully applied in patient treatments with particle beams [5]. PT-PET measures
79 the β^+ activity distribution induced by the ion beam crossing tissue with a common (commercial) or a
80 dedicated (in-beam) PET scanner. The main disadvantage of PT-PET is the signal delay of seconds to
81 minutes in correspondence with the respective decay times of the β^+ emitters. It causes a conflict
82 between optimum measurement conditions and the constraints (i) and (ii) named in section 1: The PET
83 scan should best start during the treatment and then continue at least some minutes after. This
84 maximizes collectible statistics and minimizes washout effects [6], thus leading to an optimum image
85 quality. In-beam PET measurements, however, could only be performed with a scanner that does not
86 interfere with the beam (a question of the mechanical design) and is not blinded by the prompt gamma-
87 ray flash during dose delivery (a question of detector technology and signal processing). Even if

88 dedicated instrumentation was available, the prolonged measurement after beam delivery compromised
89 the clinical workflow and reduced the patient throughput. That is why applications of in-beam PET are
90 restricted to clinical studies performed with non-commercial scanners, usually built by research teams
91 [5] [7]. The economically more efficient solution fitting with the mentioned constraints, namely
92 measurements with a commercial PET scanner after moving the patient to another room, suffers from
93 much lower statistics and the consecutive disturbance of the primary correlation between β^+ activity
94 distribution and spatial dose deposition in the patient due to biological washout by metabolism, blood
95 and lymph circulation [6].

96 That is why many research groups have focused their efforts on a promising alternative, namely
97 range verification based on prompt gamma rays (PG). This hard radiation is produced in nuclear
98 reactions triggered by beam particles hitting atomic nuclei of the penetrated tissue. It is emitted along
99 the beam track and well correlated with the dose deposition [8]. Prompt gamma-ray imaging (PGI) can
100 thus be used to reconstruct the beam track in tissue. Imaging systems with passive collimation by a pin-
101 hole [9], a linear slit [10], or multiple slits [11], have been investigated. So far the Knife-Edge Slit
102 Camera [12] developed by IBA¹, a company providing proton therapy facilities and related equipment,
103 is the only system that has ever been used for range monitoring in clinical treatments [13] [14]. This
104 camera is capable of detecting local range shifts down to 1-2 mm [15]. However, the massive and
105 heavy collimator may interfere with the patient's position and makes integration in a treatment facility
106 an expensive challenge. So it seems obvious to use active collimation instead. Several groups have
107 tackled the challenge of Compton imaging in the prompt-gamma energy domain [16] [17] [18] [19]
108 [20] [21] [22] [23]. Technical complexity, electronic expense, the huge detector load to be handled
109 during dose delivery, the low fraction of 'valid' events and the remaining background after passing all
110 coincidence and event selection criteria are intrinsic hurdles that cast doubts on the applicability of
111 Compton imaging under therapy conditions [20] [21] [22], in spite of punctually encouraging results
112 [23].

113 Some recent approaches are based on straight detection of prompt gamma rays with common,
114 unsegmented scintillation detectors:

¹ IBA Ion Beam Applications S.A., <https://iba-worldwide.com/>

- 115 – Prompt gamma-ray spectroscopy (PGS) measures intensity ratios of characteristic prompt-
116 gamma lines with detectors of adequate energy resolution [24]. The field of view of these
117 detectors is restricted to a distinct section of the beam track by using a massive slit
118 collimator. The reaction channels feeding the gamma lines are distinguished by specific
119 energy dependencies of the corresponding cross sections. Line intensity ratios therefore
120 measure the actual beam energy at the point of observation, or the residual range of beam
121 particles at the depth the collimated detector is looking at. An elaborated setup for clinical
122 use, consisting of a heavy collimator, multiple commercial $\text{LaBr}_3\text{:Ce}$ detectors, and a high-
123 throughput data acquisition system, is close to first testing in patient treatments [25].
- 124 – Prompt gamma-ray timing (PGT) analyzes the time distribution of prompt gamma rays
125 generated by a micro-bunched particle beam [26]. PGT spectra are measured with
126 uncollimated detectors relative to a bunch timing signal, actually the accelerator
127 radiofrequency (RF) tapped from the therapy facility [27] [28]. The setup resembles a
128 common time-of-flight (TOF) measurement. The width of the timing peak comprising
129 prompt events reflects the width of the time window for prompt gamma-ray emissions,
130 which equals the finite stopping time of the beam particles in tissue. The latter is defined by
131 the particle kinematics and is sensitive to their range. Tests with simple phantoms under
132 close-to-clinical conditions have proven the principle and yielded encouraging results [29].
- 133 – Prompt gamma peak integration (PGPI) determines the Bragg-peak position from prompt-
134 gamma count rate ratios measured with multiple detectors arranged around the target [30],
135 i.e., the patient's body. The individual count rates depend on the detectors' distance from
136 beam track and Bragg peak but are disturbed by interactions of the emitted radiation with
137 the body. Supposed the scattering and absorption effects could be corrected for, the count
138 rate ratios provided means for a range measurement. This technique has been demonstrated
139 in a simplified test case; its applicability in clinical scenarios has not yet been evaluated.

140 These three methods make use of common detector technologies and straight data acquisition
141 without event preselection by trigger or multiplicity logics. This promises simplicity, robustness, and
142 reduced expense.

143 A thorough and detailed review of PG-based range verification techniques is given in [31]. It is
144 worth mentioning that each of the PG-based range monitoring techniques discussed so far essentially
145 analyses just one distinct feature of the detected events: the incidence direction (correlated with the
146 emission vertices) in case of PGI, the gamma-ray energy in case of PGS, the detection time in case of
147 PGT, and the detection rate in case of PGPI. Complementary features are used for event filtering but
148 not for extracting range information: Energy cuts, for instance, select the high-energy PG events to be
149 used for PGT or PGI; time cuts are used to suppress uncorrelated background in case of PGI and PGS;
150 passive collimators restrict the incidence angle of the gamma rays analyzed for PGS.

151 There are some other techniques of range verification that have been proposed and explored. Pencil
152 beam proton radiography [32] can be used for checking the correctness of stopping power maps
153 derived from the planning CTs at reasonable expense. It is, however, in conflict with constraint (ii)
154 mentioned above since it requires patient scans with low-intensity beams in the treatment room. Beam
155 track imaging by means of secondary-electron bremsstrahlung has been demonstrated with carbon [33]
156 and proton beams [34], but the results can hardly be translated to treatment conditions. Acoustic
157 methods [35] [36] could be of advantage in case of highest beam intensities. Such techniques, however,
158 have only been explored in oversimplified scenarios and are by far not mature for clinical testing.

159 This paper focuses on techniques based on prompt gamma-ray measurements, since they are most
160 promising and closest to clinical applications. The discussion is also restricted to range verification in
161 proton therapy facilities. Those are cheaper and much more common than facilities providing beams of
162 ^4He , ^{12}C , or other ions as well, and their number is growing steadily.

163 **3. The load and statistics problem**

164 PG-based range assessment in proton therapy is faced with a serious problem posed by intensity and
165 time structure of typical treatment beams. This becomes evident if one considers key parameters of an
166 exemplary clinical treatment site.

167 Let us look, for instance, at the IBA Proteus@PLUS facility of the University Proton Therapy
168 Dresden (UPTD). It is equipped with a universal nozzle capable of providing double-scattering (DS) as
169 well as pencil-beam scanning (PBS) treatments. Meanwhile most treatments are delivered in PBS
170 mode. This is the most advanced, most economic and gentle technique of dose delivery in recent

171 clinical facilities. The tumor is scanned in three dimensions with a beam focused to about the diameter
172 of a pencil (0.5 to 1.5 cm FWHM). Lateral beam deflection by dipole magnets provides two scanning
173 dimensions, the third one is due to a stepwise variation of the beam energy and consequently of the
174 penetration depth (range). A PBS treatment plan is organized in so-called energy layers, each
175 comprising a finite number of beam spots ('single pencil beams' or PBS spots) of the same beam
176 energy but different lateral positions as defined by settings of the scanning magnets. These spots are
177 typically delivered within 2-10 ms and separated by beam breaks of about 1 ms duration for updating
178 the magnet settings. The energy layers, on the other hand, are separated by two-seconds breaks needed
179 for beam energy switching. Note that the IBA C230 cyclotron is, as most proton therapy accelerators, a
180 fixed-energy machine. The beam energy is actually set by a degrader of varying thickness, followed by
181 an energy selection system comprising an analyzing dipole magnet and slit collimators.

182 The macro time structure of PBS treatments can be visualized by monitoring the prompt gamma-ray
183 production rate. Figure 1 presents an exemplary count rate histogram measured with a PGT detection
184 unit [37] during delivery of a representative PBS treatment field to an anthropomorphic head phantom.
185 The corresponding measurement was performed in parallel to the sensitivity evaluation of a knife-edge
186 slit camera [15]. The histogram relates to the intensity-modulated proton therapy (IMPT) treatment
187 plan described in [15]. It comprises one of two irradiation fields of a single fraction, representing a
188 dose delivery of about 1 Gy (photon-equivalent dose) to the target volume. The left panel illustrates the
189 coarse structure. Energy layers can be clearly distinguished. The built-up β^+ activity causes a variable
190 pedestal in between the layers. A closer look in a single layer (right panel) reveals the varying beam
191 current (in terms of the count rate), spot duration, and spot strength (number of protons in a spot
192 reflected in the number of prompt gamma-ray detections).

193

194 Figure 1

195

196

197 In a PBS treatment, *spatially* resolved range verification means assessing the *individual* ranges of
198 distinct PBS spots. Range verification systems must therefore in general extract the necessary

199 information from statistics that can be collected during delivery of a single spot, which means in a
200 measuring period of 10 ms or less. Furthermore they have to cope with a detector load as defined by
201 the maximum rate of proton delivery in the strongest beam spots.

202 Figure 2 shows the distribution of spot strengths (proton numbers) for the same treatment field. In
203 accordance with a similar analysis published earlier [10], the spots comprise up to $1-2 \times 10^8$ protons. 10^8
204 can be considered as representative number of protons for strong (mostly distal) PBS spots; there are,
205 in general, are only few spots exceeding this limit. If delivered in 10 ms, this corresponds to a rate of
206 10^{10} protons per second or a pencil beam current of about 2 nA, which is in good agreement with the
207 regular current at nozzle exit stated for the given facility. Assuming a prompt gamma-ray production
208 yield 0.1-0.3 per proton [10] [38], this translates to $1-3 \times 10^7$ prompt gamma rays per spot emitted in 4π ,
209 and to a production rate of $1-3 \times 10^9 \text{ s}^{-1}$ during spot delivery. In other words: There are plenty of prompt
210 gamma rays per spot, but the time available for a range measurement is extremely short. The statistics
211 of ‘usable’ PG events per spot is then not essentially given by the detector efficiency, but rather by the
212 acceptable detector load, by the achievable system throughput, and finally by the fraction of events
213 passing the respective event filter criteria.

214

Figure 2

216

217

218 Table 1 compiles some key numbers. The next sections exemplarily analyze consequences and
219 limitations resulting for range verification systems on the basis of two representative RVS concepts
220 described in previous papers, namely a Compton imaging setup and a system based on straight PG
221 detection.

222

Table 1

224

225

226 *3.1. Random and combinatorial background in systems based on coincidence measurements*

227 Prompt gamma-ray imaging with Compton cameras has been explored by many research groups
 228 around the world, as summarized in [31]. Most of the published papers, however, are simulation
 229 studies. Only few systems have ever been tested with radioactive sources, and so far – to the authors’
 230 best knowledge – only one Compton camera system could demonstrate reasonable imaging of a proton
 231 pencil beam in a clinical facility, though not yet with clinical beam currents [23]. We take this system
 232 as a reference to discuss limitations for RVS based on coincidence measurements.

