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Maximum-Likelihood Estimation of Scintillation Pulse Timing

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Abstract

Including time-of-flight information in positron emission tomography (PET) reconstruction increases the signal-to-noise ratio if the timing information is sufficiently accurate. We estimate timing information by analyzing sampled waveforms, where the sampling frequency and number of samples acquired affect the accuracy of timing estimation. An efficient data-acquisition system acquires the minimum number of samples that contains the most timing information for a desired resolution. We describe a maximum-likelihood (ML) estimation algorithm to assign a time stamp to digital pulses. The method is based on a contracting-grid search algorithm that can be implemented in a field-programmable gate array and in graphics processing units. The Fisher-information (FI) matrix quantifies the amount of timing information that can be extracted from the waveforms. FI analyses on different segments of the waveform allow us to determine the smallest amount of data that we need to acquire in order to obtain a desired timing resolution. We describe the model and the procedure used to simulate waveforms for ML estimation and FI analysis, the ML-estimation algorithm and the timing resolution obtained from experimental data using a $\text{LaBr}_3\text{:Ce}$ crystal and two photomultiplier tubes. The results show that for lengthening segments of the pulse, timing resolution approaches a limit. We explored the method as a function of sampling frequency and compared the results to other digital time pickoff methods. This information will be used to build an efficient data-acquisition system with reduced complexity and cost that nonetheless preserves full timing performance.

Index Terms

PET; timing resolution; Fisher information; Maximum-likelihood estimation; LaBr_3

I. Introduction

In positron emission tomography (PET) imaging, projection data are acquired by measuring pairs of annihilation photons emitted from a radiotracer introduced into the imaging subject. If signal is detected at the same time (within a coincidence time window) in two opposite

cameras, an electron-positron annihilation event is assigned to the line of response (LOR) that connects the interaction locations. It is possible to include position information along the LOR if the time-of-flight (TOF) difference of the two detected gamma rays is measured. The spatial uncertainty is proportional to the time resolution through the relationship $\Delta x = c \Delta t/2$, where c is the speed of light. If Δx is less than the diameter of the imaging subject, TOF information can be beneficially added to the reconstruction algorithm to improve signal-to-noise ratio (SNR) of the image. In filtered-backprojection, SNR of TOF PET is improved by a factor $f = \sqrt{D/\Delta x}$ with respect to conventional PET, where D is the subject diameter [1]–[3]. For iterative reconstruction, image quality improvement is not as simple to quantify, but it has been demonstrated that TOF leads to lower background noise, higher contrast and faster convergence [4]–[6]. Benefits of image quality improvement includes reduction in scan time or radiation dose, and improved accuracy and precision of lesion uptake measurements [7].

We are developing a new generation of modular gamma-ray cameras for PET imaging, based on a design used over 20 years at the Center for Gamma-Ray Imaging [8], [9]. The modular cameras will consist of a scintillation crystal coupled to a light guide and photomultiplier tubes (PMTs) or their solid-state counterpart (SiPMs). The analog signal from each PMT is acquired with a waveform-digitizing architecture and then the information associated with an event is assembled into an event packet.

Common analog timing methods are constant-fraction discrimination (CFD) [10] and leading-edge discrimination (LED) [11]. There has been interest in applying these methods digitally. It has been demonstrated that digital CFD degrades energy and timing performance due to aliasing error if the sampling rate is not sufficiently high (above 1 GS/s for LaBr₃:Ce crystals) [12]. A coincidence-resolving time (CRT) of 100 ps FWHM has been reported using a digital-time-pickoff method similar to LED, which is implemented by interpolating the waveform data and finding the intersection with a fixed threshold. The experiment was performed with 3 mm × 3 mm × 5 mm LaBr₃:Ce crystals, silicon photomultipliers (SiPMs) and waveforms digitized at 8 GS/s [13]. While these results demonstrate the excellent timing performance of LaBr₃:Ce crystals, it is impractical to build a large system with these characteristics due to the use of high-frequency electronics and extensive post-processing. Recently, a gamma-ray detector based on digital SiPMs (dSiPMs) has been studied [14]–[18]. With this photosensor and 3 mm × 3 mm × 5 mm LSO:Ce crystals, a CRT of 121 ps FWHM has been reported [19].

