Prompt gamma-ray spectroscopy in conjunction with the Monte Carlo Library Least Squares approach: applications to range verification in proton therapy

Kyrre Skjerdal[1,*], Toni Kögler[2,3], William Lionheart[4], Kristian Smeland Ytre-Hauge[5], and Ilker Meric[1]
[1] Department of Computer Science, Electrical Engineering and Mathematical Sciences, Western Norway University of Applied Sciences, Norway
[2] OncoRay – National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden - Rossendorf, Germany
[3] Helmholtz-Zentrum Dresden - Rossendorf, Institute of Radiooncology – OncoRay, Germany
[4] Department of mathematics, The University of Manchester, UK
[5] Department of Physics and Technology, University of Bergen, Norway

(*) kyrre.skjerdal@hvl.no

***Abstract*— Prompt Gamma-ray Spectroscopy (PGS) in conjunction with the Monte Carlo Library Least Squares (MCLLS) approach was investigated for the purposes of range monitoring in proton therapy through Monte Carlo simulations. Prompt gamma-rays are produced during treatment and can be correlated to the range of the proton beam in the tissue. In contrast to established approaches, MCLLS does not rely on the identification of specific photopeaks. Instead it treats each individual constituent as a library spectrum and calculates coefficients for each spectrum, and therefore takes both the photopeaks and the Compton continuum into account. It can thus be applied to organic scintillators traditionally not used for energy spectroscopy due to their low Z number and density. Preliminary results demonstrate that the proposed approach returns a strong linear correlation between the range of the primary proton beam and the calculated library coefficients, depending on the composition of libraries. This can be exploited for range monitoring.**

***Keywords* —proton therapy, spectroscopy, Monte Carlo simulations, range verification**

I. Introduction

PARTICLE therapy is a promising alternative to traditional radiotherapy with photons. A particle beam deposits most of its energy towards the end of its range, as opposed to photon beams which deposits energy all the way through the tissue. Particle therapy is therefore a more precise form of treatment, as long as one can control the range of the beam with high precision. The range of a proton beam depends on its initial energy and physical properties of the target, such as electron density and excitation potential [1]. The proton range in a patient is normally estimated based on a CT scan of the patient. Because of uncertainties in conversion from Hounsfield units to proton stopping power, heterogeneities in the tissue organ motion as well as patient motion and positioning, there will be uncertainties in the range of the proton beam [2]. As of today, there are no systems in clinical that are routinely in daily clinical use for monitoring the proton range in proton therapy. Since the protons stop inside of the patient, the range cannot be measured directly, and one must rely on the detection of secondary radiation escaping the patient. As the particle beam traverses the tissue, it will produce neutrons and gamma-rays at a rate correlated with the range and intensity of the beam [3]. In the NOVO project (Neutron and gamma-ray imaging for real-time range verification and image guidance in particle therapy) we propose to use The NOVO Compact Detector Array (NOVCoDA) to image fast neutrons and prompt gamma-rays (PG) to monitor the range of the proton beam in real-time [4]. A prototype of the NOVCoDA is under construction. The prototype will have a total of 16 detector elements, where each detector element consists of a bar shaped organic scintillator [5] and silicon photomultipliers (SiPM) for dual-ended signal readout.

Monte Carlo studies have shown that to detect changes range shifts of the order of 1 mm with the NOVCoDA, 2×10^7 protons per spot is needed [4]. In proton therapy, especially in pencil beam scanning, it is desirable to be able to detect range changes with intensities as low as 10^6 protons per spot. Therefore, we are investigating ways to improve the efficiency of the NOVCoDA. One possibility is to use the detector for energy spectroscopy, as a large proportion of detected PGs will scatter only once or twice and can therefore not be used for imaging. The use of Prompt Gamma-ray Spectroscopy (PGS) for range monitoring in particle therapy has previously been proposed by several groups [6]–[8] and clinical trials of at least

one clinical prototype are ongoing [7]. These systems make use of the specific photopeaks in the acquired energy spectra as the intensities of these have been shown to correlate with the proton beam range in tissue.