233 The imaging setup described in [23] is based on four POLARIS-JTM detection stages by H3D²
 234 comprising large-volume, pixelated Cadmium Zinc Telluride (CZT) detectors of excellent energy
 235 resolution. The authors state a single gamma-ray detection rate of 54 kcps at 0.52 nA beam current
 236 [23]. This detector load should be basically due to prompt gamma rays. If we assume an average
 237 prompt gamma-ray production yield of 0.15 per proton, the 0.52 nA beam would generate about 5×10^8
 238 prompt gamma rays per second. We can therefore estimate the absolute PG detection efficiency to
 239 about 0.01 % per detector stage or $\varepsilon = 0.04$ % for the complete 4-stage system. Considering the ‘D2C’
 240 filter applied for suppressing events that are not suited for image reconstruction, this system provides
 241 about 1.5×10^{-6} usable events per incident proton [23]. This means not more than 150 valid (D2C
 242 filtered) events per PBS spot of 10^8 protons. This is a rather low number for detecting the end of a
 243 pencil beam track with millimeter precision since the gamma emissions are more or less randomly
 244 distributed along the beam track. The authors propose enlarging the setup by using 12 instead of only 4
 245 detection stages.

246 However, another parameter given is the coincidence resolution time of $\tau = 1.5 \mu\text{s}$ [23]. Events with
 247 detection times differing by not more than τ are assumed to form a Compton-scatter event induced by
 248 an incoming prompt gamma ray. Random coincidences occur if at least one other of the many gamma
 249 rays hitting the system generates an interaction within the time interval τ following a first detection.
 250 The corresponding probability is, according to [39], given by

$$P_{rand} = 1 - P(0)$$

251 where

² H3D, Inc., <https://h3dgamma.com/specialtyProducts.php>

$$P(0) = e^{-r\tau} = e^{-\varepsilon R\tau}$$

252 means the probability to detect *no* other hit in the time interval τ following a first detection, r the
 253 true event rate, R the total gamma production rate, and ε the absolute gamma detection efficiency of
 254 the system.

255 As a matter of principle the fraction of registered Compton events that are not contaminated with an
 256 additional gamma-ray detection in the coincidence time window somewhere else cannot exceed $P(0)$.
 257 Therefore rate of true coincidences due to (undisturbed) Compton-scatter events cannot exceed the
 258 value

$$r_{true}^{max} = r \cdot P(0)$$

259 Figure 3 exhibits the random coincidence fraction P_{rand} and the maximum true coincidence rate
 260 r_{true}^{max} for different coincidence resolution times τ as a function of the absolute system detection
 261 efficiency ε , calculated for a total gamma production rate of $R = 2 \times 10^9 \text{ s}^{-1}$ in accordance with Table 1.
 262 It is evident that random coincidences would represent at least about two thirds of the coincidence rate
 263 measured under treatment conditions with the 4-stage Compton camera system of 0.04% detection
 264 efficiency. With the larger 12-stage system of 0.12 % efficiency, random coincidences would by far
 265 dominate the acquired event rate; the fraction of true coincidences could not exceed 2%. Moreover, the
 266 wide coincidence window of 1.5 μs generally restricts the applicable detection efficiency. Once the
 267 efficiency reaches 0.03 %, a further increase does not rise but even reduces the maximum detectible
 268 rate of true coincidences caused by Compton scattering of a single gamma ray.

269

270 Figure 3

271

272

273 A weaker but more general limit of systems based on coincidence measurements is due to the
 274 simultaneous detection of two or more prompt gamma rays generated in the same micro-bunch. Such
 275 coincidences cannot a priori be distinguished from Compton-scattering events. According to Table 1, a

276 single proton micro-bunch generates up to 30 prompt gamma rays. Given a system with detection
 277 efficiency ε , the probability $P_{M(N)}$ of detecting just M out of the N prompt gamma rays per bunch is

$$P_{M(N)} = \binom{N}{M} \cdot \varepsilon^M \cdot (1 - \varepsilon)^{N-M}$$

278 Corresponding single-hit ($M = 1$), multi-hit ($M > 1$), and total event rates ($M > 0$) are given by

$$r_{M=1} = f \cdot P_{1(N)}$$

$$r_{M>1} = f \cdot \sum_{m=2}^N P_{m(N)} = f \cdot (1 - P_{0(N)} - P_{1(N)})$$

$$r_{M>0} = f \cdot \sum_{m=1}^N P_{m(N)} = f \cdot (1 - P_{0(N)})$$

279 where f means the repetition rate of proton micro-bunches.

280 Figure 4 shows these rates as a function of the system detection efficiency ε for $N = 20$ and a micro-
 281 bunch frequency $f = 106$ MHz in accordance with Table 1. Obviously the ‘combinatorial’ background
 282 sets an absolute limit for the applicable system detection efficiency: If the detection efficiency
 283 approaches 5 %, the increase of the total detection rate is predominantly due to the growing rate of
 284 multiple detections. The single-hit rate saturates at $\varepsilon \approx 5$ % and finally decreases. Note that this limit is
 285 independent of the coincidence resolving time, at least as long as the time resolution is not in the few-
 286 picoseconds range.

287

288 Figure 4

289

290

291 It is evident that random coincidences affect the applicability of Compton imaging systems in
 292 clinical treatments. One could argue that intelligent event filtering would reduce the random fraction.
 293 However, filters are usually distinguished by finite efficiency and lower the rate of usable events. It is
 294 also clear that filtering cannot reduce the system load caused by the background. As shown in the

295 example, random coincidences could even dominate the acquired event rate. In any case,
296 corresponding estimates and investigations have to be part of related research and must be considered
297 in the instrument designs as well as in publications.

298

299 *3.2. Load and throughput constraints in systems based on straight detection*

300 The importance of load and throughput constraints can be best illustrated by looking at a system
301 based on straight prompt gamma-ray detection. The PGT experiments at OncoRay have been
302 performed with detection units consisting of common $\varnothing 2'' \times 2''$ and $\varnothing 2'' \times 1''$ CeBr₃ scintillation
303 detectors by Scionix³, coupled to high-throughput digital energy and timing spectrometers U100 by
304 Target⁴ [37]. The count rate plots shown in Figure 1 were measured with a $\varnothing 2'' \times 2''$ detector at 40 cm
305 distance from the isocenter while delivering the representative clinical treatment field describe above.
306 During strong PBS spots the registered count rate was around 600 kcps (Figure 1, right panel). The
307 U100 is distinguished by a fixed dead time of 1 μ s per event. The throughput of 600 kcps then
308 translates to a detector load of 1.5 Mcps relating to energy depositions above the trigger threshold of
309 80-100 keV. Though an asymptotic throughput of 1 Mcps could be achieved, a further increase of the
310 detector load distinctly raises the percentage of system dead time as well as the fraction of pulse
311 pileups. In PGT experiments performed with clinical beam currents at OncoRay, detector-target
312 distances have mostly been chosen in the 40-60 cm range to keep detector loads well below 3 Mcps,
313 best in the 1 Mcps range corresponding to 500 kcps throughput. This means collecting 5000 events per
314 detector in the typical 10 ms period of spot delivery.

315 In PGT (and all other PG-based approaches to range verification) the number of registered events is
316 larger than the number of ‘valid’ or ‘usable’ events. Event filtering is applied to suppress background
317 and to select data comprising rather undisturbed range information. In case of PGT, only events with
318 energy depositions in the detector between 3 and 7 MeV are considered to reduce the background
319 caused by uncorrelated gamma rays, in particular annihilation radiation and 2.2 MeV gamma-ray
320 emissions following neutron capture on ¹H. This energy cut rejects about 90 % of all events, leaving

³ Scionix Holland B.V., <https://scionix.nl/configurations-general/#tab-id-2>

⁴ Target Systemelektronik GmbH & Co. KG, <http://target-sg.com/u100.html>

321 only 500 usable events per spot and detector. This number can be gradually improved by raising the
322 trigger threshold and fully exploiting the load capability of the detector itself, i.e. by shifting the
323 bottleneck from electronic throughput to constraints given by the detector physics. However, a
324 noticeable improvement of the statistics can only be achieved by using more detectors.

325 It must be emphasized that this limit is not due to an insufficient prompt-gamma production per spot
326 but due to the finite event rates the detectors and electronics are able to process. In case of PGT, the
327 interaction rates in the detectors could be raised by a factor of 4 or more just by reducing the detector
328 distance from the isocenter to a about 20 cm, a distance often supposed in simulation studies. Then,
329 however, neither detectors nor electronics could handle the load.

330 In conclusion, detector load and the bandwidth needed for data acquisition and processing are key
331 parameters that must be considered in design studies of PG-based RVS. Neglecting this aspect could
332 lead to investments in failing concepts.

333

334 *3.3. Detector stability at strong and irregular load leaps*

335 The count rate histograms in Figure 1 disclose another issue: Detection systems for prompt gamma
336 rays are exposed to frequent, abrupt, irregular load leaps challenging the stability of detectors and
337 electronics. Figure 5 exhibits count rate and Q - t histograms for a time section of the same
338 measurement comprising selected energy layers of treatment field. The parameters Q and t mean the
339 pulse charge (i.e., the raw energy) as delivered by the U100 spectrometer, approximately calibrated in
340 MeV, and the time elapsed since start of data acquisition. The ridge at $Q \approx 0.5$ represents 511 keV
341 annihilation gamma rays that are fully absorbed in the detector. Its slope changes at the same time as
342 the beam is switched on or off. The load steps obviously induce retarded gain shifts [40] [41].

343 More detailed but not yet published investigations [42] confirm that the detector timing is affected
344 as well. Timing effects seem, however, to be reasonably well correlated with the gain. This could allow
345 correcting for time shifts by tracking the gain. Monitoring the position of the omnipresent 511 keV
346 annihilation peak is meanwhile a standard procedure in PGT measurements anyway [40] [41] [29].
347 Such effects are not surprising for high-grade scintillators with ultimate light yield and short decay
348 time combined with light readout by photomultiplier tubes (PMT). The light flood caused by the huge

349 flux of prompt gamma rays leading to considerable energy depositions in the crystal, eventually
350 boosted by scattered protons crossing the scintillator, could easily provoke space charge effects in the
351 tube, either in the photocathode or in the anode regions. Those could affect the PMT gain as well as the
352 electron transit time and thus the timing. Note that excellent stabilization of anode and dynode voltages
353 in view of the expected light load, as considered in the U100 design, is inevitable for such applications.

354

355 Figure 5

356

357

358 It is worth noting that similar effects could occur with other detector types or configurations as well.
359 In case of the PGT detection systems, the gain and timing instabilities have been revealed in dedicated
360 experiments with clinical beam intensities and time structures, and they have been observed in spite of
361 stabilization means that prevented such drifts in less extreme operating conditions. We conclude that
362 the stability of detector system to be used in RVS has to be proven at clinical modes of beam delivery;
363 extrapolating laboratory experience to treatment conditions might be misleading.

364 **4. Generalized approach to proton range verification based on prompt gamma-ray detection:**

365 **Multi-feature range verification**

366 Manufacturers of proton therapy facilities race towards higher beam currents and shorter treatment
367 times. This is a question of economy (patient throughput, new accelerator types as synchrocyclotrons
368 saving cost and space), safety and precision (reduction of dose blurring caused by unwanted motions of
369 the patient, better treatment of moving tumors), as well as of convenience for the patients. Obviously,
370 the rate and statistics problem inherent in prompt-gamma based range verification will not ease but
371 sharpen in the coming years. Is there a way out?

372 As already mentioned, PGI and PGS make use of a tight event selection by (passive or electronic)
373 collimation and filter criteria being part of the data analyses. This reduces the number of valid events
374 but increases their ‘information content’, meaning their value for the respective analysis. An alternative
375 strategy is measuring without collimation but compensating the lower ‘information content’ per event

376 by a much larger number of counts. PGT and PGPI follow this strategy. Both use, however, only one
377 distinct feature for range reconstruction – detection time (PGT) or detection rate (PGPI). Best results
378 could be expected if all aspects of information carried by every single gamma ray irrespective of their
379 ‘sharpness’ would be considered in a comprehensive, generalized analysis, thus maximizing the overall
380 information deployed for range assessment under the constraint of limited statistics. To illustrate this
381 idea and to derive a corresponding hardware concept, we briefly discuss preliminary data obtained at
382 OncoRay without going into much detail.