It has been demonstrated that maximum-likelihood (ML) timing estimation can be used favorably as a digital timing method [20], [21]. ML-estimation algorithms for position and energy can be implemented in field-programmable gate arrays (FPGAs) or in graphics processing units (GPUs) [22], [23]. The purpose of this work is to design an ML-timing-estimation algorithm that can be implemented in-line in FPGAs, which have pipelining capabilities, or alternatively post acquisition in GPUs, which carry out operations in a parallel fashion. The need for look-up-table storage in FPGAs makes implementation in GPUs more straightforward.

The disadvantage of waveform capture is the large amount of data in event packets. For this reason, we have interest in collecting as few digital samples as possible, while maintaining a temporal resolution suitable for TOF PET. We analyze the estimation problem using a Fisher-information-matrix approach [24], which quantifies the amount of timing information that can be extracted from segments of a sampled waveform with different numbers of digital samples.

Other groups have implemented the Fisher information (FI) analysis for temporal distribution [25]–[28]. Their approaches imply systems that detect and timestamp individual scintillation photons, while our system acquires waveform pulses. Our analysis is different in that the likelihood model represents the amplitude distribution of waveform samples instead of the photon timestamp distribution.

Here we describe the ML algorithm for timing estimation of scintillation pulses, the FI analysis used to quantify the timing information that can be extracted from the waveforms, and experimental results from a LaBr₃:Ce crystal that show the minimum amount of data needed to extract the most timing information using the ML algorithm at various sampling rates. We compare the coincidence resolving times achievable with ML estimation versus digital CFD and LED.

II. Methods

A. Maximum-likelihood-estimation algorithm

The waveform data is represented as a random vector $\mathbf{g}$ of amplitude samples conditioned on the vector parameter $\boldsymbol{\theta} = (A_o, t_o)$, where A_o is the pulse amplitude which is assumed to be proportional to the energy of the gamma-ray, and t_o is the interaction time. The likelihood function is $\text{pr}(\mathbf{g}|\boldsymbol{\theta})$. Maximum-likelihood (ML) estimation is implemented by finding the parameters $\hat{A}_o$ and $\hat{t}_o$ that maximize the likelihood, or equivalently, the logarithm of the likelihood [29],

$$\hat{\boldsymbol{\theta}}_{ML} = \underset{\boldsymbol{\theta}}{\text{argmax}} \ln \text{pr}(\mathbf{g} | \boldsymbol{\theta}). \quad (1)$$

The elements of $\mathbf{g}$ follow Gaussian statistics due to the contribution of many photoelectrons to each sample, as stated by the central limit theorem, and the addition of electronic noise. Thus we propose the following model for the likelihood,

$$\ln \text{pr}(\mathbf{g} | \boldsymbol{\theta}) = -C - \frac{1}{2}[\mathbf{g} - \bar{\mathbf{g}}(\boldsymbol{\theta})]^T \mathbf{K}^{-1}(\boldsymbol{\theta})[\mathbf{g} - \bar{\mathbf{g}}(\boldsymbol{\theta})] \quad (2)$$

where the constant C contains terms dependent on the number of samples and the determinant of the covariance matrix, $\bar{\mathbf{g}}(\boldsymbol{\theta})$ is the mean signal, and $\mathbf{K}(\boldsymbol{\theta})$ is the covariance matrix given by [30],

$$\mathbf{K}(\boldsymbol{\theta}) = \langle [\mathbf{g} - \bar{\mathbf{g}}(\boldsymbol{\theta})][\mathbf{g} - \bar{\mathbf{g}}(\boldsymbol{\theta})]^\top \rangle. \quad (3)$$

The bracket indicates an average over many pulses corresponding to the same $\boldsymbol{\theta}$.

The vector parameter $\boldsymbol{\theta}$ that maximizes (2) does not change if we choose to minimize it with the opposite sign,

$$\hat{\boldsymbol{\theta}}_{ML} = \underset{\boldsymbol{\theta}}{\operatorname{argmin}} \{ \lambda(\boldsymbol{\theta}) \}. \quad (4)$$

where $\lambda(\boldsymbol{\theta}) = [\mathbf{g} - \bar{\mathbf{g}}(\boldsymbol{\theta})]^\top \mathbf{K}^{-1}(\boldsymbol{\theta}) [\mathbf{g} - \bar{\mathbf{g}}(\boldsymbol{\theta})]$.

