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Andrew Chacon

Australian Nuclear Science and Technology Organisation

Marissa Kielly

University of Wollongong

Harley Rutherford

University of Wollongong

Daniel R. Franklin

University of Technology Sydney

Anita Caracciolo

Politecnico di Milano

Luca Buonanno

Politecnico di Milano

Ilenia D'Adda

Politecnico di Milano

Anatoly Rosenfeld

University of Wollongong

Susanna Guatelli

University of Wollongong

Marco Carminati

Politecnico di Milano

Carlo Fiorini

Politecnico di Milano

Mitra Safavi-Naeini (✉ mitras@ansto.gov.au)

Australian Nuclear Science and Technology Organisation

Research Article

Keywords: Neutron Capture Enhanced Particle Therapy, ratio of true / false positives (RTF)

Posted Date: December 3rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1125832/v1>

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Prompt gamma based detection and discrimination of neutron capture events for NCEPT dose quantification

Andrew Chacon¹, Marissa Kielly^{1,2}, Harley Rutherford^{1,2}, Daniel R. Franklin³, Anita Caracciolo^{4,5}, Luca Buonanno^{4,5}, Ilenia D'Adda^{4,5}, Anatoly Rosenfeld², Susanna Guatelli², Marco Carminati^{4,5}, Carlo Fiorini^{4,5}, and Mitra Safavi-Naeini^{1,2,*}

¹Australian Nuclear Science and Technology Organisation (ANSTO)

²Centre for Medical Radiation Physics, University of Wollongong, Australia

³Faculty of Engineering & IT, University of Technology Sydney, Australia

⁴Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, Milano, Italy

⁵Istituto Nazionale di Fisica Nucleare (INFN), Sezione di Milano, Milano, Italy

*mitras@ansto.gov.au

ABSTRACT

Neutron Capture Enhanced Particle Therapy (NCEPT) boosts the effectiveness of particle therapy by capturing thermal neutrons produced by beam-target nuclear interactions in and around the treatment site, using tumour-specific ^{10}B or ^{157}Gd -based neutron capture agents. Neutron captures release high-LET secondary particles together with prompt gamma photons with energies of 478 keV (^{10}B) or 7.94 MeV (^{157}Gd). A key requirement for NCEPT's translation is the development of in vivo dosimetry techniques which can measure both the direct ion dose and the dose due to neutron capture. In this work, we report signatures which can be used to discriminate between photons resulting from neutron capture and those originating from other processes. A Geant4 Monte Carlo simulation study into timing and energy thresholds for discrimination of prompt gamma photons resulting from thermal neutron capture during NCEPT was conducted. Three simulated $300 \times 300 \times 300 \text{ mm}^3$ cubic PMMA targets were irradiated by ^4He or ^{12}C ion beams with a spread out Bragg peak (SOBP) depth range of 60 mm; one target is homogeneous while the others include $10 \times 10 \times 10 \text{ mm}^3$ neutron capture inserts (NCIs) of pure ^{10}B or ^{157}Gd located at the distal edge of the SOBP. The arrival times of photons and neutrons entering a simulated $50 \times 50 \times 50 \text{ mm}^3$ ideal detector were recorded. The majority of photons resulting from neutron capture were found to arrive at the detector at least 60 ns later than photons created by other processes. A range of candidate detector and thermal neutron shielding materials were simulated, and detections meeting the proposed acceptance criteria (i.e. falling within the target energy window and arriving 60 ns post beam-off) were classified as true or false positives, depending on their origin. The ratio of true / false positives (R_{TF}) was calculated; for targets with ^{10}B and ^{157}Gd NCIs, the detector materials which resulted in the highest R_{TF} were cadmium-shielded CdTe and boron-shielded LSO, respectively. The optimal irradiation period for both carbon and helium ions was 1 μs for the ^{10}B NCI and 1 ms for the ^{157}Gd NCI.

1 Introduction

Neutron Capture Enhanced Particle Therapy (NCEPT) is a new type of radiotherapy first proposed by Safavi-Naeini et al. [1]. The principal aim of NCEPT is to boost the effectiveness of particle therapy (either proton or heavy ion therapy) by capturing the internally generated thermal neutrons produced in and around the treatment site as a byproduct of the particle therapy process, using a ^{10}B or ^{157}Gd -based neutron capture agent (NCA) which concentrates in cancer cells. Neutron capture by these (stable) isotopes results in the production of high-LET secondary particles (which are responsible for the main therapeutic benefits of both NCEPT and conventional neutron capture therapy) together with the emission of gamma photons at several specific energies [2, 3, 4, 5, 6].

Planning, optimisation and delivery of NCEPT is more complex than for conventional particle therapy, since the internally-generated thermal neutron fluence depends on several factors, including treatment volume size and depth, and the cellular concentration of the NCA. A critical step in the translation of NCEPT is the development of in-vivo techniques for measurement of the total dose delivered to the patient, including both the ion dose and the dose due to neutron capture. Since virtually none

of the primary radiation emerges from the patient, this must be performed indirectly via detection of prompt gamma radiation emitted at specific wavelengths during the boron or gadolinium neutron capture reactions. Therefore, it is necessary to develop an imaging system capable of localising these high energy prompt gamma photons and to develop techniques which allow the estimation of the dose resulting from boron and/or gadolinium neutron capture.