383 Figure 6 (left panel) shows a 2D histogram representing the energy-time correlation for gamma rays
384 measured with a PGT detection unit during continuous irradiation of a beam-stopping polymethyl
385 methacrylate (PMMA) target with 225 MeV protons delivered by the IBA Proteus®PLUS facility at
386 OncoRay/UPTD. The exemplary data of excellent statistics were taken in a few-minutes run with
387 stationary pencil beam just to illustrate the potential of combining energy and time analyses. E in the
388 diagram means the energy deposition measured in the detector, $t-t_{RF}$ the gamma-ray detection time with
389 respect to the time reference, the accelerator RF signal. The time period just covers one micro-bunch
390 cycle of the cyclotron. At the proton energy chosen, distinguished by lowest possible energy loss in the
391 degrader, the system time resolution is in the 200-300 ps range [28]. The width of the timing peak is
392 here essentially given by the proton stopping time in the target, the effect PGT is based on. This means
393 the gamma-ray detection time is correlated with the penetration depth of the protons when generating
394 the gamma rays. One could expect that a time cut is then equivalent with the kind of spatial collimation
395 applied in PGS. In fact, the variation of distinct gamma line intensities along the time scale, observable
396 by eye already in the 2D plot (left panel), becomes evident in time cuts as shown in the right panel.
397 This suggests that the prompt gamma-ray timing and spectroscopy techniques, PGT and PGS, could be
398 merged in a comprehensive data analysis simultaneously deploying time and energy information of PG
399 events collected with an uncollimated detection system. Statistics and time resolution of a single-
400 detector measurement for a single spot in a PBS treatment would of course be much worse than in
401 Figure 6. However, one could use many detectors (instead of a bulky collimator), and develop methods
402 of statistical data analysis to reconstruct the most probable prompt-gamma emission profile along the
403 given beam track.

404

405

406 Figure 6

407

408

409 Detector segmentation is another aspect. In contrast to prompt gamma-ray imaging (PGI), the
410 ‘straight’ methods of prompt gamma-ray spectroscopy (PGS), timing (PGT), and peak integration
411 (PGPI) do not a priori require detectors with spatial resolution. However, segmentation with individual
412 readouts and electronics per segment is very useful for two reasons:

- 413 1. Segmentation distributes the count rate from a single to multiple detectors and electronic
414 channels and thus multiplies the overall event rate that can be acquired. 3×3 arrays of
415 $1.5\times 1.5\times 5\text{ cm}^3$ scintillators, for instance, represent about the same active area, volume, and
416 scintillator mass as single $\varnothing 2''\times 2''$ crystals, but could tolerate an overall load (detector) and
417 provide an overall throughput (electronics) exceeding that of the monolithic detector by
418 about an order of magnitude. As mentioned in section 3.2, higher detector load could be
419 reached by reducing the detector-target distance.
- 420 2. Once the detector is segmented, additional information about the incidence direction of
421 incoming gamma rays and thus on the source position could be extracted from Compton-
422 scattering events sharing their energy depositions between two or more detector elements.
423 The corresponding technique has been introduced as Single-Plane Compton Imaging (SPCI)
424 [43].

425 SPCI builds on the idea of directional gamma radiation detectors (DGRD) as elaborated in [44] [45]
426 [46]. In contrast to usual Compton cameras, where individual scattering angles are determined event-
427 by-event, the DGRD extracts a *mean* incidence angle from ‘conditional’ energy spectra measured with
428 detectors arranged in a single plane. The condition is a coincident energy deposition in two (adjacent)
429 detector elements, preferably of a given sum energy, which is most likely due to Compton scattering in
430 one element followed by a second interaction in the other one. SPCI generalizes this concept [43]:
431 Maximum Likelihood Expectation Maximization (MLEM) algorithms disentangle the directional
432 information comprised in multiple conditional spectra acquired with a multi-pixel array for

433 reconstructing complex activity distributions. In case of PG-based range verification, the image space
 434 is basically reduced to a single dimension, the penetration depth along the beam track. This should
 435 facilitate a corresponding analysis. On the other hand, the statistics of usable events is very restricted.
 436 Though Compton scattering dominates over photoabsorption and pair production in the PG energy
 437 range, not every interaction leads to energy depositions in multiple detector segments. According to
 438 explorative simulations [47], the corresponding fraction is expected to reach a few up to about twenty
 439 percent or even more, depending on the detector geometry, granularity, and filter criteria (sum energy
 440 cut, number of the segments involved, energy thresholds in the detector segments, etc.). In combination
 441 with the gain in load capability one could, however, anticipate a number of potential SPCI events as
 442 high as the number of usable events in case of PGT with unsegmented detectors.

443 The usability of the DGRD principle, so far only considered for energies below 1-2 MeV, has
 444 meanwhile been confirmed for prompt gamma rays of 4.45 MeV [47]. Two pairs of PGT detection
 445 units, arranged head-to-head with axes parallel to a proton beam penetrating a beam-stopping PMMA
 446 target, registered prompt gamma rays produced by a stationary proton pencil beam. Coincidences
 447 between adjacent ‘upstream’ and ‘downstream’ detectors were analyzed, considering only events with
 448 corresponding energy depositions E_u and E_d above 511 keV and a sum energy $E_{sum} = E_u + E_d$
 449 around 4.45 MeV. Mean energies $\langle E_u \rangle$ and $\langle E_d \rangle$ were computed for the conditional single-detector
 450 spectra tagged with the coincidence and filter conditions. Finally, a Figure of Merit (FOM) was
 451 introduced as

$$FOM = \frac{\langle E_d \rangle - \langle E_u \rangle}{E_{sum}}$$

452 Figure 7 shows a sketch of the setup and presents FOM as a function of the target position for the
 453 exemplary proton energy of 90 MeV. It is evident that the target position, related to the ‘average
 454 location’ of the prompt-gamma source, is retrievable from FOM . This justifies the assumption that
 455 SPCI could contribute to the reconstruction of the prompt-gamma emission profiles along the beam
 456 axis. We have to note that the data presented comprise about 1000 times the statistics obtainable from a
 457 single PBS spot. Furthermore, the results turned out to be very sensitive to detector gain drifts.
 458 Actually a dedicated calibration procedure took care for an almost negligible calibration uncertainty
 459 (translating to corresponding virtual gain stability) of around 0.1 % [47].

460

461 Figure 7

462

463

464 Future systems for PG-based range verification could therefore consist of multiple detector
465 segments, distinguished by excellent energy and time resolution, arranged side-by-side, each provided
466 with an individual electronics channel performing high-throughput time and energy spectroscopy.
467 Detection time, sum energy, and energy sharing between detector segments had to be measured for
468 every detected gamma ray. A comprehensive data analysis, based e.g. MLEM formalisms, would
469 consider these complementary aspects for reconstructing the most probable gamma-ray emission
470 profile along the pencil beam track, i.e., for determining the range of an individual PBS spot.

471 **5. Detectors for multi-feature range verification systems**

472 This concept, below referred to as multi-feature range verification system (MRVS), combines PGS,
473 PGT, and PGI (in the form of SPCI) in a single detection system. Though corresponding data analysis
474 schemes have not yet been developed, the hardware to be used can already be sketched. The key
475 parameters derived and discussed below are summarized in Table 2.

476 *5.1. Detector construction*

477 SPCI requires the system to consist of detector pixels with individual readouts. For reasons of
478 flexibility and scalability, a modular construction is advisable. At first glance, detector modules
479 developed for PET-MR (see e.g. [48]) look promising for SPCI as well as for PGT. They usually
480 consist of LSO or LYSO scintillator pixels read out with silicon photomultipliers (SiPM) or avalanche
481 photodiodes (APD). Their time resolution is excellent. However, the relatively high internal activity of
482 these scintillators, caused by β^- decays of ^{176}Lu accompanied by gamma-ray cascades from of the
483 excited daughter nuclide ^{176}Hf , would generate many true β - γ coincidences in adjacent detector pixels
484 contaminating the useful SPCI (i.e., Compton-scattering) events. Furthermore, the mediocre energy
485 resolution of these crystals would not be sufficient for PGS.

486 Nevertheless it is obvious to translate the construction principle of PET-MR detectors to an MRVS.
487 This means using pixels of fast and bright scintillator materials, distinguished by excellent linearity and
488 negligible internal activity, providing them with individual Si-based light sensors, and arranging a
489 reasonable number of such pixels in an array forming an MRVS detection module. The size of the
490 scintillator pixels has to be chosen as a compromise between cost (strongly affected by the number of
491 readout channels) and reasonable granularity. The pixel depth should fit with the absorption length for
492 4-5 MeV gamma rays. Considering the active area of available light sensors and an acceptable depth-
493 to-base ratio, pixel bases of 6-10 mm and pixel depths of 3-5 cm seem reasonable cornerstones.

494 5.2. Energy resolution

495 The energy resolution of MRVS pixels must be good enough for PGS. Reference [25] states a
496 resolution of 1.3 % at 6.1 MeV gamma-ray energy achieved with the $\varnothing 2'' \times 3''$ LaBr₃:Ce detectors of a
497 clinical PGS system at clinical dose rates. PGT detection units with $\varnothing 2'' \times 2''$ CeBr₃ detectors exhibited
498 3.5 %, 2.5 %, and 1.2 % energy resolution at 1.3 MeV, 2.5 MeV, and 6.1 MeV, respectively [41] [49].
499 These data can be considered as benchmark for MRVS pixels.

500 5.3. Time resolution

501 Requirements for time resolution are equivalent with those resulting from PGT. We have to consider
502 that the time resolution of PGT *systems* is basically limited by the finite width of the proton micro-
503 bunches [28]. At first glance, one could suppose a start detector with ultimate time resolution and rate
504 capability providing an individual timing signal for every proton would overcome this limitation.
505 However, the finite proton stopping time in the target is much larger than time intervals between
506 consecutive protons crossing the hypothetical detector. (Note that, at clinical beam currents, this would
507 hold even if the beam was not bunched but continuous.) Consequently the spread of the period between
508 proton passage and correlated prompt gamma-ray emission, or between proton passage and correlated
509 gamma-ray detection, is much larger than the average period between consecutive proton detections.
510 Therefore a single gamma ray could never be attributed to a distinct proton. In other words: The proton
511 bunch signal is the only time reference on hand. A start detector could in fact be useful for improving
512 the time reference for proton *bunches*, but not for providing distinct time references for single protons
513 and the corresponding prompt gamma rays.

514 At UPTD the minimum proton bunch width is about 250 ps (FWHM), measured at a relatively short
515 beamline at maximum proton energy (225 MeV). For energies between 90 and 160 MeV a much larger
516 bunch width was observed, ranging from 1 to 2 ns, which could even be worsened by a longer
517 beamline [28]. The PGT detection systems were designed to essentially not affect the system time
518 resolution, even in the best case of maximum proton energy. This led to a required (and later on
519 proven) time resolution of ~250 ps in the energy range of prompt gamma-rays [37]. This requirement
520 could, however, be relaxed in view of clinical applications.

521 *5.4. Tolerable detector load*

522 A benchmark for load tolerance of the detectors and electronics throughput is set by the available
523 PGT detection systems [37]. Lower load and throughput limits per channel could be acceptable since
524 the envisaged segmentation in relatively small pixels allowed increasing the overall detection rate even
525 at reduced load per channel.

526 *5.5. Gain stability*

527 The SPCI technique relies on the detection and quantification of small mean shifts and shape
528 variations of energy spectra measured with different detector pixels. Such variations could be feigned
529 by gain instabilities of individual detectors. As already mentioned, the clear correlation between FOM
530 and source position shown in Figure 7 could only be revealed by using an elaborated calibration
531 procedure correcting for potential gain shifts at an accuracy level of 0.1%. This calibration is based on
532 the mutual matching of straight energy spectra obtained with the individual detectors [47] [51] and
533 works well because of the good statistics of these measurements.

534 In MRVS, gain fluctuations due to load leaps may occur at a time scale of milliseconds, see Figure
535 5. Active gain stabilization seems unavoidable. A recent approach, based on a quantification of ‘noise’
536 caused by statistically fluctuating single-photoelectron contributions to the detector signal [52], might
537 provide the necessary stability at time scales in the sub-second range.

538 *5.6. Challenge and potential approach*

539 Each of the characteristics listed in Table 2 has already been reached with detector systems at hand.
540 However, achieving *simultaneous* compliance with *all* requirements is difficult.