Estimation of amplitude and timing of a pulse must be performed jointly. The reason for this is that if an event suffers a time shift less than the sampling period, the amplitude value of each sample will change, and the amplitude of the sampled pulse will be different. Thus we use a 2D-version of the contracting-grid algorithm that has been successfully used for position estimation in modular gamma-ray cameras [22].

The first iteration of the algorithm computes $\lambda(\boldsymbol{\theta})$ for 16 mean pulses corresponding to combinations of four interaction times and four amplitudes in an equally-spaced rectangular grid. Throughout the iterations, the grid is reduced by a factor of two in each dimension, and the new grid is centered at the $\hat{\boldsymbol{\theta}}_{ML}$ location found at the previous iteration. The process is repeated a fixed number of times, until the estimates are obtained at a desired precision. The contracting-grid algorithm is illustrated in Fig. 1.

B. Simulation of scintillation pulses

In order to calculate (4), mean signals and covariance matrices are required for known pulse amplitudes and event times. The parameters used to simulate those pulses are calibrated by analyzing experimental photomultiplier waveforms. Pulse-to-pulse variations originate in the randomness in the underlying point process that describes the arrival of scintillation photons and conversion to primary photoelectrons.

The current waveform $i(t)$ from one gamma-ray interaction is simulated as the convolution of a point process $p(t)$ and the single-electron response (SER) of the photomultiplier tube (PMT) [30],

$$i(t) = i_0(t) * p(t). \quad (5)$$

The PMT SER is modeled using a Gaussian function of the form

$$i_o(t) = e^{-t^2/2\sigma^2}. \quad (6)$$

where the variance σ^2 determines the width of the SER. The point process $p(t)$ is defined as

$$p(t) = \sum_{n=1}^N \delta(t - t_n), \quad (7)$$

where N is the number of photoelectrons, and t_n is the time of occurrence of the n^{th} photoelectron (Fig. 2). In order to find t_n we describe the probability $\Pr(1 \text{ photon in } t_i)$ of detecting a scintillation photon in a short time interval of duration $t_i = t_i - t_{i-1}$ using the model for the emission of scintillation photons that has been described for a $\text{LaBr}_3:\text{Ce}$ crystal [31],

$$\Pr(1 \text{ photon in } \Delta t_i) = \sum_{k=1}^3 \left(A_k e^{-t_i/\tau_{d_k}} - B_k e^{-t_i/\tau_{r_k}} \right), \quad (8)$$

where τ_d and τ_r are the crystal decay and rise constants, respectively. We determine t_n with an acceptance-rejection method, which consists in assigning a uniformly-distributed random number and a number from the distribution that corresponds to (8) to every t_i . If the random number is less than the number obtained from (8), a photoelectron event is assigned to t_i and the value of t_i is assigned to t_n in (7).

The current pulse $i(t)$ is then multiplied by a gain G , characteristic of the readout electronics. Lastly, independent gaussian electronic noise with standard deviation $\sigma_n = 0.03 \text{ V}$ is added, as determined from computing the standard deviation of the experimental data in a segment where there is no signal. The result is the random vector $\mathbf{g}_s$ with elements given by $g_{sm} = G \times i(t_m) + n_{\sigma_n}$, an example of which is shown in Fig. 3. This model allows us to calculate $\bar{\mathbf{g}}(\boldsymbol{\theta})$ and $\mathbf{K}(\boldsymbol{\theta})$ from many realizations of simulated data [24]. In this simulation, the elements of $\boldsymbol{\theta} = (A_o, t_o)$ are the maximum value of the mean pulse and the time of occurrence of the first photoelectron of the point process. Using these precomputed data, $\hat{\boldsymbol{\theta}}_{ML}$ can be estimated for an experimental test pulse $\mathbf{g}$.