The prompt gamma spectrum produced during conventional particle therapy (i.e. in the absence of ^{10}B or ^{157}Gd in the target) has been previously reported in the literature for a variety of target materials and beam types, both experimentally and via simulation [7, 8, 9]; it includes a continuum, which decreases as an approximately exponential function of energy, and a number of spectral peaks due to deexcitation of oxygen or carbon nuclei to their ground state (notably at 4.44 MeV and 6.13 MeV, respectively) [7]. These excited states are very short-lived; the photons are mostly emitted within a few nanoseconds of the interaction between the target and the ion (hence the term *prompt gamma*). Several schemes to utilise these photons for range verification in particle therapy have been proposed [10, 11, 12, 13, 14]; the use of a temporal window to improve discrimination of prompt gamma photons from neutrons has also been explored by several authors [14, 15, 16, 17].

Neutron capture processes involving ^{10}B or ^{157}Gd result in the emission of gamma photons with well-defined principal energies of 478 keV and 7.94 MeV, respectively [2, 3, 4]. In the context of particle therapy, the emission of the majority of these neutron-capture-associated gamma photons occurs some time after the arrival of the beam pulse, due to the time required for thermalisation after the neutrons are generated via fragmentation.

Acquisition and accurate identification of neutron-capture prompt gamma photons is challenging due to their high energy and the confounding presence of free neutrons and other particles in the radiation field. The ideal detector for this application should be able to reject neutrons (since the objective is to quantify neutron capture in the target rather than the detector) while also being able to clearly discriminate between prompt gamma photons emitted by the de-excitation of nuclear fragments created during irradiation and prompt gamma photons emitted during neutron capture.

In this work, we explore the timing and energy characteristics of prompt gamma photons originating from thermal neutron capture by ^{10}B or ^{157}Gd during irradiation with carbon or helium ions. For the first time we report unique signatures which can be used to discriminate between photons resulting from neutron capture and those originating from other processes. Finally, we estimate the achievable performance of both ideal and realistic detector models utilising these signatures for neutron capture discrimination, and identify suitable materials for shielding the detector from thermal neutrons without compromising gamma photon detection performance.

First, a Monte Carlo simulation model is constructed, in which a target phantom is irradiated by a spread out Bragg peak (SOBP) helium or carbon ion beam with a 60 mm depth range. The detectors are positioned proximal to the Bragg peak and orientated towards the region of interest, which minimises the number of neutrons interacting directly with the simulated detectors (since neutrons are predominately created with initial momentum parallel to the beam [14, 17]). Three phantoms are used in the simulation: the first is a solid homogeneous block of poly(methyl methacrylate) (PMMA), while the second and third include pure ^{10}B and ^{157}Gd inserts located at the distal end of the SOBP. The energy and time of arrival (relative to the time of primary particle generation) of all neutrons entering the insert region of each phantom are scored; the time of arrival (also relative to the time of primary particle generation) and energy of photons which exit the phantom were also scored. Based on these results, a temporal mask and energy window suitable for neutron capture discrimination are designed.

The temporal mask and energy window are applied to all particles arriving at an ideal detector (perfect absorption, infinite energy resolution, no dead time) and the numbers of true and false positive and negative classifications (where the ground truth is the known origin of each detected event) are counted. True positive/negative detections are defined as those where the detection is correctly classified as neutron capture or non-capture; false positives are those detections which satisfy the timing and energy acceptance window but are not related to neutron capture events, and false negatives are those where the detection *was* related to neutron capture, but either energy has been lost due to scattering outside of the detector volume such that the photon falls outside of the acceptance windows, or the photon arrives early or late due to an unusually rapid or slow neutron thermalisation prior to capture.

For the final part of the study, realistic detector simulation models are used, and the same evaluation of true/false positive/negative detection is performed. Several alternative detector materials are evaluated, including direct-detection CdTe, CZT (for boron neutron capture) and $\text{LaBr}_3\text{:Ce}$, LSO:Ce , BGO and PbWO_4 scintillator-based detectors (for both boron and gadolinium neutron capture); these detectors are simulated both unshielded and with thin layers of several alternative thermal neutron shielding materials.

The remainder of this paper is divided into the following sections. The configuration used for the simulation is described in Section 2. Results from the work are presented in Section 3 and the discussion of the results is presented in Section 4. A final

Table 1. Physics models used in all simulations

Interaction	Energy Range	Geant4 Model
Radioactive Decay	N/A	G4RadioactiveDecayPhysics
Particle Decay	N/A	G4Decay
Hadron Elastic	0–100 TeV	G4HadronElasticPhysicsHP
Ion Inelastic	0–110 MeV	Binary Light Ion Cascade
	100 MeV–10 GeV	BIC
	9.99 GeV–1 TeV	FTFP
Neutron Capture	0–20 MeV	NeutronHPCapture
	19.9 MeV–100 TeV	nRadCapture
Neutron Inelastic	0–20 MeV	NeutronHPInelastic
Neutron Elastic	0 eV–20 MeV	NeutronHPElastic
	20 MeV–100 TeV	hElasticCHIPS
Proton Inelastic	0–9.9 GeV	Binary Cascade

summary and conclusions are presented in Section 5.