541 It seems an obvious approach to rely on the construction scheme and the SiPM light sensors of
542 recent PET-MR detectors but to replace the LSO or LYSO crystals by CeBr_3 or $\text{LaBr}_3:\text{Ce}$. The high
543 light yield of these scintillators, however, combined with the high energies of prompt gamma rays,
544 conflicts with the limited number of microcells comprised in a SiPM. Prompt gamma rays of 4-6 MeV
545 could easily generate $2\text{-}4 \times 10^5$ scintillation photons per pulse and thus drive every commercial SiPM
546 into saturation. Though saturation effects can be corrected for, they could seriously deteriorate the
547 energy resolution just in the energy range most relevant for PGS. Careful measurements comparing the
548 energy resolution of CeBr_3 , NaI:Tl , and CsI:Tl scintillators if read out with silicon photomultipliers or
549 common photomultiplier tubes confirmed the clear disadvantage of SiPM in case of the fast and bright
550 CeBr_3 but even for the much slower NaI:Tl crystals in the energy range up to 6.1 MeV [53]. Reducing
551 the light collection efficiency is not an option since this would raise the statistical contribution to
552 energy resolution. Another weak point is the sensitivity of SiPM gains to external factors as bias
553 voltage and ambient temperature. Though gain stabilization at the percent level can be achieved by
554 temperature monitoring and voltage control, reaching the 0.1% mark might be a problem.

555 In view of the high gamma-ray energies of interest, light sensors without internal gain could be a
556 feasible alternative. PIN photodiodes (PD) have been used in gamma-ray spectroscopy with
557 scintillators, for instance with CsI:Tl , for decades. The energy resolution of a scintillator-PD
558 combination suffers from noise contributions of diode and preamplifier. That is why PD readout is not
559 competitive for spectroscopy in the low-energy range of common radioactive sources. On the other
560 hand, photodiodes are distinguished by outstanding detection efficiency for optical photons (quantum
561 efficiency) by far exceeding the quantum efficiency of PMTs or the photodetection efficiency of
562 SiPMs. The different scaling of noise and statistical contributions to the energy resolution with
563 growing photon number (i.e. increasing energy deposition) leads to an advantage of PD readout if
564 compared with PMT readout for energies above 1-2 MeV. This was demonstrated in corresponding
565 measurements with $\text{LaBr}_3:\text{Ce}$ crystals [54]. CeBr_3 or $\text{LaBr}_3:\text{Ce}$ detectors with photodiode readout are
566 thus expected to be compatible with the energy resolution and gain stability criteria given in Table 2.
567 Critical points are the achievable time resolution and load tolerance.

568 Developing suitable detection systems for multi-feature range verification system is obviously not a
569 straightforward exercise but a challenge. Recent efforts at OncoRay and HZDR are focused on
570 comparative studies of readout options considering realistic treatment conditions.

571 **6. Summary and conclusions**

572 Range verification of proton beams in radio-oncological treatments is a challenge many research
573 groups have been engaged in. The clinical environment and workflow as well as time structure and
574 intensities of therapeutic beams define constraints for range verification systems that are not always
575 considered in depth in simulation studies or system designs. This could lead to misguided investments,
576 also in terms of wasted effort and manpower.

577 The paper therefore analyzed and discussed general constraints for range verification systems based
578 on the detection of prompt gamma rays. Range verification for a single, strong pencil beam spot at
579 clinical rate of dose delivery is set as benchmark. The short duration of a single spot delivery, the
580 immense gamma-ray production rate during delivery, the finite load tolerance of detectors, and
581 electronic throughput limits were identified as major factors limiting the event statistics that can be
582 collected for a single pencil beam spot. For Compton cameras and other systems based on coincidence
583 measurements, rate and fraction of random coincidences may restrict the applicable overall detection
584 efficiency and thus further reduce the achievable statistics. Note that in practice few pencil beam spots
585 could be summed up to lower range uncertainties on the expense of spatial resolution. This means,
586 however, a gradual but not a principal relief. Reference to a single spot is, to our opinion, a useful
587 benchmark to compare systems of different designs.

588 In conclusion a generalized concept for prompt-gamma based range verification is proposed. The
589 gamma rays should be measured with scintillation detector modules consisting of multiple pixels with
590 individual readouts. This would increase the number of prompt gamma rays that can be detected per
591 pencil beam spot, and would allow extracting as much information as possible from every gamma-ray
592 event in order to assess the range of clinical proton beams with ultimate precision. Though similar
593 detector modules have been developed for applications as PET-MR, the envisaged measurement of
594 prompt gamma rays is much more demanding with respect to dynamic range, energy resolution, load
595 acceptance, and stability.

596 It is worth noting that such detection modules could also be used for measuring annihilation gamma
597 rays, even in parallel to the prompt gamma rays produced during dose delivery. This opens the way for
598 additional in-beam PET imaging, supposed that multiple detector modules are arranged in PET-
599 compatible geometry.

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605

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778 Table 1.

779 Key parameters of pencil-beam scanning (PBS) treatments at the IBA Proteus®PLUS facility at the University

780 Proton Therapy Dresden (UPTD)

781

Parameter	Value			
	general	per microbunch	per PBS spot	per second
Cyclotron RF	106 MHz			
Microbunch separation	9.6 ns			
Beam current ^a	≈2 nA			
Prompt gamma production yield per proton [10][38]	0.1 – 0.3			
Number of protons ^a		100	10^8	10^{10}
Number of prompt gamma rays ^a		10-30	$1-3 \times 10^7$	$1-3 \times 10^9$

782 ^aTypical values during delivery of strong (distal) pencil beam spots.

783

784 Table 2.

785 Intended key parameters of detectors to be used for range verification based on prompt gamma rays according to
786 the generalized multi-feature range verification concept

787

Parameter	Value
Approximate size	1 cm ² × 3...5 cm
Tolerable detector load	1 Mcps ^a
Electronic throughput at tolerable detector load	500 kcps ^a
Energy resolution	3.5% @ 1.3 MeV ^a 2.5% @ 2.5 MeV ^a 1.2-1.3% @ 6.1 MeV ^{a,b}
Time resolution (CRT)	250 ps @ 4.5 MeV ^a
Gain stability	0.1 % ^c

788 ^a Values achieved with PGT detection units [37] [40] [41] [49]

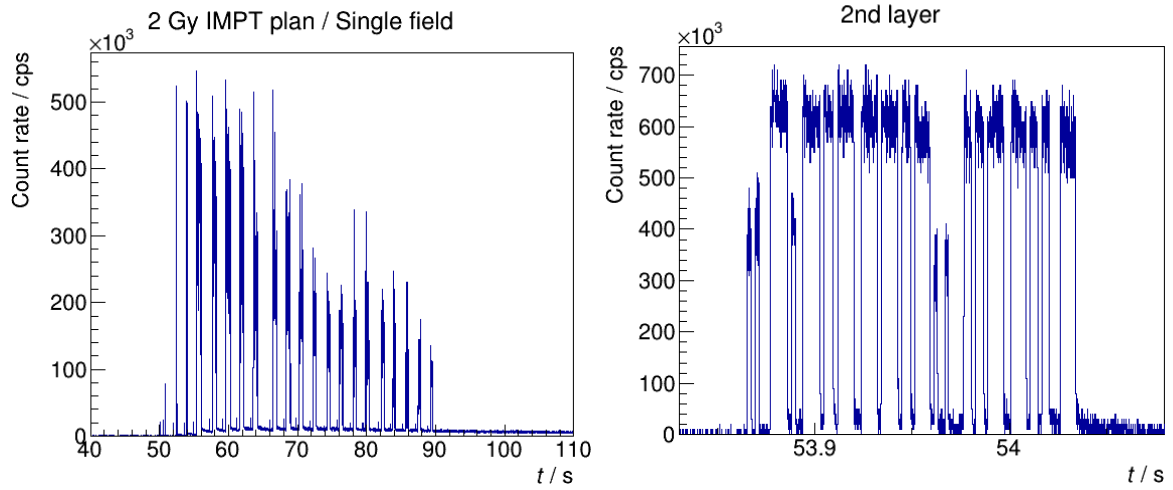
789 ^b Resolution stated in [25]

790 ^c Gain accuracy achieved by means of a dedicated calibration procedure [47]

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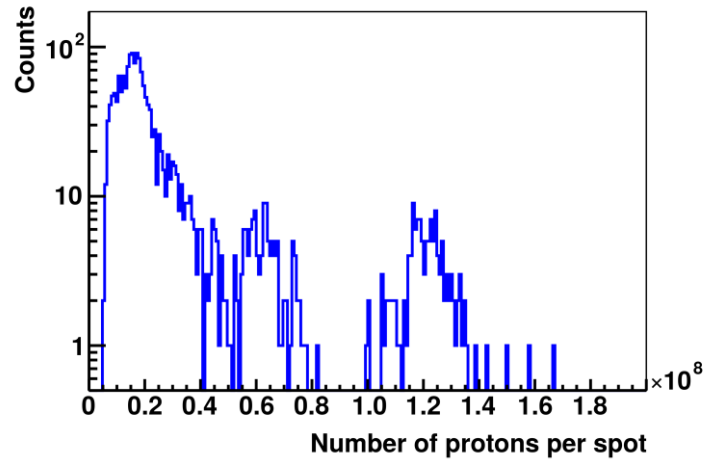
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795 Figure 1. Count rate (throughput at $1 \mu\text{s}$ dead time per event) measured with a PGT detection
 796 unit [37] during delivery of a realistic IMPT treatment field to an anthropomorphic head phantom.
 797 Parameter t denotes time elapsed since start of data acquisition. The histograms disclose the time
 798 structure of dose delivery: Energy layers are separated by few-seconds breaks for beam-energy
 799 switching (left panel). Each layer is structured in distinct PBS spots of few-milliseconds duration
 800 (right panel). Note the extreme load variations at a millisecond time scale.

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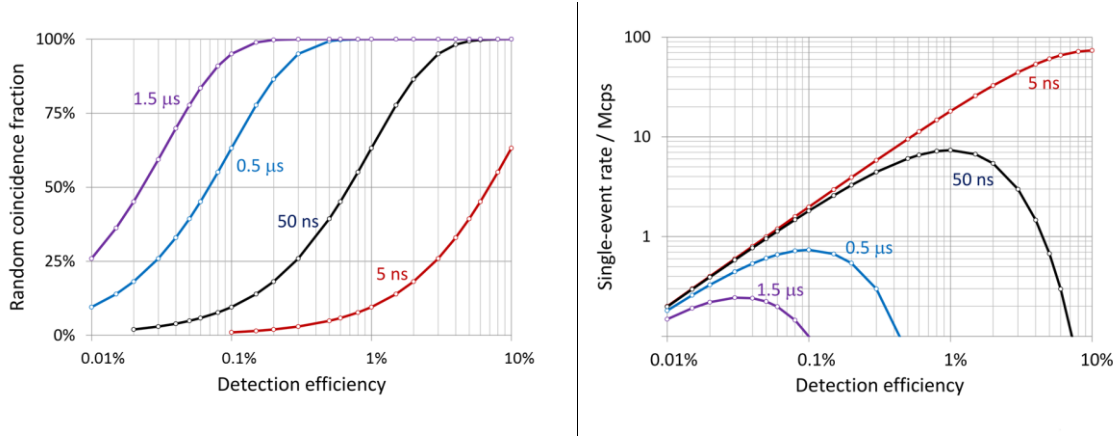
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806 Figure 2. Distribution of PBS spot strengths (in terms of protons per spot) of the IMPT treatment
807 field referred to in the text and in Figure 1.

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Figure 3. Minimum random coincidence fraction (left panel) and maximum true coincidence rate (right panel) of a Compton camera as function of system detection efficiency and coincidence time resolution. A prompt-gamma production rate of $2 \times 10^9 \text{ s}^{-1}$ was assumed, which corresponds to realistic treatment conditions (see Table 1).