The variables that we need for the precomputation of the mean pulses are the two fast decay-time constants τ_{d1} and τ_{d2} , one slow decay-time constant τ_{d3} , two rise-time constants τ_{r1} and τ_{r2} , the SER full width at half maximum (FWHM), the Gaussian-electronic-noise standard deviation σ_n , a gain G , and the event time. Intensities A_k and B_k were taken from [31]. A least-squares fit using 2D- and 3D-versions of the contracting-grid algorithm was used to estimate these parameters using simulated pulses $\mathbf{g}_s$ fitted to averaged experimental pulses downsampled to 5 GS/s (Fig. 4). The experimental pulses were obtained as explained in Section III. The results of this procedure were used to compute (4). The measured values

for rise and decay time constants are shown in Table I and compared to literature values [31], [32]. The observed rise and decay times of the waveform are not parameters intrinsic from the crystals, since we let them vary freely in order to compensate other variations of the experiment, e.g. SER, to improve fitting. The rise-time and decay-time constants we compute are not proposed to have a physical interpretation such as describing exciton properties, but are the parameters needed to accurately describe the observed pulse shape.

C. Fisher-information analysis

In order to quantify the information conveyed by segments of the pulse, we performed a Fisher information (FI) analysis. The FI matrix can be used to quantify the amount of timing information that an unbiased estimator, such as the ML estimator, can at best extract from the waveforms. The components of the FI matrix are given by [30]

$$F_{jk} = \left\langle \left[\frac{\partial}{\partial \theta_j} \ln \text{pr}(\mathbf{g} | \boldsymbol{\theta}) \right] \left[\frac{\partial}{\partial \theta_k} \ln \text{pr}(\mathbf{g} | \boldsymbol{\theta}) \right] \right\rangle_{\mathbf{g} | \boldsymbol{\theta}} \quad (9)$$

where the derivative of the log-likelihood is calculated by taking the derivative of (2),

$$\frac{\partial}{\partial \theta} \ln \text{pr}(\mathbf{g} | \boldsymbol{\theta}) = -\frac{1}{2} \frac{\partial}{\partial \theta} [\mathbf{g} - \bar{\mathbf{g}}(\boldsymbol{\theta})]^\top \mathbf{K}^{-1}(\boldsymbol{\theta}) [\mathbf{g} - \bar{\mathbf{g}}(\boldsymbol{\theta})]. \quad (10)$$

The components of the FI matrix can be interpreted as an indication of the degree of curvature of the average log-likelihood [30], which relates how accurately the maximum of the curve can be determined.

The ML estimator is asymptotically unbiased and its variance may achieve the Cramér-Rao lower bound (CRLB), which is given by the diagonal components of the inverse of the FI matrix [30],

$$\text{Var}(\hat{\theta}_j) \geq [\mathbf{F}^{-1}]_{jj}. \quad (11)$$

The CRLB sets the lower bound on the variance of an unbiased estimator. We use the CRLB as a figure of merit on how much timing information can be extracted from the data using the ML estimator under ideal circumstances.

III. Experimental setup

In order to obtain absolute timing resolution, (different from coincidence timing resolution) we acquired two simultaneous observations of the same gamma-ray event, as shown in Figure 5. The scintillation pulses were obtained using a single 1 mm × 10 mm × 10 mm LaBr₃:Ce(5%) crystal coupled to two Hamamatsu R9880U-210 photomultiplier tubes

(PMTs) which had their protective plastic covers removed. A thin crystal was used to eliminate variations in the position of interaction along the y axis. The source was Cs-137, and the radiation was collimated in order to reduce variations in the position of interaction along the x and z axes. The signals were recorded using a two-channel Tektronix DPO72004B oscilloscope. An imperfect impedance match between PMTs and the oscilloscope causes a weak reflected signal that creates minor oscillations in the mean experimental pulse, as can be seen in Figure 4. The data were acquired at 50 GS/s, and later down sampled to 5 GS/s to simulate the waveform-digitizing rates we are planning to use in the data-acquisition system during calibration measurements, i.e., to determine the mean pulse parameters in Table 1. For the coincidence timing-resolution analysis, the data were down sampled to 250, 500, 1000, and 2000 MS/s.