Organic scintillators are usually not used for energy spectroscopy due to their low effective atomic number, Z_{eff}, and density, which means that photoelectric absorption is very unlikely in these materials, especially at the PG energies of several MeV present in proton therapy. The library least squares (LLS) method makes use of the whole detected spectrum and not only the photopeaks as in conventional spectroscopy. This will reduce the dependency on being able to identify the peaks in the spectrum for quantitative analysis. The LLS method relies on so called libraries, which are PG energy spectra from the individual elements of the sample that is irradiated. These library spectra are challenging to generate experimentally, and in this study we therefore use Monte Carlo (MC) simulations to generate the libraries needed. This is called the Monte Carlo library least squares (MCLLS) approach [9]–[13]. The MCLLS approach has previously been applied to numerous inverse radiation analyser problems [12], but never in the context of range monitoring in proton therapy. In this study we want to investigate whether it is possible to use the NOVCoDA for quantitative spectroscopy in conjunction with the MCLLS approach. If successful, the NOVCoDA could then also be used for PGS, despite the fact that it is based on the use of organic scintillators. Successful application of the MCLLS approach would allow it to be used as an alternative to conventional spectroscopy in the context of range monitoring in proton therapy.

II. Methods

A. The Monte Carlo Library Least Squares approach

As mentioned in the introduction the LLS approach makes use of the whole PG spectrum, both the specific energy peaks and the Compton continua [11]. This automatically treats unresolved spectral features and returns residuals that may reveal whether or not there are missing spectral contributions in the quantitative analysis. The main assumption is that the total PG spectrum is a linear combination of the relevant library spectra, i.e., the individual spectra of each constituent in a given sample. The counts in each channel (energy histogram bin) can then be formulated mathematically as follows [10]:

$$R_i = \sum_{j=1}^{m} \alpha_j R_{j,i} + e_i, \; i = 1, 2, 3, \ldots, n \qquad (1)$$

Here R_i is the total counts in channel i for the unknown sample, α_j is the multiplier coefficient for component j in the unknown sample, m is the number of elements, $R_{j,i}$ is the counts in channel i for component j (the library spectrum of the jth component), e_j the statistical uncertainty in channel i, and n is the number of channels. The coefficients α_j are obtained through a least squares analysis by minimizing the reduced chi-square:

$$\chi_v^2 = \sum_{i=1}^{n} \frac{e_i^2}{(n-m)\sigma_i^2} \qquad (2)$$

Here $(n-m)$ is the number of degrees of freedom and σ_i is the standard deviation in channel i [10]. The minimization of the chi-square values is done by setting the derivatives with respect to the library multiplier coefficients equal to zero. When the coefficients are obtained, the unknown spectrum should be reconstructed by using the library coefficients in (1). The residuals in each channel can be calculated with the formula

$$Res_i = \frac{R_i - \sum_{i=1}^{m} \alpha_j R_{j,i}}{\sigma_i}. \qquad (3)$$

The linearity assumption is normally violated since the formation of composite PG spectra is an inherently non-linear process. The contribution to the library spectrum from one element will not only depend on the amount of that element, but also all other elements [12]. In the Monte Carlo library least squares approach the elemental library spectra are therefore generated with accurate forward Monte Carlo (MC) radiation transport simulations, which will take into account the non-linear matrix effects mentioned above and generate accurate library spectra [11].

The MCLLS approach proceeds in three steps [11]:

1. Generate elemental library spectra with MC simulations for a sample of an assumed composition.
2. Obtain the total PG spectrum of an unknown sample of the same elements (normally obtained experimentally).
3. Obtaining fitting coefficients by performing a least squares analysis using the libraries generated in step 1 and the gamma-ray spectrum in step 2.

B. Simulations

A Geant4 (v11.0.2) MC simulation framework for generation of the elemental library spectra [14]–[16] was applied in the present study. The pre-packaged reference physics list QGSP_BIC_HP was used in the simulations.

The simulation geometry, shown in Fig. 1, consists of a phantom and a monolithic detector.

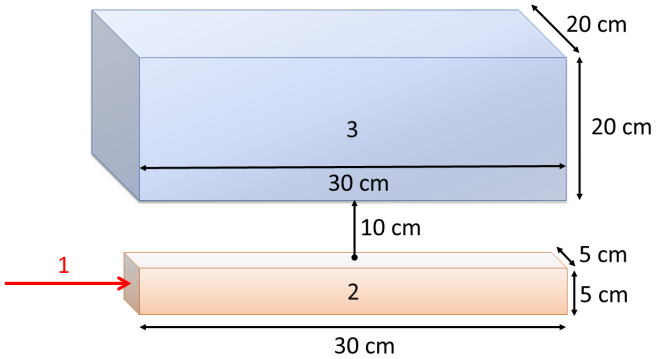

Fig. 1. The simulated geometry. The incoming proton beam (1) is impinging on the short end of the phantom (2), and the prompt gamma-rays are detected by the detector (3).