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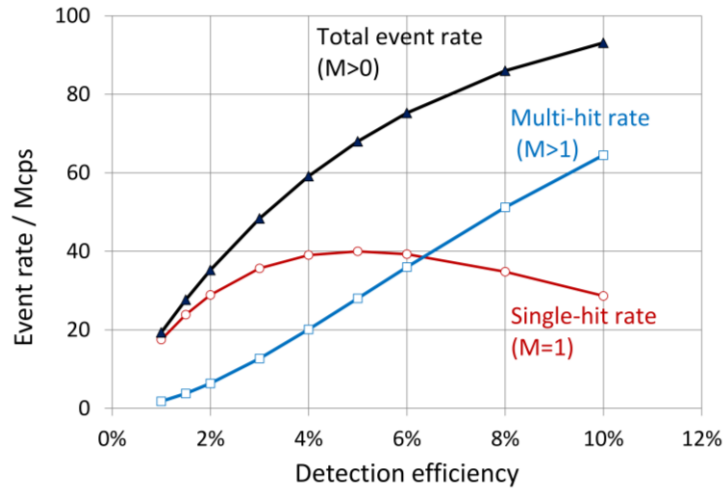
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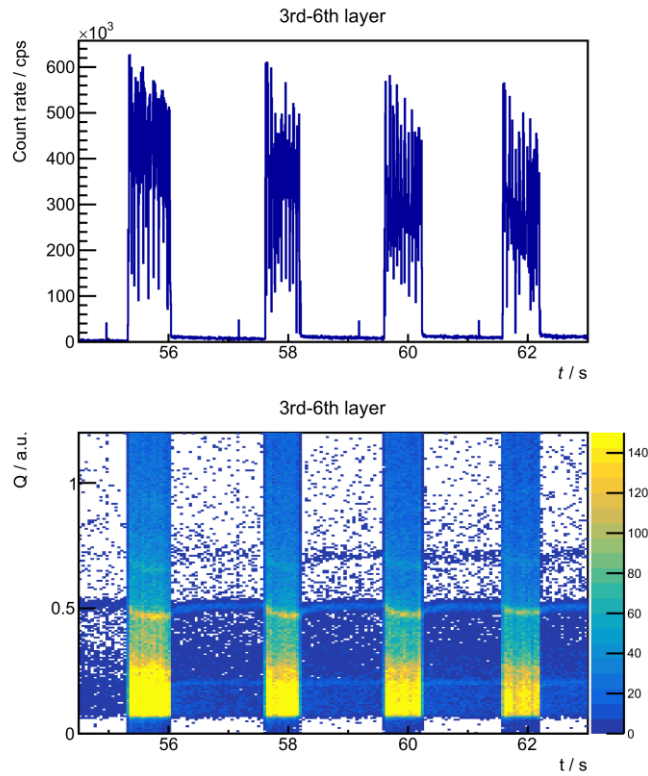
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820 Figure 4. Single- and multi-hit rates compared with the total event rate as function of the system
 821 detection efficiency. A bunch repetition frequency of 106 MHz and an (average) number of 20
 822 prompt gamma rays produced per bunch were assumed in accordance with Table 1. Multi-hits are
 823 caused by simultaneous detections of two or more prompt gamma rays of the same micro-bunch.
 824 Their fraction increases with the system detection efficiency on the expense of single-hit detections,
 825 finally leading to decreasing single-hit rate.

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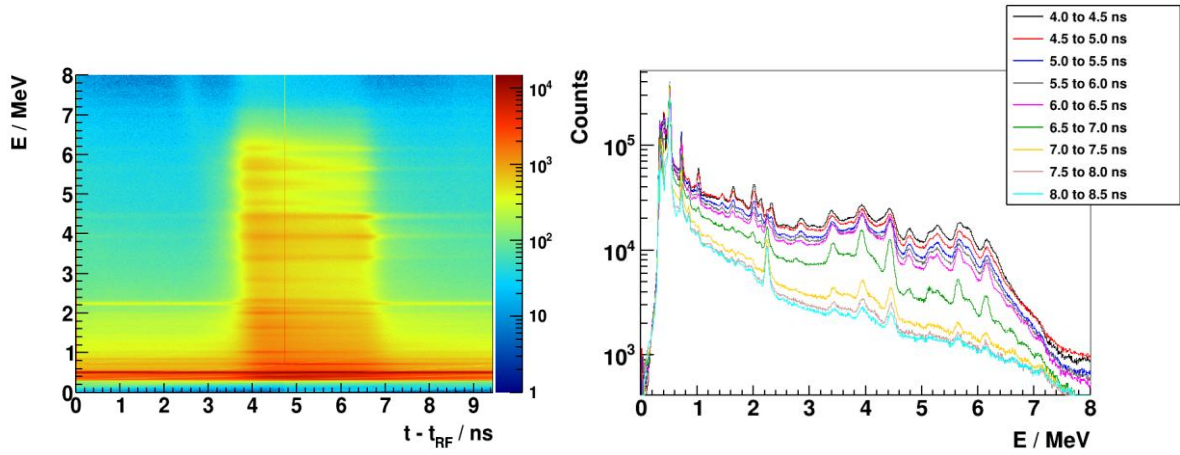
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830 Figure 5. Count rate (upper graph) and Q - t histograms (lower graph) for the 3rd to 6th layer of the
 831 IMPT treatment field referred to in the text and in Figure 1. The parameters Q and t mean the pulse
 832 charge (raw energy without gain drift correction, approximately calibrated in MeV), and the time
 833 elapsed since start of data acquisition. Retarded gain shifts caused by load leaps are clearly visible
 834 in the ridge representing 511 keV annihilation gamma rays absorbed in the detector ($Q \approx 0.5$).

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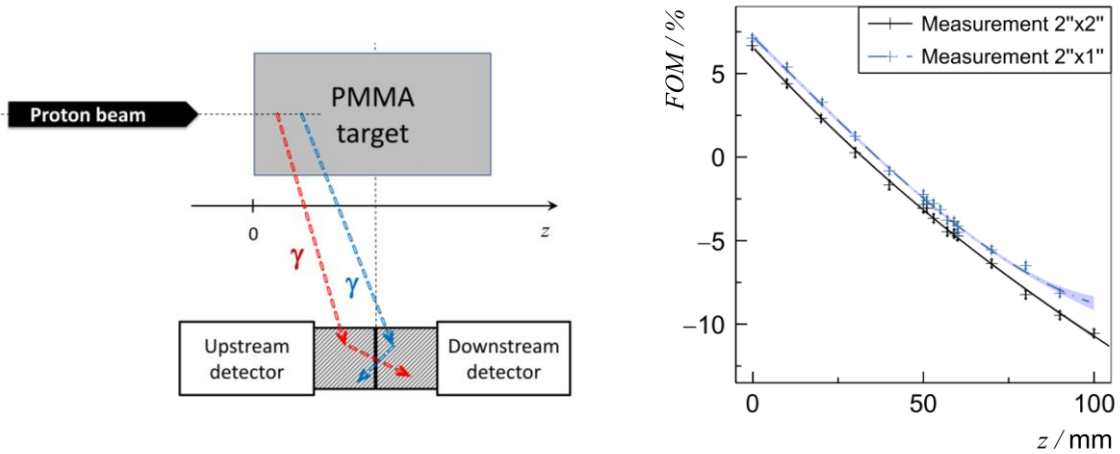
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839 Figure 6. Energy-time histogram of gamma rays emitted from a PMMA target during irradiation
 840 with a stationary 225 MeV proton beam (left panel), measured with a PGT detection unit
 841 comprising a Ø2”×2” CeBr₃ scintillation detector. Time cuts in these data correspond to spatial
 842 collimation; they disclose the variation of line intensities with the penetration depth of the protons
 843 as deployed for PGS (right panel).

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848 Figure 7. Sketch of the setup for testing the DGRD principle with prompt gamma rays (left
 849 panel), and Figure of Merit (right panel) denoting the relative difference of mean energies,
 850 computed for conditional spectra of the 'upstream' and 'downstream' detectors, as function of the
 851 PMMA target position [47]. The condition comprises a coincidence between both detectors, an
 852 energy cut around the 4.45 MeV sum energy peak, and an energy threshold for each detector
 853 suppressing events with energy depositions of 511 keV or less. *FOM* is given for two distinct
 854 measurements with PGT detection units comprising $\varnothing 2'' \times 2''$ or $\varnothing 2'' \times 1''$ CeBr₃ scintillation
 855 detectors at 90 MeV proton energy, respectively. In both cases it is well correlated with the target
 856 position.

Figure 1a
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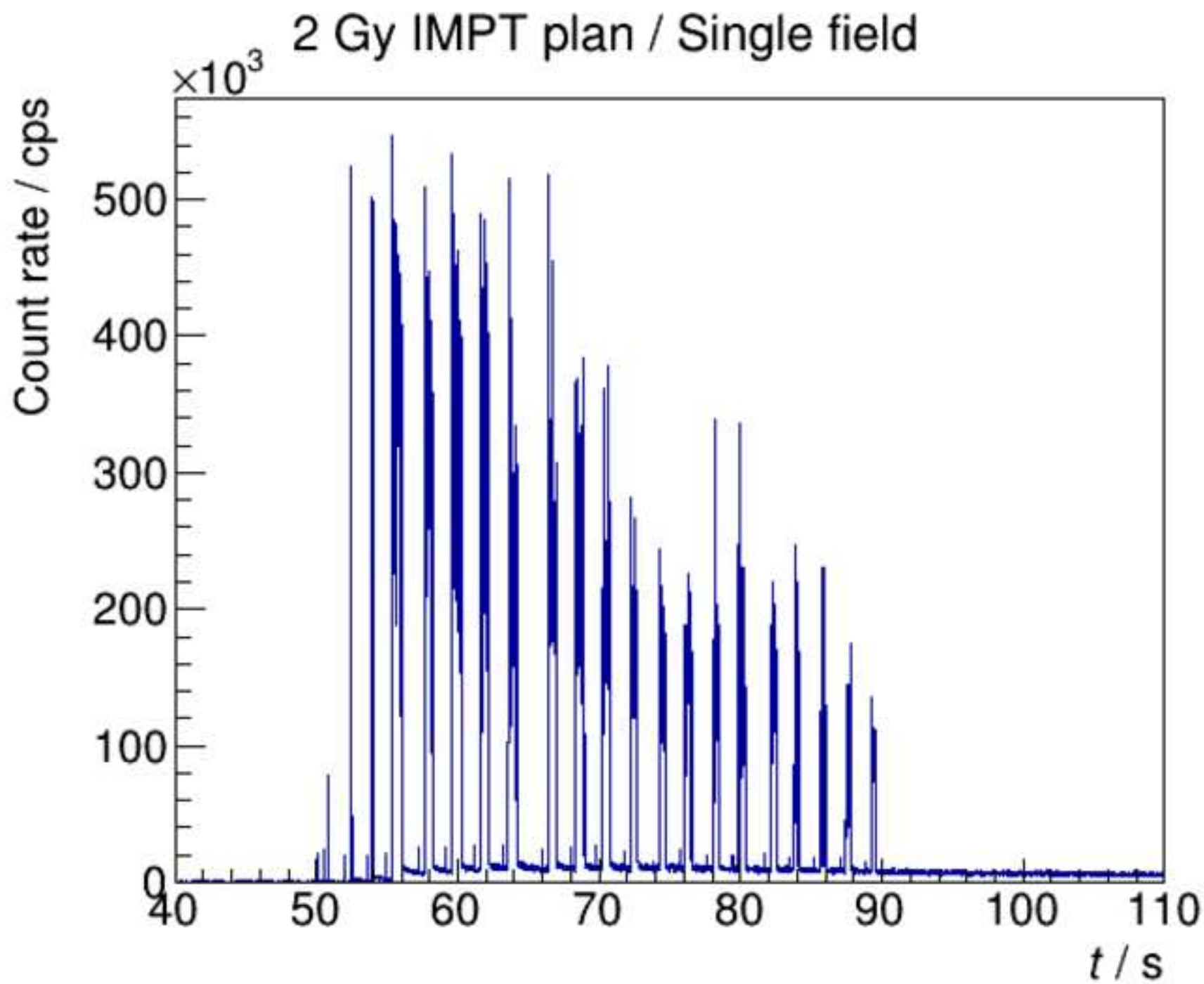