IV. Results

A. Cramér-Rao lower bound

We computed the CRLB on the timing estimation for the first N samples of simulated waveforms, where N goes from the first sample to the last sample (cutoff point). The results show that the CRLB approaches a limit as the waveform segment lengthens. It can be seen in Fig. 6 that all of the timing information can be extracted using just the first 10 samples of the waveform for a LaBr₃:Ce(5%) crystal and a sampling rate of 500 MS/s, the rate chosen as the minimum that ensures at least one sample on the rising edge. For two identical detectors, this CRLB leads to a coincidence timing resolution FWHM of $\sim\sqrt{2} \times 100 \text{ ps} \approx 140 \text{ ps}$. In this case, acquiring more than 10 samples past the rising edge does not significantly improve timing resolution.

B. Maximum-likelihood timing estimation of experimental scintillation pulses

Event times were estimated for the scintillation pulses obtained experimentally. A typical sampled experimental pulse is shown in Fig. 7. The square root of the variance of the time difference between pairs of pulses in the two channels was multiplied by the factor 2.355 to estimate the coincidence timing resolution FWHM. Similar to the CRLB analysis, we implemented the ML-estimation algorithm for different lengths of the scintillation pulses by varying the cutoff sample, at 250, 500, 1000, and 2000 MS/s.

In order to compare ML-estimation results with common timing methods, digital CFD and LED timing estimates were computed by linearly interpolating between data samples, and subsequently finding the intersection with a constant-fraction threshold and a fixed threshold, respectively. It can be seen in Fig. 8 that the ML estimation outperforms CFD and LED as long as the sampling rate is high enough to ensure at least one sample on the rising edge of each pulse, but that the advantage disappears in the limit of very fast sampling ($> 2 \text{ GS/s}$).

The experimental coincidence timing resolution achieved with ML-estimation was 1853.5 ± 45.2 , 400.4 ± 10.8 , 230.6 ± 2.3 and $255.4 \pm 4.5 \text{ ps FWHM}$ for 250, 500, 1000, and 2000 MS/s, respectively (Fig. 8). The results in Fig. 9 confirm that for lengthening segments of the pulse, the coincidence time resolution approaches a limit. This only happens when there

is at least one sample at the rising edge of every pulse. This is not the case for the 250 MS/s rate with the rapid rise times characteristic of $\text{LaBr}_3\text{:Ce}$.

Imperfect mean-pulse calibration limits performance in the ML-estimation method, and is the most likely source of difference between the lower bound calculated from simulation and the experimental results.

Other pulse shapes and sampling rates will have a different cutoff point. For crystals with higher aspect ratio, an additional modeling term that describes distributions of optical path length is needed. In our pulse simulation model, this additional term can be convolved with the SER function.

V. Conclusions

A Fisher-information analysis was implemented to quantify the timing information carried in sampled scintillation pulses from 662 keV photons interacting in a $1\text{ mm} \times 10\text{ mm} \times 10\text{ mm}$ $\text{LaBr}_3\text{:Ce}(5\%)$ crystal. The motivation is to acquire just the exact amount of data that will achieve a desired timing resolution, reducing the complexity of the data-acquisition system.

We found that the Cramér-Rao lower bound approaches a limit when the length of the segment analyzed increases. Thus, the desired resolution can be achieved with a subset of the full waveform.

We corroborated the analysis using experimental scintillation pulses, in which we found that the coincidence timing resolution obtained with the ML-estimation algorithm indeed approached a limit when the number of samples was increased beyond the cutoff where the CRLB achieves its lower value. We found that with $\text{LaBr}_3\text{:Ce}(5\%)$ read out at 500 MS/s and 1 GS/s, rates at which there are at least one sample on the rising edge, the ML-estimation method yields timing resolution a factor of 5 better than the A/D sampling period, and performs better than digital CFD and digital LED detection. This advantage disappeared at sampling rates higher than 2 GS/s, which we attribute to increasing sensitivity to any imprecision in the high-frequency components of the pulse model needed for ML estimation.

Efforts from other groups towards achieving sub-100 ps resolution are important to set a benchmark for future generations of TOF PET systems [33]–[36]. However, the characteristics at which the experiments were performed (high-frequency electronics, extensive post processing and photodetectors in development) are impractical to reproduce in a low-cost and low-complexity system with current technology, in contrast with the motivations and methods presented in this article.