2 Materials and Methods

Geant4 version 10.2.p03 is used for all simulations, since it has been previously identified as providing the best agreement with experimental fragmentation measurements in particle therapy [18, 19, 20]. Electromagnetic interactions were modelled using the standard Geant4 physics option 3 model (G4EmStandardPhysics_option3), while the other physics models (including hadronic interactions) used in the simulation are listed in Table 1.

The three simulated target phantoms are $300 \times 300 \times 300$ mm³ PMMA cubes; one is a homogeneous block of PMMA, while the other two include a 10 mm cubic insert embedded within the PMMA phantom, with its centre at a depth of 140 mm (i.e. extending from 135 to 145 mm along the path of the beam, corresponding to the distal 10 mm of the spread-out Bragg peak) and centred laterally and vertically (in x and y), consisting of either pure ¹⁰B or ¹⁵⁷Gd. The physical properties of the materials used in the simulations, including elemental compositions and density, are based on the library of standard materials defined by the National Institute of Standards and Technology (NIST) [21].

Polyenergetic beams of ¹²C and ⁴He are synthesised with energy ranges of 225–294 MeV/u and 113–156 MeV/u, respectively, so as to create an approximately flat biological dose between depths of 85 mm and 145 mm in the phantom¹. The ion beams are rotationally symmetric, with a 20 mm FWHM Gaussian beam profile, and are generated at the surface of the phantom, parallel to the z -axis of the phantom, with 10^8 particles simulated for each beam and phantom combination. The energy deposited in the target phantom by each beam is scored as a function of depth across the full width at tenth maximum of the ion beam and normalised to the energy deposited at the entrance.

2.1 Neutron and gamma characterisation

For phantoms with a neutron capture insert (NCI), the energy and arrival time of neutrons entering into the insert region are recorded. A two-dimensional spectrogram illustrating neutron arrival time (horizontal axis) vs. kinetic energy (vertical axis) is constructed, with 50 logarithmically spaced temporal bins (from 0.1 ns to 10^8 ns), and 50 logarithmically spaced energy bins (from 10^{-5} eV to 10^{10} eV). For each particle, time is measured relative to the instant at which the incident carbon or helium particle is generated at the surface of the phantom.

The energy and time of arrival of photons and neutrons entering the detector are scored and an energy (horizontal axis) vs. photon arrival time (vertical axis) spectrogram is produced. Arriving photons are distributed into 1000 linearly spaced energy bins (each 10 keV in width, from 0 to 10 MeV), and 100 logarithmically spaced arrival time bins (from 0.1 ns to 10^{10} ns). Arriving neutrons are distributed into 130 logarithmically spaced energy bins (from 10^{-10} MeV to 10^3 MeV), and 100

¹The procedure used to create a flat biological dose is fully described in [1].

Figure 1. Schematic of the simulation configuration.

Table 2. Detector materials, including a range of scintillators and two direct-detection materials.

Material	Density (g/cm ³)	Yield (ph/MeV)	Decay time (ns)	Energy resolution (%)	Emission wavelength (nm)	Data source
LSO:Ce	7.10-7.40	30000	40	10.5	420	[22]
BGO	7.13	8000-10000	300	9.7	480	[23]
LaBr ₃ :Ce	5.06	63000	16-25	2.2-2.6	380-385	[24, 25]
PbWO ₄	8.28	400-500	6/30	36	440/530	[26, 27]
CdTe	5.85	N/A (direct)	N/A (direct)	2.4	N/A (direct)	[28]
CZT	5.8	N/A (direct)	N/A (direct)	2-3	N/A (direct)	[25]

logarithmically spaced arrival time bins (from 0.1 ns to 10¹⁰ ns). Again, time is measured relative to the instant at which the primary particle is generated.

2.2 Detector material, irradiation period and shielding optimisation

The second part of the study aims to determine the accuracy with which photons resulting from thermal neutron capture in the neutron capture insert can be distinguished from photons originating from other processes using several alternative detector models.

An ideal detector is modelled as a simple geometric volume which records the identity, creating process, time of arrival and energy of any particle entering the detector volume. The detector volume is cubic, with dimensions of 50 mm × 50 mm × 50 mm³. The detector is positioned as shown in Figure 1, with the normal vector of its front face oriented towards the centre of the distal edge of the SOBP region in the phantom. The front face of the detector is a distance of 47.32 cm from the centre of the distal edge of the SOBP, at an angle of $\theta = 60^\circ$ (about the vertical axis) relative to the ion beam.