Figure 1b
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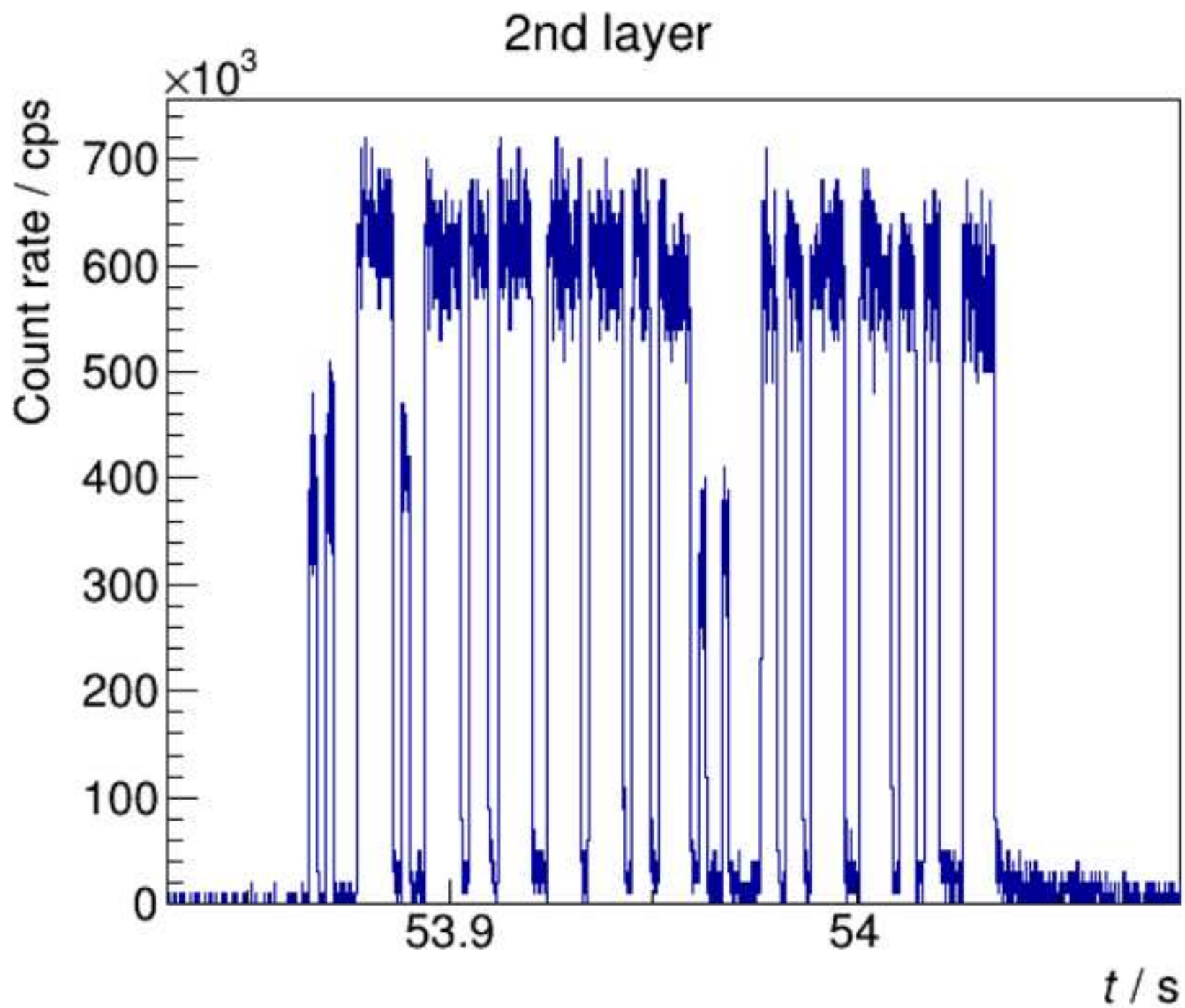


Figure 2
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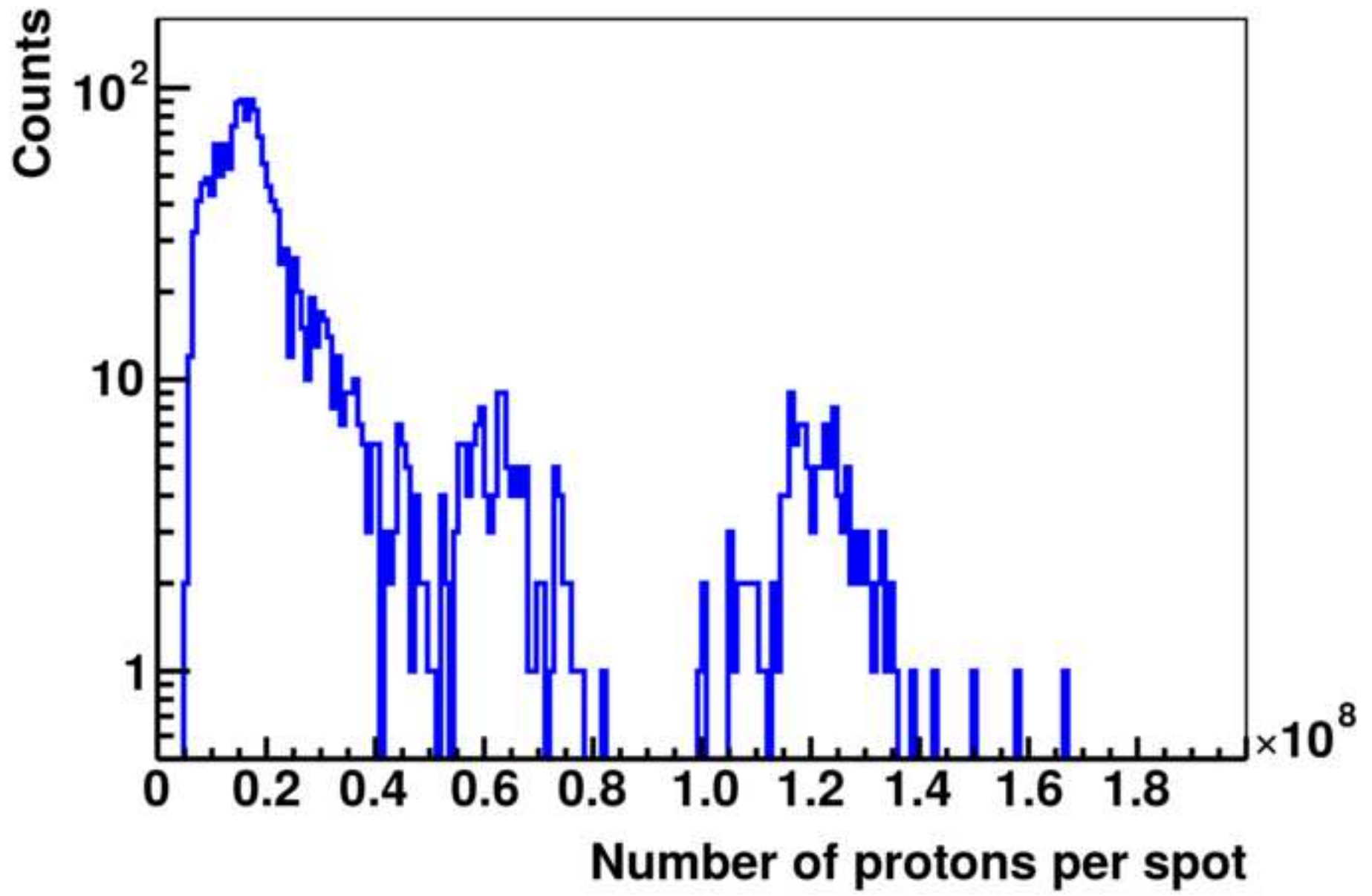


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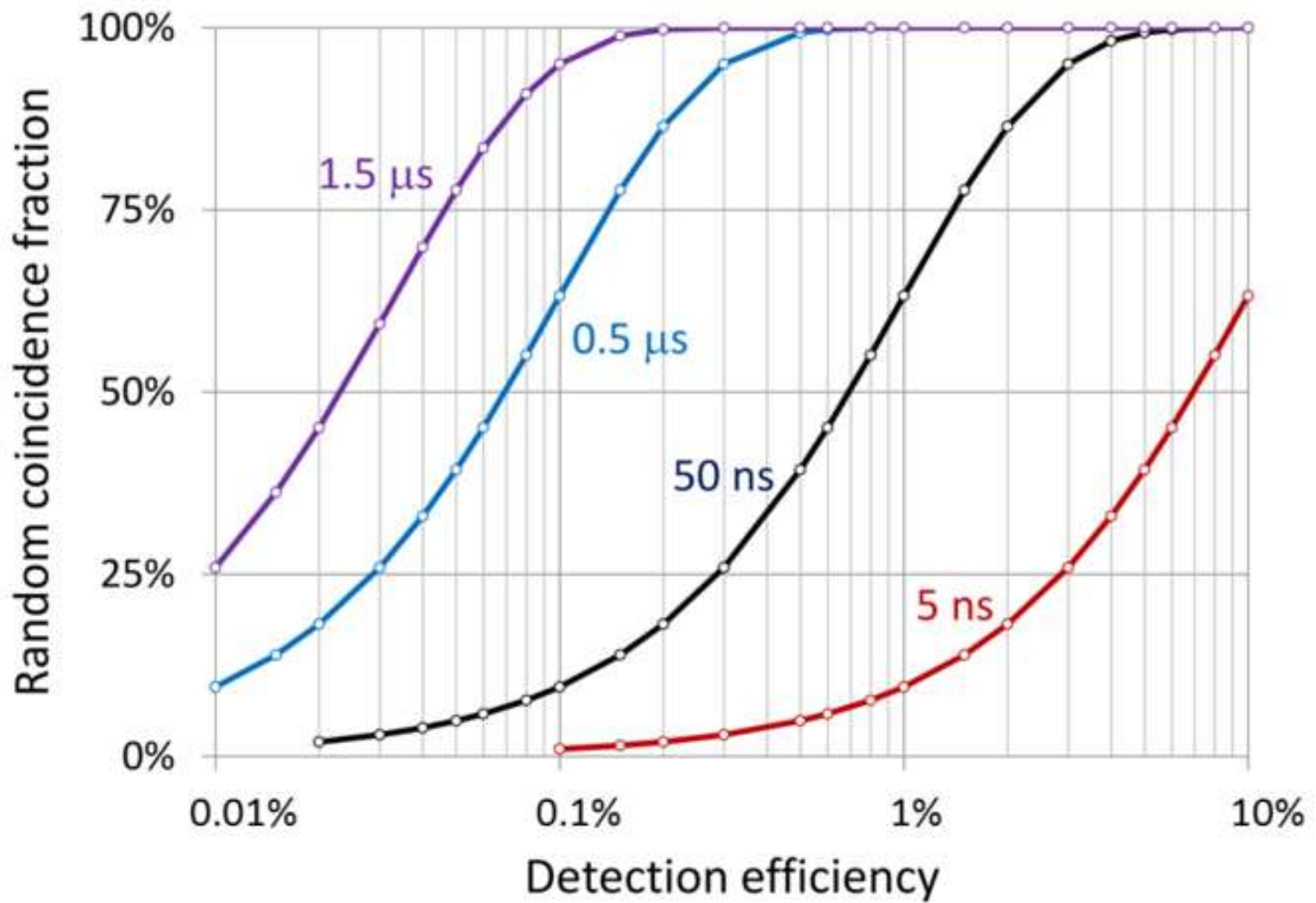