The phantom has the dimensions 5 cm × 5 cm × 30 cm and is made of polymethyl methacrylate (PMMA) with the chemical formula $C_5O_2H_8$. The detector is a 20 cm × 20 cm × 30 cm organic glass scintillator (OGS). The composition of the OGS material is implemented as 53.2 % carbon (C), 45.6 % hydrogen (H) and 1.2 % silicon (Si), with a density of 1.09

g/cm^3. The detector is placed 10 cm lateral to the phantom and centred at 15 cm depth for the reference case without range shift.

The known PG spectra were generated by simulating a pencil beam of 10^9 protons with an energy of 150 MeV, impinging on the short end of the phantom, as shown in Fig. 1. To introduce range shifts PMMA was added or removed from the phantom where the beam enters. The PMMA was added or removed in steps of 2 mm, from -10 mm to 10 mm. For each geometry, 10^9 primary protons were simulated.

The deposited energies of the gamma-rays interacting in the detector was recorded and resampled from a Gaussian distribution to account for the energy resolution of the detector, using the ROOT data analysis framework (v6.18.04) [17]. The resolution defined by the FWHM was calculated with the formula [18]

$$\frac{\Delta E}{E} = \sqrt{A^2 + \frac{B^2}{E} + \frac{C^2}{E^2}}, \quad (4)$$

where E is the deposited energy, and $A = 0.0497 \pm 0.0031$, $B = 0.0000 \pm 8.4221$, and $C = 0.0349 \pm 0.0011$ are measured from an OGS bar of 1.0 cm × 1.0 cm × 10 cm [4], [19].

C. *Analysis of the generated prompt gamma-ray spectra*

The spectra generated were analysed using the code CEARLLS [13], [20], which is developed by The Center for Engineering Applications of Radioisotopes (CEAR), for MCLLS analysis. The elemental spectra were divided into two library spectra, one for the sum of the spectra coming from scatters of hydrogen, carbon, and oxygen (HCO), and one from prompt gamma-rays coming from other processes (OP), including events with pile-up of several PG's interacting in the detector simultaneously. Further, the combination of the sum of the spectra from scatters of hydrogen and carbon (HC), and the sum the spectra of scatters of oxygen and from other process (OOP) has been evaluated. Only two library spectra were used because the spectra from some of elements, especially the spectrum from scatters of hydrogen, contains significantly fewer entries than other spectra.

The elemental libraries were generated from the reference case with no range shift, and the total spectra of all detected PGs from each of the range shifted cases were used as the unknown spectra.

The analysis was done using both all 10^9 primary protons, and by choosing 10^8 primary proton events randomly. In the latter case, the process was repeated 10 times and the average fitting coefficients calculated.

The uncertainty in each channel is taken from Poisson statistics as the square root of the counts in each channel, $\sigma_i = \sqrt{R_i}$. This is used for the weighting in the calculation of the reduced chi-square value.

III. Results and Discussion

A. *Produced and detected prompt gamma-ray spectra*

The generated PG energy spectra are shown in Fig. 2a, and in Fig. 2b the detected PG spectra including detector resolution, coming from scatters from the different elements in the PMMA phantom, are shown. The PG spectra produced include the expected specific energy peaks on top of the continuum. As expected, these peaks are smeared out when the gamma-rays are detected by the organic scintillator detector.