The realistic detector models use the same geometry as the ideal detectors, and a range of different detector materials as listed in Table 2. LaBr₃, CZT and CdTe are suitable for detecting the gamma photons from ¹⁰B neutron capture, since they provide the highest energy resolution, while the higher densities of LSO:Ce, BGO and PbWO₄ are more appropriate for detecting the higher energy photons emitted during ¹⁵⁷Gd neutron capture.²

Total irradiation periods of 1 μs, 10 μs, 1 ms, 10 ms and 100 ms are simulated. Over these intervals, the beam's timing nanostructure is modelled as a pulse sequence with a period of 200 ns and a beam-on period of 11 ns (a duty cycle of 5.5%) as shown in Figure 2 [29, 30]. A total of 10⁹ primary particles are used for each simulation, with the particles injected periodically at a constant rate during each nano-spill; the particle injection rate dependent on the total irradiation period such that the total number of particles delivered during the macroscopic irradiation period is the same. For any particle which deposits energy in the detector, the particle type, creating process, time of arrival, total deposited energy, and location(s) of energy deposition in

²It is assumed that several scintillator crystals or semiconductor detectors were stacked and optically/electronically coupled to form a single detector unit.

Figure 2. The micro-structure of the beam during the first 500 ns. This pattern is repeated for the entire irradiation period. The red hashed region indicates the range of the timing mask, during which events are rejected; events occurring outside of this range will be accepted. Mask intervals of 0, 11, 22, 30, 40, 50, 60, 70 and 80 ns are evaluated.

the detector are scored (see Figure 1); all individual energy depositions resulting from multiple-interaction events (e.g. multiple Compton interactions) are summed. The optical scintillation process is not modelled in simulation³. It is assumed that the area under the output pulse from the optical photodetector is proportional to the deposited energy.

Since the ion beams, target geometry and composition are the same as in the first part of this study, a phase space record of the prompt gamma photons generated in the previous simulation (including the energy, time, position and responsible process of particle creation within the phantom) is used to drive this simulation, substantially reducing the required simulation time.

Based on the results presented in the first part of this study, an energy window and temporal mask are defined to differentiate between neutron capture photons and photons unrelated to neutron capture in the NCI region. Energy deposited into the detector during the masked-out intervals was not scored. Eight different temporal masks are investigated:

- 0 ns - no mask applied;
- 11 ns - masking during beam on period);
- 11 ns + $T_{\text{prompt}} = 22$ ns total- masking during beam on period plus prompt gamma emission period (to be determined based on the outcome of the first part of the study); and
- 11 ns + $T_{\text{prompt}} + T_{\text{neutron}} = 30, 40, 50, 60, 70, 80$ ns total - masking during beam on period plus prompt gamma plus neutron emission period).

The temporal masks are applied from the start of each nano-spill and extend over the total irradiation interval.

For each irradiation interval, ion beam (carbon and helium), and detector model (ideal plus each of the realistic models), the following performance metrics are calculated:

- The sensitivity, defined as the number of true positive, false positive, true negative and false negative detections normalised by the number of photons reaching the detector; and
- The fraction of true positive, false positive, true negative and false negative detections, where these classes are defined as follows:

³Modelling the optical scintillation process in Geant4 is possible but increases the execution time by several orders of magnitude, and is not important for this study.

- True positives: neutron capture events which are detected during the temporal acceptance window and which fall within the defined energy acceptance window;
- True negatives: non-neutron capture events which are detected either outside of the temporal acceptance window or which do not fall within the energy acceptance window;
- False positives: non-neutron capture events which are detected during the temporal acceptance window and which fall within the defined energy acceptance window, and are therefore incorrectly classified as neutron capture events; and
- False negatives: neutron capture events which are detected either outside of the temporal acceptance window or which do not fall within the energy acceptance window, and therefore are incorrectly classified as non-neutron capture events. These may arise either due to unusually fast or slow neutron thermalisation (leading to long but low-probability tails in the temporal distribution of neutron captures), Compton scattering of the emitted photon in the phantom (resulting in a lower energy and an altered photon trajectory), Compton scattering in the detector (in the case of the realistic detector models) followed by the escape of the scattered photon (resulting in only part of the photon's energy being deposited in the detector), or the detection of particles other than photons (e.g. fast neutrons, protons or other fragments) in the detector.

Using (1) raw true and false positive sensitivity performance metrics, and (2) the *true positives : false positives* ratio (R_{TF}), which is a metric for selectivity, a series of separate comparisons were performed to optimise different aspects of the detector design:

2.2.1 Comparison of detector materials

The performance metrics were evaluated for each of the different detector materials across a range of timing mask intervals with a fixed irradiation period. For the ^{10}B NCI target, an irradiation period of $1\ \mu\text{s}$ was chosen based on the results of the first part of the study, since after this period the relative numbers of 511 keV and 2.23 MeV photons begin to increase, which will make it difficult to discriminate between the background and the 478 keV photons from boron neutron capture. For the ^{157}Gd NCI target, the irradiation period is less critical to absolute sensitivity and selectivity, therefore an arbitrary irradiation period of 1 ms was selected. Irradiation periods were subsequently optimised via the method described in Section 2.2.2.