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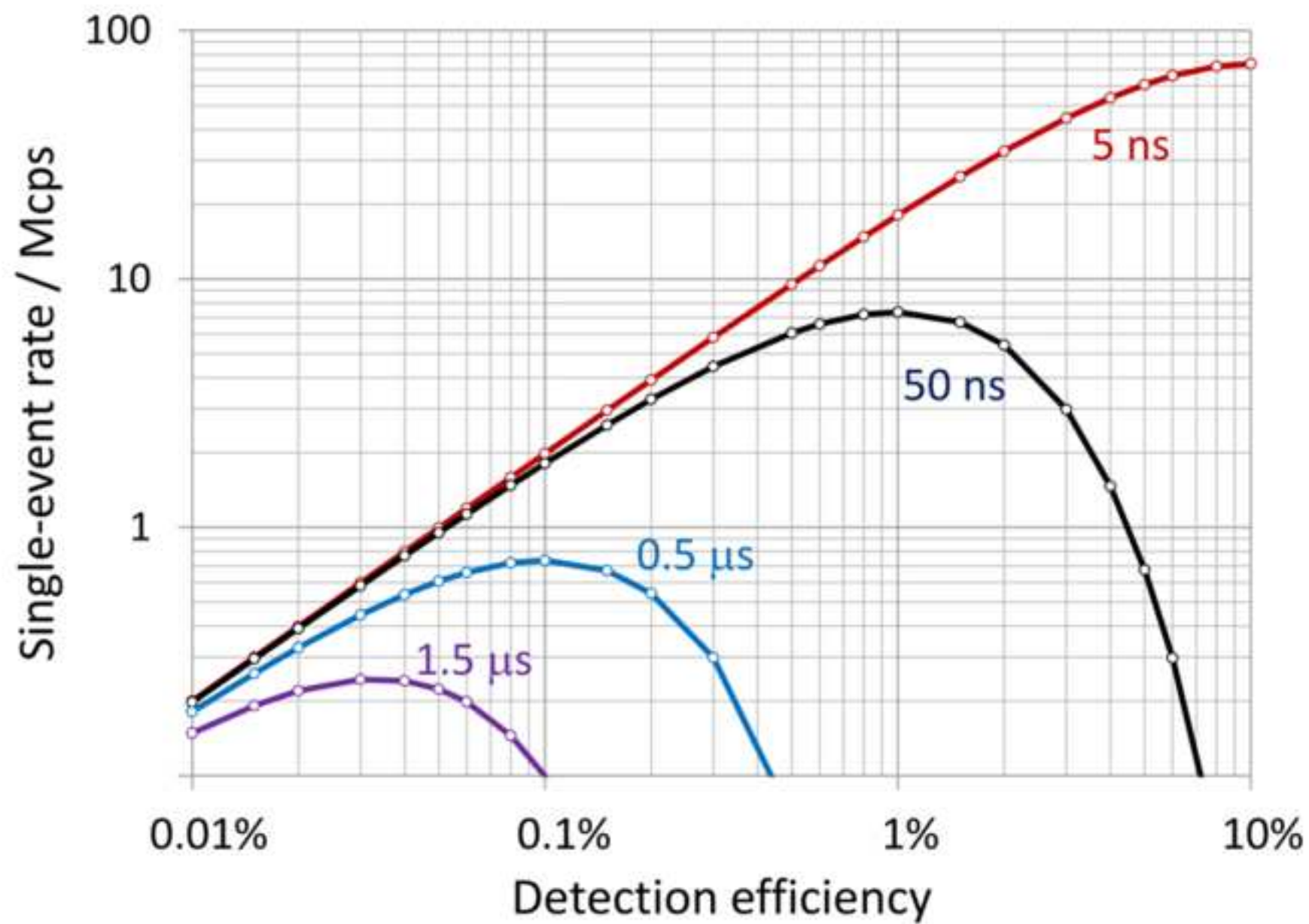


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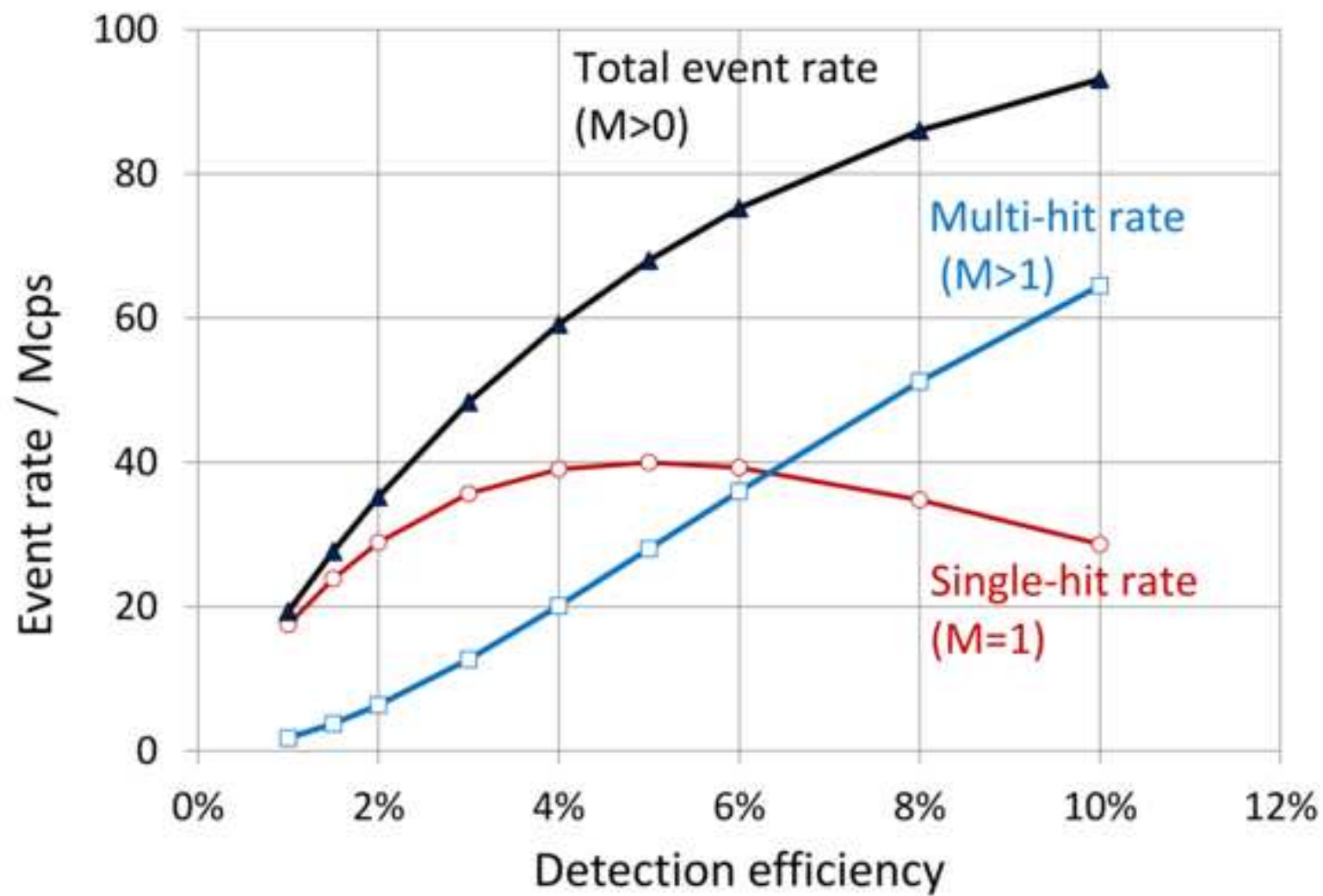


Figure 5
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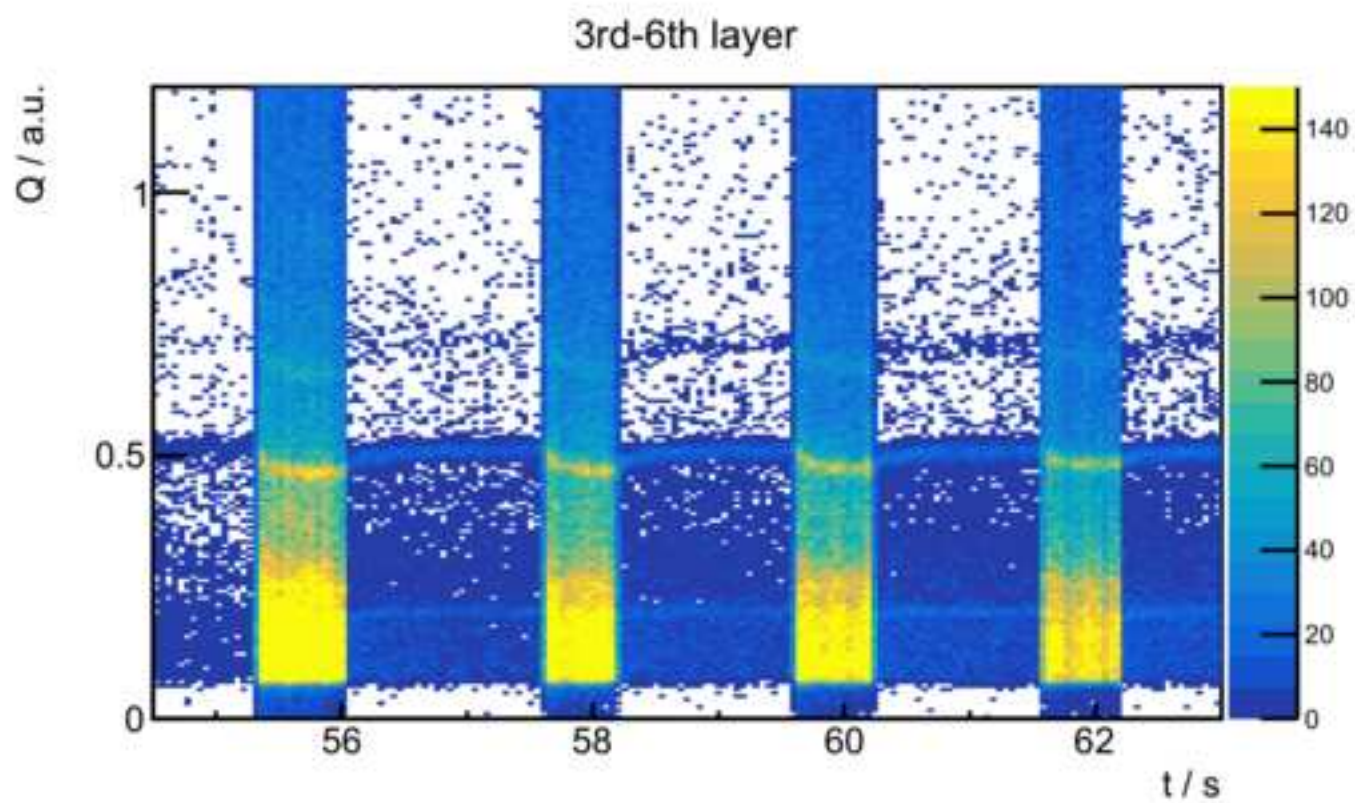
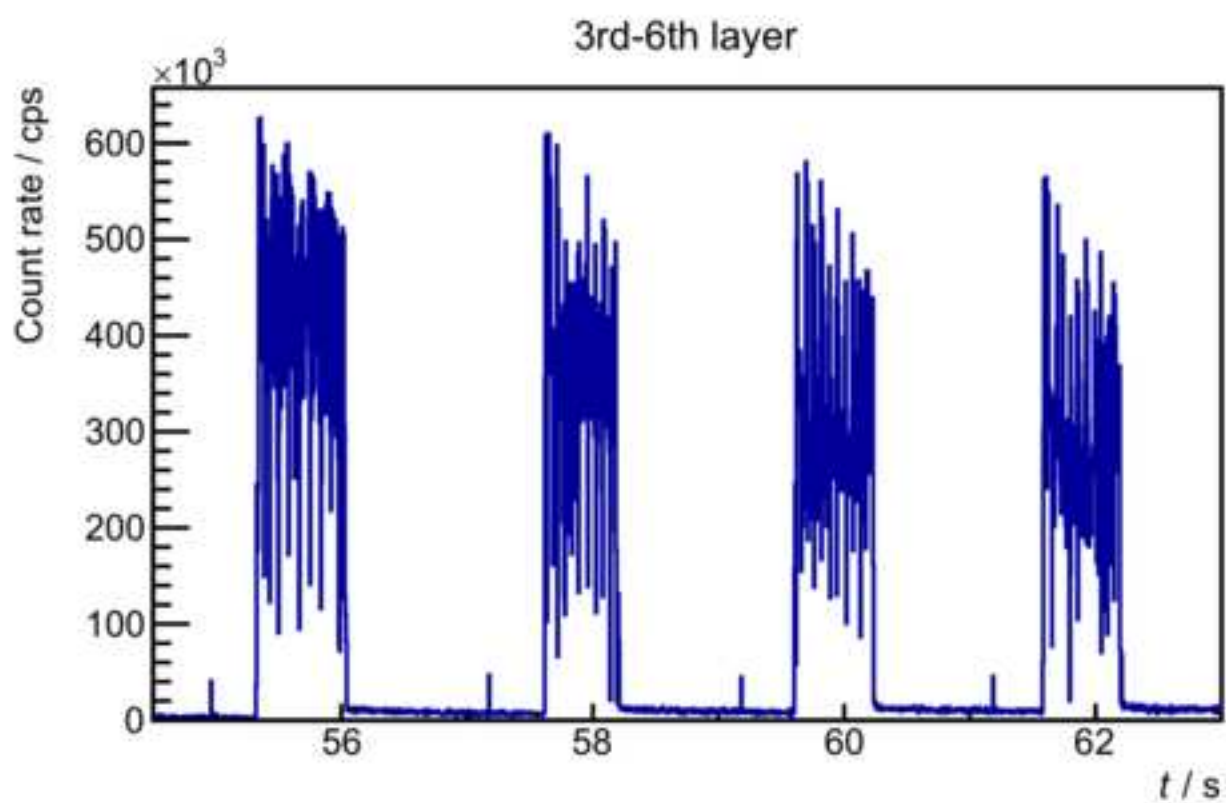