The results obtained in this work can be used to build an efficient data-acquisition system for PET imaging, that will minimize the amount of waveform data that must be acquired and stored while achieving a timing resolution suitable for TOF PET.

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References

1. Budinger TF. Time-of-flight positron emission tomography: status relative to conventional PET. *J Nucl Med.* Jan; 1983 24(1):73–78. [PubMed: 6336778]
2. Moses WW. Recent advances and future advances in time-of-flight PET. *Nucl Instr Meth Phys Res A.* Oct; 2007 580(2):919–924.
3. Conti M. Focus on time-of-flight PET: the benefits of improved time resolution. *Eur J Nucl Med Mol Imaging.* Jan; 2011 38(6):1147–1157. [PubMed: 21229244]
4. Karp JS, Surti S, Daube-Witherspoon ME, Muehllehner G. Benefit of time-of-flight in PET: experimental and clinical results. *J Nucl Med.* Mar; 2008 49(3):462–470. [PubMed: 18287269]
5. Kolthammer, JA., Tang, J., Perkins, AE., Muzic, RF. Time-of-flight precision and PET image accuracy. *IEEE Nucl. Sci. Symp. Conf. Rec;* Nov. 2010; p. 3657-3660.
6. Conti M, Eriksson L, Westerwoudt V. Estimating image quality for future generations of TOF PET scanners. *IEEE Trans Nucl Sci.* Feb; 2013 60(1):87–94.
7. Cates JW, Levin CS. Advances in coincidence time resolution for PET. *Phys Med Biol.* Feb; 2016 61(6):2255–2264. [PubMed: 26914187]
8. Milster TD, Selberg LA, Barrett HH, Easton RL, Rossi GR, Arendt J, Simpson RG. A modular scintillation camera for use in nuclear medicine. *IEEE Trans Nucl Sci.* Feb; 1984 31(1):578–580.
9. Milster TD, Aarsvold JN, Barrett HH, Landesman AL, Mar LS, Patton DD, Roney TJ, Rowe RK, Seacat RH III. A full-field modular gamma camera. *J Nucl Med.* Jun.1990 31:632–639. [PubMed: 2341900]
10. Gedcke DA, McDonald WJ. A constant fraction of pulse height trigger for optimum time resolution. *Nucl Instr and Meth.* May.1967 55:377–380.
11. Kinbara S, Kumahara T. A leading-edge time pickoff circuit. *Nucl Instr and Meth.* Jul.1969 67:261–266.
12. Nakhostin M, Podolyak Zs, Regan PH. Digital processing of signals from LaBr3:Ce scintillation detectors. *J Instrum.* Dec.2014 9:C12049.
13. Schaart DR, Seifert S, Vinke R, van Dam HT, Dendooven P, Lohner H, Beekman FJ. LaBr3:Ce and SiPMs for time-of-flight PET: achieving 100 ps coincidence resolving time. *Phys Med Biol.* Mar; 2010 55(7):N179–N189. [PubMed: 20299734]
14. Frach, T., Prescher, G., Degenhardt, C., de Gruyter, R., Schmitz, A., Ballizany, R. The digital silicon photomultiplier - principle of operation and intrinsic detector performance. *IEEE Nucl. Sci. Symp. Conf. Rec;* Oct. 2009; p. 1959-1965.
15. Tabacchini V, Westerwoudt V, Borghi G, Seifert S, Schaart DR. Probabilities of triggering and validation in a digital silicon photomultiplier. *J Instrum.* Jun.2014 9:P06016.
16. Schaart DR, Charbon E, Frach T, Schulz V. Advances in digital SiPMs and their application in biomedical imaging. *Nucl Instr Meth Phys Res A.* Feb.2016 809:31–52.
17. Liu Z, Gundacker S, Pizzichemi M, Ghezzi A, Auffray E, Lecoq P, Paganoni M. In-depth study of single photon time resolution for the Philips digital silicon photomultiplier. *J Instrum.* Jun.2016 11:P06006.
18. Brunner SE, Gruber L, Hirtl A, Suzuki K, Marton J, Schaart DR. A comprehensive characterization of the time resolution of the Philips Digital Photon Counter. *J Instrum.* Nov.2016 11:P11004.