2.2.2 Comparison of irradiation periods

The impact of (macroscopic) irradiation period on detector sensitivity and R_{TF} for a range of timing mask intervals were evaluated for the best-performing materials identified in Section 2.2.1: firstly, for only the photons depositing energy in the detector, and secondly, for all particles depositing energy in the detector. The chosen detectors for this comparison (based on the results in Section 2.2.1) were the CdTe detector for the ^{10}B NCI and the LSO detector for the ^{157}Gd NCI.

2.2.3 Comparison of shielding materials

Utilising the best-performing detector materials identified in Section 2.2.1 (CdTe for the ^{10}B NCI and LSO for the ^{157}Gd NCI), a range of different high thermal neutron cross-section front-face shielding materials were evaluated. The shield is a $50\times 50\times 1\ \text{mm}$ layer of the evaluated material, applied to the front face of the detector only. For phantoms with a ^{10}B NCI, (natural) gadolinium, cadmium and hafnium are evaluated as potential thermal neutron shielding materials, while for those with the ^{157}Gd NCI, (natural) boron, cadmium and hafnium are evaluated.

3 Results

The depth-dose profiles (normalised to entrance dose) and the energy weights used to generate the beams are shown in Figure 3.

The two-dimensional spectrograms of neutron arrival time into the NCI region vs. energy are presented in Figure 4 for carbon and helium ion beams.

The energy and time of arrival of photons arriving at the detector volume are presented in Figure 5.

The energy and time of arrival of neutrons arriving at the detector are presented in Figure 6.

3.1 Detector material, irradiation duration and shield optimisation

An exhaustive search for the best timing mask and detector was undertaken; in summary, the CdTe detector with a $1\ \mu\text{s}$ irradiation period was determined to be the optimal combination for the ^{10}B neutron capture insert, since it provided the highest *true positives : false positives* ratio (R_{TF}), both for the unshielded detector and a detector shielded with 1 mm of cadmium. For the ^{157}Gd neutron capture insert, the LSO:Ce detector with a 1 ms beam duration was the optimal combination, again providing

Figure 3. Depth-dose profiles (upper plot; blue = dose, green = predicted biological dose) and energy spectra (lower plot) of polyenergetic carbon and helium ion beams; a red 'X' along the axis denotes the location of the NCI region.

Figure 4. The arrival-time/energy spectrograms of neutrons entering the NCI region per incident particle following irradiation by polyenergetic carbon and helium ion beams. A horizontal red dashed line is drawn at energy = 0.4 eV.

Figure 5. The energy/arrival-time spectrograms of photons entering the detector following an instantaneous irradiation by polyenergetic carbon and helium ion beams.

Figure 6. The energy/arrival-time spectrograms of neutrons entering the detector following irradiation by polyenergetic carbon and helium ion beams.

Figure 7. Sensitivity (upper plot) and R_{TF} (lower plot) of events detected using different detector materials following irradiation by a carbon ion beam. For the ^{10}B NCI, magenta denotes the LaBr_3 detector, green the CdTe detector and blue the CZT detector. For ^{157}Gd NCI, red denotes the BGO detector, black the LSO detector and light blue the PbWO_4 detector. In the upper plots in each subfigure, square markers ($\square$) joined by unbroken lines denote true positives, while cross markers ($\times$) joined by dashed lines denote false positives.

the highest (R_{TF}) for both the unshielded detector and a detector shielded with 1 mm of boron. For brevity, only a small selection of results for carbon ion irradiation are presented; specific plots comparing detector materials, irradiation duration and shielding materials are presented in Sections 3.1.1-3.2. Corresponding results for helium ion irradiation are included in the Sections 1-3 of the Supplementary Material (Supplementary Figures 1-3); the best-performing detector materials with the helium ion beam were the same as for the carbon ion beam - CdTe (with optimal irradiation duration of 1 μs) and $\text{LSO}:\text{Ce}$ (with optimal irradiation duration of 10 μs) for the ^{10}B and ^{157}Gd inserts, respectively.

3.1.1 Comparison of detector materials

Plots comparing the different detector material sensitivity and R_{TF} are presented in Figure 7 for realistic detector models irradiated by a carbon ion beam.

3.1.2 Comparison of total irradiation periods

Plots of sensitivity and R_{TF} as a function of temporal mask duration for the two best detector materials for the ^{10}B and ^{157}Gd NCIs following irradiation by a carbon ion beam for a range of total irradiation periods are presented in Figure 8 and 9, for photons only and for all detected events, respectively.

3.2 Comparison of shielding materials

The plots of sensitivity and R_{TF} for realistic detectors using different front shielding materials following carbon ion irradiation are presented in Figure 10.

4 Discussion

From the energy and timing distribution of the neutrons entering the NCI region (Figure 4), it is apparent that arrival time of the neutrons depends on the energy of the neutron. Neutrons which are created with high initial kinetic energies must scatter multiple times to reach thermal equilibrium, which takes time. The neutron spectrograms for both carbon and helium ion beams exhibit similar characteristics, with thermal neutrons reaching the NCI region between ~ 12 ns and 10^6 ns after creation. As a result of the delay between primary particle arrival and thermal neutron arrival time in the NCI region, it is expected that gamma emissions due to the thermal neutron capture process within the NCI will start to be observed between 12 ns and 10^6 ns after the onset of a beam pulse.