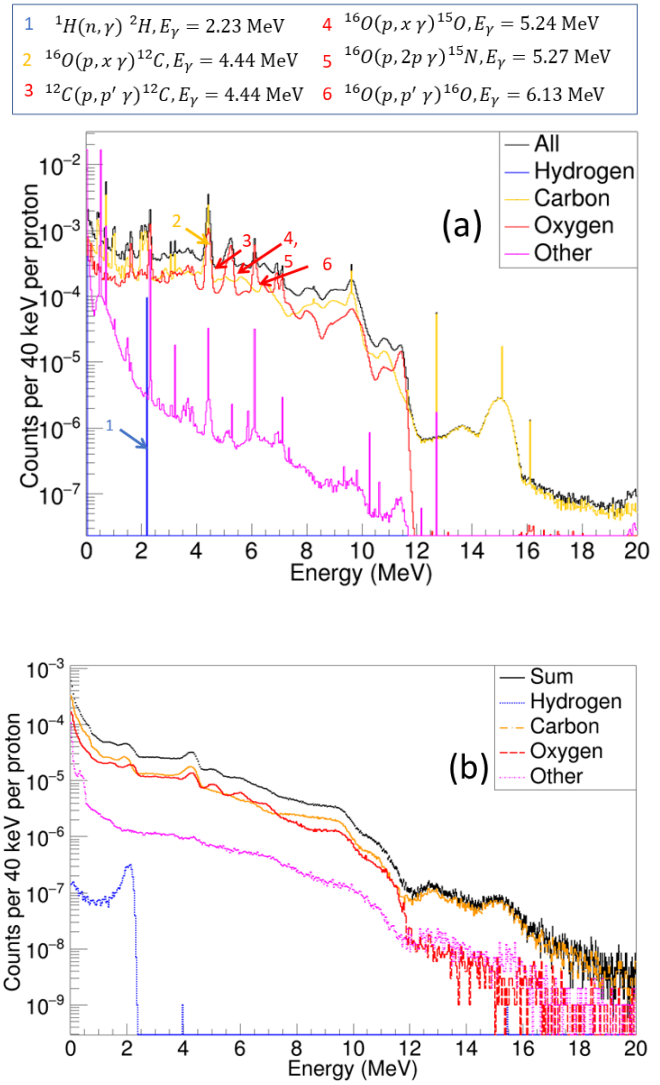

Fig. 2. The energy spectra of the generated (a) and detected (b) prompt gamma-rays.

B. *Results from 10^9 primary protons*

In Fig. 3 the original total PG spectrum, and the spectrum reconstructed using the library coefficients from the MCLLS analysis and the library spectra, are shown. The residuals, calculated with (3), are indicated in the lower subplot.

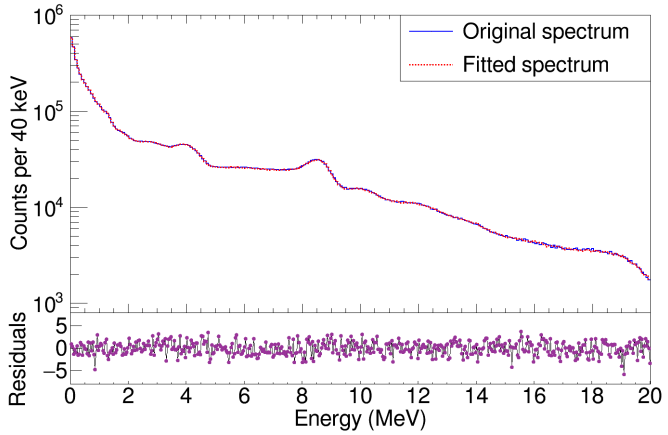

Fig. 3. Comparison of the original and the reconstructed spectra for 10 mm range shift for 10^9 primary protons. The residuals in number of standard deviations are indicated in the lower subplot.

The fitting coefficients for 10^9 primary protons for range shifts from -10 mm to 10 mm in steps of 2 mm are shown in Fig. 4. The reduced chi-square values for each range shift are indicated in the lower subplot. For each of the two libraries the fitting coefficients are linearly dependent on the range shifts, with $R^2 = 0.992$ for the HCO library spectrum and $R^2 = 0.953$ for the OP library spectrum.

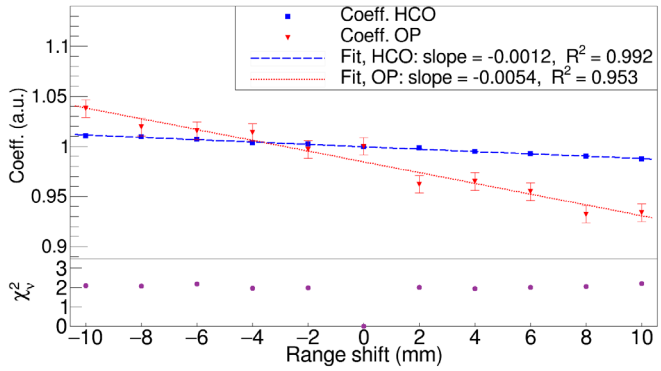

Fig. 4. The fitting coefficients for range shifted PG spectra from 10^9 primary protons. The chi-square values for each of the geometries are indicated in the lower subplot.