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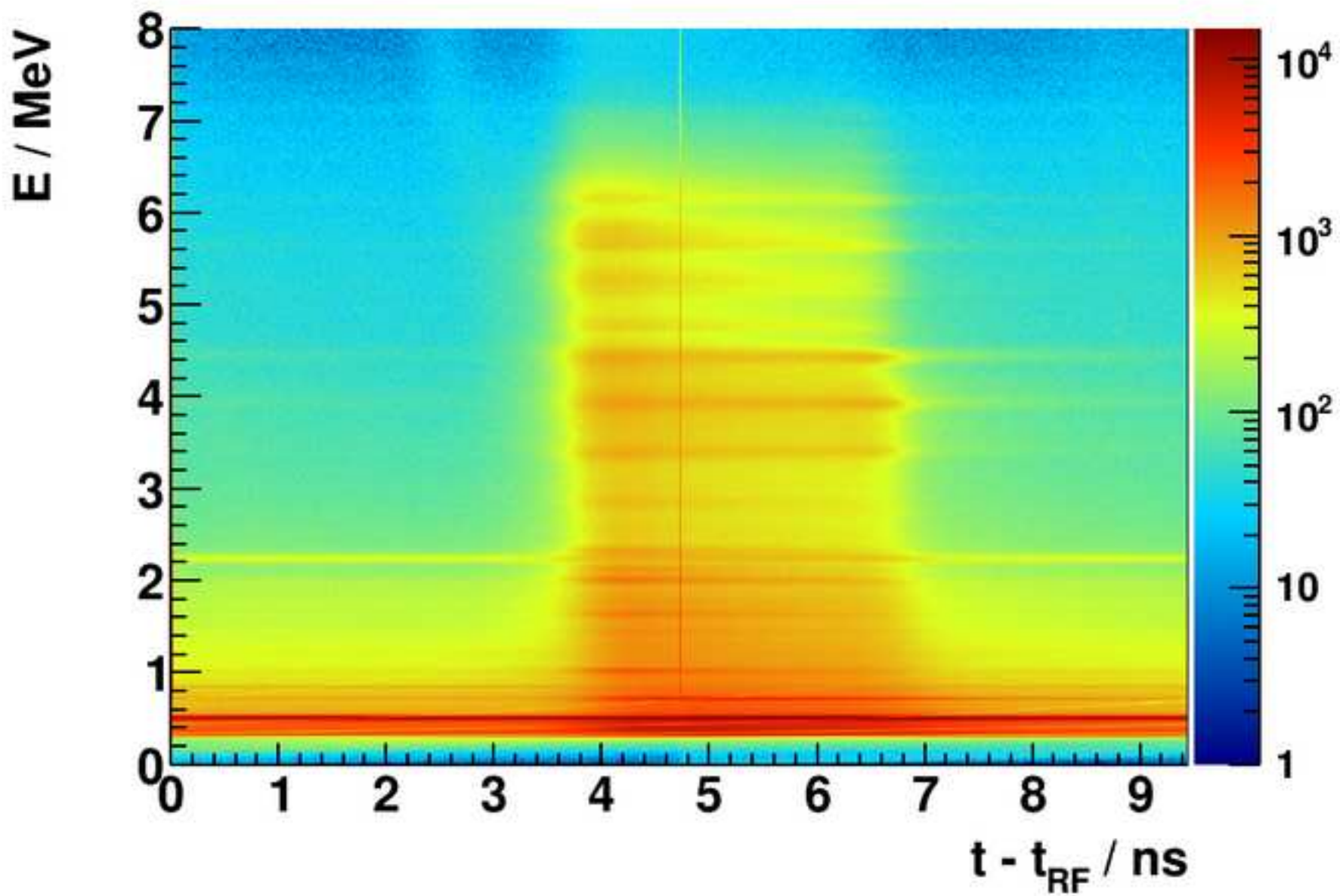


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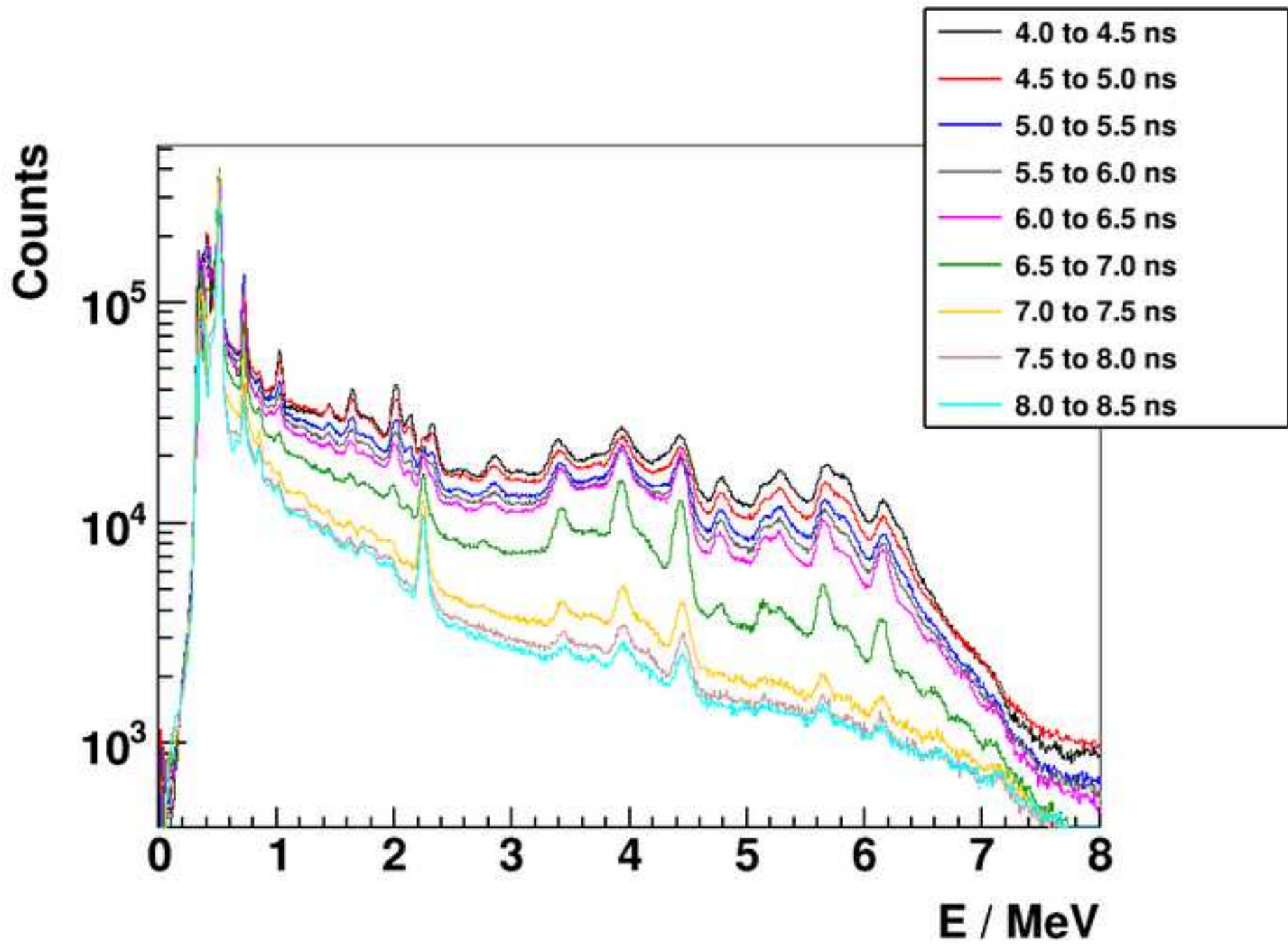


Figure 7a
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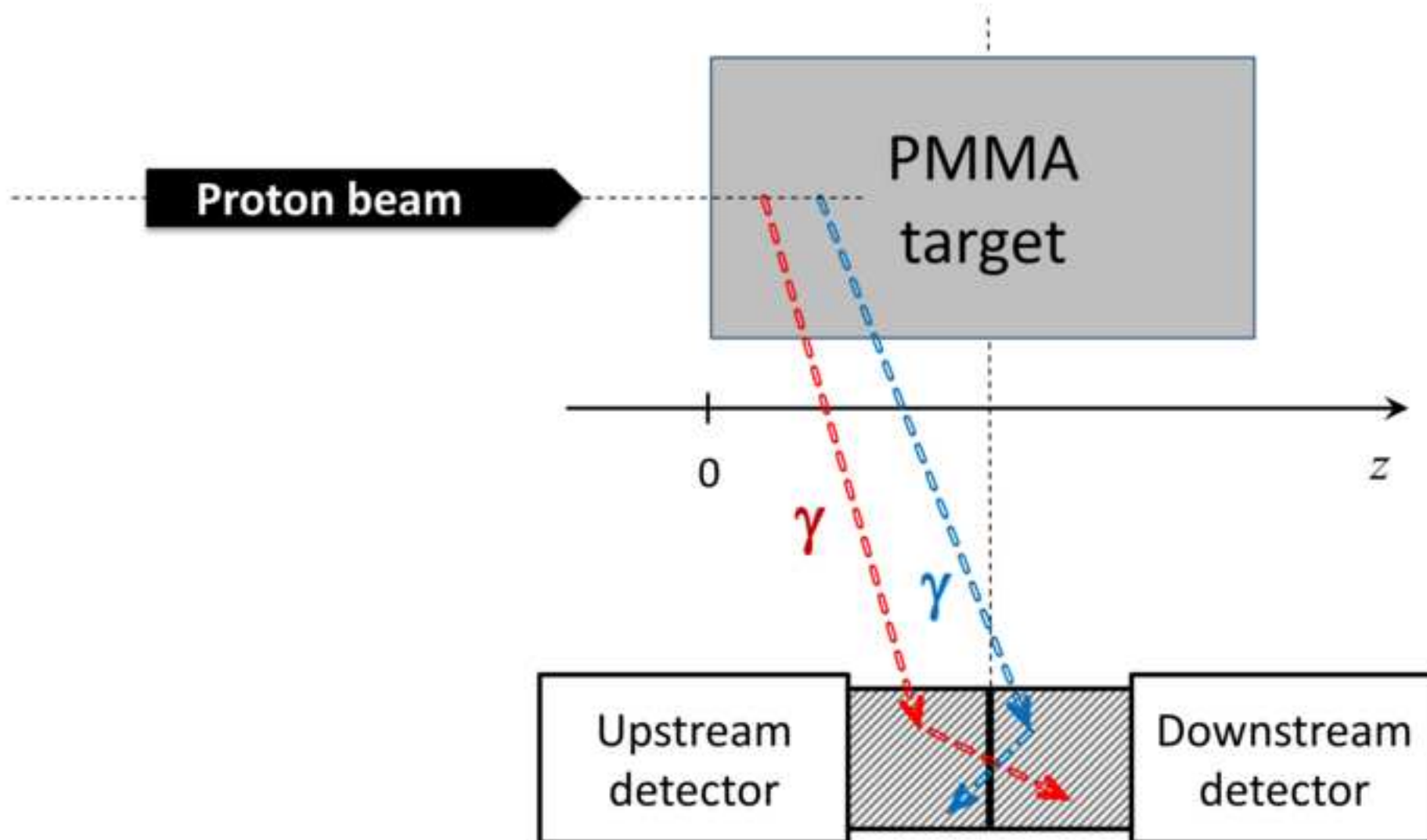


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