In phantoms without the NCI (Figure 5(a) and 5(b) for carbon and helium ion beams, respectively), all prompt (non-neutron-capture) photons arrive at the detector during the first 11 ns after the primary particle is generated. As previously discussed, thermalisation takes time, and as such, thermal neutrons principally appear during the 12 ns- 10^6 ns temporal window (as can be seen from the 2.23 MeV hydrogen neutron capture line), with virtually none appearing outside of this window. Therefore,

(a) ^{10}B NCI; CdTe detector

(b) ^{157}Gd NCI; LSO detector

Figure 8. Sensitivity (upper plot) and R_{TF} (lower plot) for **photon detections only** following target irradiation by a carbon ion beam as a function of temporal mask duration for a range of different irradiation periods. In all plots, the red markers denote a total irradiation time of $1\ \mu\text{s}$, green $10\ \mu\text{s}$, blue $1\ \text{ms}$, magenta $10\ \text{ms}$ and black $100\ \text{ms}$. In the upper plots in each subfigure, square markers ($\square$) joined by unbroken lines denote true positives, while cross markers ($\times$) joined by dashed lines denote false positives.

(a) ^{10}B NCI; CdTe detector

(b) ^{157}Gd NCI; LSO detector

Figure 9. Sensitivity (upper plot) and R_{TF} (lower plot) for **all detected events** following target irradiation by a carbon ion beam as a function of temporal mask duration for a range of different irradiation periods. In all plots, the red markers denote a total irradiation time of $1\ \mu\text{s}$, green $10\ \mu\text{s}$, blue $1\ \text{ms}$, magenta $10\ \text{ms}$ and black $100\ \text{ms}$. In the upper plots in each subfigure, square markers ($\square$) joined by unbroken lines denote true positives, while cross markers ($\times$) joined by dashed lines denote false positives.

Figure 10. Sensitivity (upper plot) and R_{TF} (lower plot) for events recorded in a detector shielded by different materials with high thermal neutron cross-section, following target irradiation by a carbon ion beam. In all plots, the red markers denote an unshielded detector, green cadmium shielding, blue gadolinium shielding (^{10}B NCI only), black boron shielding (^{157}Gd NCI only), and magenta hafnium shielding. In the upper plots in each subfigure, square markers (□) joined by unbroken lines denote true positives, while cross markers (×) joined by dashed lines denote false positives.

the use of the 12 ns- 10^6 ns timing window for thermal neutron capture discrimination is justified. In phantoms both with and without the NCI, the 511 keV annihilation line starts to appear at approximately 10^4 ns and grows in intensity as time increases and the positron-emitting fragmentation products decay.⁴

In the phantoms with the ^{10}B NCI (Figure 5(c) and 5(d) for carbon and helium ion beams, respectively), the 478 keV line from ^{10}B thermal neutron capture is visible during the period extending from approximately 12 ns to 10^6 ns, corresponding to the period when thermal neutrons are present in the phantom. However, the presence of the strong 511 keV positron annihilation signal nearby is a confounding factor in neutron capture discrimination, demanding high energy resolution from candidate detectors. The 2.23 MeV hydrogen neutron capture contributes to background at a broad range of lower energies, due to Compton scatter.

In the case of phantoms with the ^{157}Gd NCI (Figure 5(e) and 5(f) for carbon and helium ion beams, respectively), the 7.94 MeV photon line from ^{157}Gd neutron capture is visible over the same time window as the ^{10}B NCI line - from ~ 12 ns- 10^6 ns. However, unlike the ^{10}B case, there is no significant scatter background due to the absence of nearby decay or capture peaks.

In all phantoms, the time of arrival of neutrons at the detector depends on its energy (Figure 6). For the purposes of this study, there are three energy and timing bands for neutrons arriving at the detector:

- Fast neutrons - energies above 1 MeV, with most neutrons arriving before 50 ns;
- Intermediate-energy neutrons - energies between 0.4 eV and 1 MeV, with most neutrons arriving between 50 ns and 10^4 ns; and
- Thermal neutrons - energies below 0.4 eV, which most neutrons arriving between 10^4 and 10^7 ns.

Fast and intermediate neutrons can potentially deposit enough energy in the detector to satisfy the energy window for neutron-capture prompt gamma detection, thereby creating false positives. Shielding against these neutrons is impractical, since stopping energetic neutrons at these requires large amounts of shielding material, which would also attenuate the gamma photons emitted during neutron capture processes in the target. The detection of fast neutrons can be greatly reduced by using a 50 ns timing mask post irradiation, since any fast neutrons arriving at the detector will do so within approximately 50 ns of the end of the beam pulse (providing that the detector itself does not become activated with long-lived radio-isotopes). Intermediate energy neutrons arrive at the detector in lower fluences and over a longer timescale compared to fast and thermal neutrons; while they potentially can deposit enough energy to trigger a false positive, they are much fewer in number compared to fast neutrons, and in any case, cannot be effectively blocked by shielding without compromising detector sensitivity.

⁴Note that binning is logarithmic in the time direction.