In the OP library spectrum, the slope of the linear fit is steeper than in the HCO library spectrum and should therefore be more sensitive to changes in the range than the HCO library spectrum. On the other hand, the OP library spectrum has larger uncertainties (about one order of magnitude) in the fitting coefficients, and they are more sensitive to small changes in the initial conditions, also changes that does not come from range shifts. This is due to the limited size of the OP library, which make up 5.3% of the detected prompt gamma-rays, compared to the HCO library.

C. Results from 10 iterations of 10^8 primary protons

In Fig. 5 and Fig. 6 the results from the analysis of the 10 samples of 10^8 primary protons are shown. In Fig. 5 a comparison of the original spectrum for one sample of 10 mm range shift is shown.

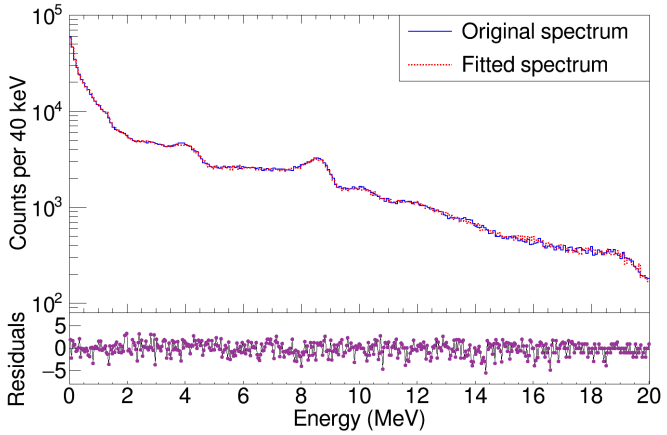

Fig. 5. Comparison of the original and reconstructed spectra for 10 mm range shift for 10^8 primary protons. The residuals in number of standard deviations are indicated in the lower subplot.

The average fitting coefficients are shown in Fig. 6, with the standard deviation indicated by the error bars. The fitting coefficients are still linearly dependent on the range shift with $R^2 = 0.983$ for the HCO library spectrum and $R^2 = 0.949$ for the OP library spectrum.

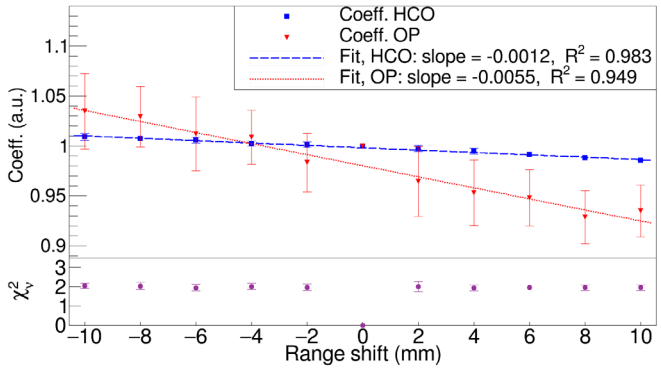

Fig. 6. The average fitting coefficients for range shifted PG spectra from 10 iterations 10^8 primary protons. The average chi-square values for each of the geometries are indicated in the lower subplot.

The same trend as in the previous section can be observed when using 10^8 primary protons. There is a linear correlation for both the HCO library spectrum and the OP library spectrum, with a steeper slope for the latter. Especially for the OP library spectrum, there is a large variation for a single range shift between the various samples, as indicated by the error bars. It was therefore decided to use an average of 10 different samples. This comes again from the fact that the OP library spectrum only makes up approximately 5% of the detected PGs and is therefore much more sensitive to small random changes.

D. Using another library composition

In the library used above the HCO library spectrum contains in the order of 95% of the detected PGs. To make the two libraries more equal in size, using the library spectra of the sum of the spectra from scatters of hydrogen and carbon (HC), and the sum the spectra of scatters of oxygen and from other process (OOP) has been evaluated. The HC library spectrum makes up approximately 56% of the detected PGs, while the OOP library

spectrum makes up the other 44%. In Fig. 7 the comparison of the original and fitted spectra with residuals indicated underneath for the 10 mm range shifted spectra, is shown. The fitting coefficients for all the range shifted spectra are shown in Fig. 8. The fitting coefficients are still linearly dependent on the range shift, but with weaker correlation for the library of the sum of oxygen and others. The R^2 is 0.949 for the HC library, and 0.748 for the OOP library.

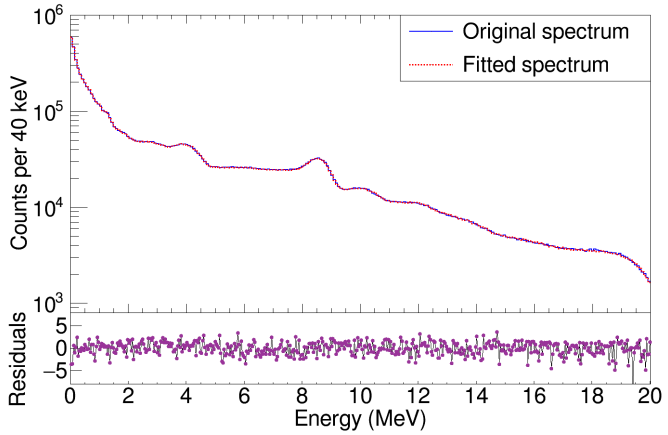

Fig. 7. Comparison of the original and the fitted spectrum using the libraries HC, and OOP. The residuals in number of standard deviations are indicated in the lower subplot.

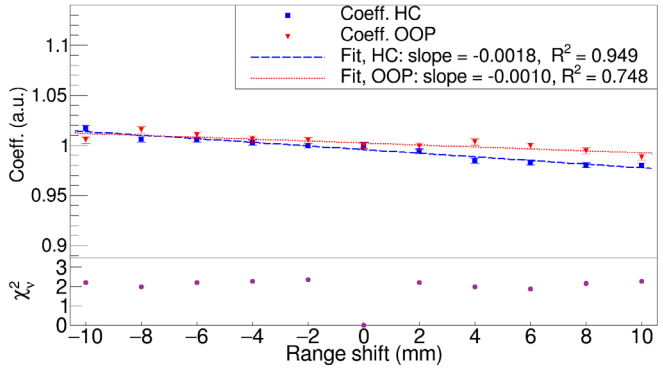

Fig. 8. The fitting coefficients for range shifted PG spectra using the libraries HC, and OOP. The chi-square values for each of the geometries are indicated in the lower subplot.

In this case, the results are more similar for the two library spectra, with uncertainties of the same order of magnitude, but with a weaker linear correlation for the OOP library spectrum. This library spectrum also has a very low slope, almost equivalent to zero, and it is therefore unclear it is feasible to apply this library spectrum for range shift detection.

IV. Conclusions and Outlook

The purpose of this work is to investigate if it is possible to use the NOVCoDA detector for PGS in conjunction with the MCLLS approach, despite it being based on organic scintillators, in the aspect of range verification in proton therapy.

A framework for simulation of a proton beam and recording the energies of the PGs generated in a phantom, has been built. Prompt gamma-ray spectra were successfully generated for 11 different scenarios, emulating a reference case and 10 different scenarios with range shifts from −10 mm to 10 mm in steps of 2 mm increments.

For the analysis of the PG spectra from 10^9 primary protons the MCLLS fitting coefficients have a linear dependence on the range shifts for both the HCO and OP library spectra, where the HCO library spectrum contains the energies detected prompt gamma-rays from scatters of hydrogen, carbon and oxygen, and the OP library spectrum contains the energies of detected PGs from other processes. The slope is steeper for the latter library, but with larger uncertainties. For the analysis using 10 iterations of 10^8 primary protons, the same trend can be observed. The linear correlation of the library coefficients with the change in range can be exploited for detecting range shifts in proton therapy, by measuring these spectra and detect deviations in the library coefficients.

When using the library spectra HC and OOP, the results and uncertainties of the library coefficients are more similar for the two library spectra. However, the linear correlation is weaker for the OOP library spectrum, and therefore it is uncertain if this library composition can be used for detecting range shifts. This needs to be investigated further with a statistical classification analysis.

As explained in the introduction the NOVCoDA will be a detector array consisting of bar shaped detector elements, and not a monolithic detector as simulated in this work. Each detector element will be read out separately, and therefore the different detector elements will have different gain drift. This will have to be accounted for in future work, both in simulation studies and when doing experiments. In addition, effects such as event pile-up might become a challenge when using experimental data. These events should be filtered out based on the pulse shape.

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