For all ideal photon detectors, when the target includes a ^{10}B neutron capture insert (Figure 8(a)), R_{TF} increases as the temporal mask is widened up to 22 ns, after which the ratio begins to fall. This is because a 22 ns timing mask is sufficient to suppress detection of non-neutron-capture prompt gamma emission, since they are only produced up to 11 ns post (end of) beam injection. R_{TF} decreases with increased beam duration, due to the resulting increase in photon fluence at the higher-energy emission peaks, since these photons can Compton-scatter and potentially deposit energy in the detector within the 478 keV energy window (Figure 5(a)). In the case of ^{157}Gd neutron capture insert (Figure 8(b)), R_{TF} increases as the timing mask is widened, reaching a maximum value with a 40 ns mask interval. However, because the absolute number of true and false positive counts is very low (i.e. the sensitivity is poor) with this mask, the 22 ns timing mask produces the best overall balance between selectivity and sensitivity for ideal photon detectors. Furthermore, R_{TF} increases with increased beam duration, reaching a maximum value when the beam duration is 1 ms. This is due to the absence of high-energy emission peaks above 7.94 MeV. By increasing the beam duration, and hence acquisition time, a higher proportion of photons from the neutron capture insert (true positives) can be detected without increasing the false positive rate.

For all evaluated physical detector materials, and for both ^{10}B and ^{157}Gd neutron capture inserts irradiated by carbon ions, R_{TF} increases to its maximum value as the temporal mask duration is increased to ~ 60 ns, after which the ratio starts to plateau (Figure 9). Fast neutrons cannot be effectively shielded, and any which deposit energy in the detector will do so within the first 60 ns, increasing the false negative count and decreasing R_{TF} . For phantoms with a ^{10}B neutron capture insert, R_{TF} falls with increasing beam durations due to the increasing prevalence of scattered photons with initial energies above the neutron capture photopeak. For the ^{157}Gd NCI, R_{TF} continues to increase as irradiation time increases due to both a lack of higher energy photons, and the very small number of fast and intermediate-energy neutrons capable of depositing energy in the acceptance window. Therefore, 60 ns appears to be the optimal choice for the temporal mask duration. Helium ion irradiation results are shown in Supplementary Figure 2; the optimal temporal mask for ^{10}B NCI is also 60 ns, however for ^{157}Gd , R_{TF} plateaus at 40 ns for the optimal irradiation duration of 1 ms.

For a carbon ion beam with a 60 ns temporal mask, the material which achieves the highest R_{TF} with the ^{10}B NCI is CdTe ($R_{TF} = 2.07 \pm 0.01$), followed by CZT ($R_{TF} = 1.645 \pm 0.009$) and finally LaBr₃ ($R_{TF} = 1.402 \pm 0.007$) (Figure 7(a)).

For a carbon ion beam and a 60 ns temporal mask, the detector material achieving the highest R_{TF} with the ^{157}Gd NCI was LSO ($R_{TF} = 5.52 \pm 0.06$), followed by BGO ($R_{TF} = 1.454 \pm 0.008$) and finally PbWO₄ ($R_{TF} = 0.442 \pm 0.002$) (Figure 7(b)). Unlike the ^{10}B NCI case, there is an absence of scatter from high energy photons, which implies that all false positives will be a result of neutron interactions within the detector. The PbWO₄ detector had the highest absolute sensitivity to true positives, however, for all timing masks, the false positive rates were higher than the true positive rates. This suggests that if the detector could be sufficiently shielded against intermediate energy neutrons to reduce the rate of false positives, it might be a more competitive choice of detector material. Additionally, the detector with the highest R_{TF} was the LSO detector despite having the lowest sensitivity to true positives, since neutrons caused the lowest rate of false positives compared to the other detectors.

The optimal irradiation duration for carbon ions was 1 μs for the ^{10}B NCI and 1 ms for the ^{157}Gd NCI. In both cases, these irradiation durations result in the highest R_{TF} when the temporal mask duration exceeds 30 ns (including the optimal value of 60 ns as determined previously; see Figure 9). Unfortunately, in the case of the ^{10}B NCI, the 1 μs irradiation duration also results in the poorest sensitivity over the useful range of temporal mask values. This is not the case for the ^{157}Gd insert, where the sensitivity with the optimal 1 ms interval is almost the same as the best-case irradiation interval of 100 ms, while the R_{TF} is much better than the other irradiation intervals. The equivalent result for helium, shown in Supplementary Figure 2, result in the same optimal irradiation durations (although the highest R_{TF} is obtained for the ^{157}Gd insert with a 10 μs irradiation duration, the sensitivity is greatly reduced, so 1 ms remains a good compromise solution between near-maximum sensitivity and good selectivity).

Thermal neutrons start to arrive at the detector in significant numbers after 10^4 ns. Due to their low kinetic energy, thermal neutrons do not directly contribute to false positives; however, they can cause the detector itself to become activated, contributing to an increase in background radiation, which, in turn, can result in the detection of false positives (depending on the wavelengths of emitted gamma radiation). As the detector ages, this problem will progressively increase; therefore, it is desirable to block thermal neutrons from the detector. Thermal neutrons can be almost entirely absorbed by a thin layer of certain materials with high thermal neutron cross sections, which will not significantly attenuate neutron capture gamma photon fluence - provided that the shielding material is distinct from the neutron capture isotope used during NCEPT treatment.

The addition of a thin layer of any of the evaluated shielding materials on the front face of the detector results in a very small decrease in R_{TF} when using phantoms with a ^{10}B neutron capture insert (Figure 10(a)). This is a result of slightly increased attenuation and scatter of the neutron capture gamma photons prior to reaching the sensitive volume of the detector, while there is minimal impact on the background level of scattered photons, fast and intermediate neutrons. The same result is observed for

both carbon and helium ion irradiation (see Supplementary Figure 4a).

In the case of the ^{157}Gd neutron capture insert, the addition of boron or hafnium front shielding on the detector results in a substantial increase in R_{TF} relative to the unshielded case (both for carbon and helium ion irradiation; see Supplementary Figure 4b), since the false positives are predominantly caused by neutron interactions within the detector (Figure 10(b)). By contrast, the use of cadmium shielding with a ^{157}Gd NCI in the target results in a very substantial decrease in R_{TF} , since the ^{113}Cd neutron capture reaction results in the emission of high energy photons at 8.48 MeV and 9.04 MeV, which will cause single and double escape peaks to fall in the 7.94 MeV energy acceptance band [31].

Since the addition of thermal neutron shielding almost entirely eliminates the problem of thermal neutron activation of the detector while having minimal negative impact on the sensitivity and specificity of the prompt gamma detector system (with the exception of cadmium shielding in the case of a ^{157}Gd -bearing target), the use of thermal neutron shielding to prolong the life of the detector is justified; the best choice are cadmium for a ^{10}B target and boron for the ^{157}Gd target, both for carbon and helium ion beams.

5 Conclusion

The feasibility of the proposed method for discriminating between ^{10}B or ^{157}Gd neutron capture events and other sources of prompt gamma radiation from the target volume during particle therapy, via energy windowing and temporal masking relative to the beam pulse arrival time, has been established. Overall, for targets containing a ^{10}B NCI, the detector which obtained the highest R_{TF} was the CdTe detector with a 60 ns timing mask and 1 μs irradiation duration. For the ^{157}Gd NCI, the LSO detector provided the highest R_{TF} with a 60 ns timing mask and 1 ms beam duration. The addition of a thin thermal-neutron shield to the front face of the detector results in a slight reduction in sensitivity and selectivity when using a boron NCI, however it allows almost all of the thermal neutrons to be absorbed before reaching the detector, avoiding the problem of neutron activation. In the case of the gadolinium NCI, the addition of front face shielding results in an increase in the R_{TF} as the false positives are caused by neutron interactions within the detector.

6 Acknowledgements

This research/project was undertaken with the support of the high performance computing resources at the National Computational Infrastructure (NCI), which is supported by the Australian Government and the Tesla high performance computing cluster at ANSTO. The authors wish to acknowledge the support of the ANSTO Graduate Institute Industry Fellowship, the Australia Government Research Training Program Scholarship and the Australian Institute of Nuclear Science and Engineering (AINSE) Honours Scholarship.

Author Contributions

Dr A. Chacon implemented and carried out the Monte Carlo simulations, contributed to the development of the data analysis and visualisation, the shielding strategy, and the discussion of results and contributed to the writing of the manuscript.

Ms M. Kielly carried out detailed simulation Monte Carlo studies focusing on the angular placement of the detectors and the shielding strategy, and contributed to the writing and proofreading of the manuscript.

Mr H. Rutherford assisted with the manuscript preparation and proofreading.

Ms A. Caracciolo, Mr L. Buonanno, Ms I. D'Adda, Prof M. Carminati and Prof C. Fiorini assisted with the selection of the detector material, provided theoretical and experimental timing and energy specifications for several detector options relevant to this study, contributed the discussion of the results and assisted with the manuscript preparation and proof-reading.

Dr D. Franklin contributed to analysis of the simulation data, interpretation of the results, provided input in the choice of performance metrics and the selection of suitable detector materials and assisted with manuscript preparation and proof-reading.

Dist Prof A. Rosenfeld and A Prof S. Guatelli provided feedback on the theoretical and simulation methodology.

A Prof M. Safavi-Naeini proposed the idea of the use of neutron capture gamma for dose quantification in NCEPT. She designed the Monte Carlo simulations, proposed the statistical methods and metrics used establishing the ground truth and assessing the performance of different detector material for the quantification of the boron and gadolinium neutron capture gamma. A Prof Safavi-Naeini organised and composed the manuscript and has provided the overall leadership of the project.

Competing Interest

The authors declare no competing interests.

Data Availability

Full datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request; sensitivity and selectivity results and additional timing and spectral plots are included as CSV files in the Supplementary Materials, with the CSV file format described in Section 4 of the Supplementary Materials PDF. Alternatively, all CSV files can be downloaded from the following repository: <https://bitbucket.org/msafavi/promptgammadatabase>

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