19. van Dam HT, Borghi G, Seifert S, Schaart DR. Sub-200 ps CRT in monolithic scintillator PET detectors using digital SiPM arrays and maximum likelihood interaction time estimation. *Phys Med Biol.* Apr; 2013 58(10):3243–3257. [PubMed: 23611889]
20. Bousselham A, Bohm C. Sampling pulses for optimal timing. *IEEE Trans Nucl Sci.* Apr; 2007 54(2):320–326.
21. Furenlid, LR., Bousselham, A., Barrett, HH. Maximum-Likelihood estimation of pulse amplitude and timing. presented at the IEEE Nuclear Science Symp. and Medical Imaging Conf; Honolulu, HI. 2007;
22. Hesterman JY, Caucci L, Kupinski MA, Barrett HH, Furenlid LR. Maximum-likelihood estimation with a contracting-grid search algorithm. *IEEE Trans Nucl Sci.* Jun; 2010 57(3):1077–1084. [PubMed: 20824155]
23. Caucci L, Furenlid LR. GPU programming for biomedical imaging. *Proc SPIE.* 2015; 9594:G1–G15.
24. Ruiz-Gonzalez M, Furenlid LR. Fisher information analysis of digital pulse timing. *Proc SPIE.* 2015; 9594:B1–B7.
25. Seifert S, van Dam HT, Schaart DR. The lower bound on the timing resolution of scintillation detectors. *Phys Med Biol.* Mar; 2012 57(7):1797–1814. [PubMed: 22410975]
26. Vinke R, Olcott PD, Cates JW, Levin CS. The lower timing resolution bound for scintillators with non-negligible optical photon transport time in time-of-flight PET. *Phys Med Biol.* Sep; 2014 59(20):6215–6229. [PubMed: 25255807]
27. Cates JW, Vinke R, Levin CS. Analytical calculation of the lower bound on timing resolution for PET scintillation detectors comprising high-aspect-ratio crystal elements. *Phys Med Biol.* Jun; 2015 60(13):5141–5161. [PubMed: 26083559]
28. Gundacker S, Auffray E, Jarron P, Meyer T, Lecoq P. On the comparison of analog and digital SiPM readout in terms of expected timing performance. *Nucl Instr Meth Phys Res A.* Jul.2015 787:6–11.
29. Barrett HH, Hunter WCJ, Miller BW, Moore SK, Chen Y, Furenlid LR. Maximum-likelihood methods for processing signals from gamma-ray detectors. *IEEE Trans Nucl Sci.* Jun; 2009 56(3): 725–735. [PubMed: 20107527]
30. Barrett, HH., Myers, KJ. *Foundations of Image Sciences.* New York: Wiley; 2004.
31. Glodo J, Moses WW, Higgins WM, van Loef EVD, Wong P, Derenzo SE, Weber MJ, Shah KS. Effects of Ce concentration on scintillation properties of LaBr₃:Ce. *IEEE Trans Nucl Sci.* Oct; 2005 52(5):1805–1808.
32. Seifert S, Steenbergen JHL, van Dam HT, Schaart DR. Accurate measurement of the rise and decay times of fast scintillators with solid state photon counters. *J Instrum.* Sep.2012 7:P09004.
33. Seifert S, van Dam HT, Vinke R, Dendooven P, Lohner H, Beekman FJ, Schaart DR. A comprehensive model to predict the timing resolution of SiPM-based scintillation detectors: theory and experimental validation. *IEEE Trans Nucl Sci.* Feb; 2012 59(1):190–204.
34. Gundacker S, Knapitsch A, Auffray E, Jarron P, Meyer T, Lecoq P. Time resolution deterioration with increasing crystal length in a TOF-PET system. *Nucl Instr Meth Phys Res A.* Feb.2014 737:92–100.
35. Nemallapudi MV, Gundacker S, Lecoq P, Auffray E, Ferri A, Gola A, Piemonte C. Sub-100 ps coincidence time resolution for positron emission tomography with LSO:Ce codoped with Ca. *Phys Med Biol.* May; 2015 60(12):4635–4649. [PubMed: 26020610]
36. Gundacker S, Acerbi F, Auffray E, Ferri A, Gola A, Nemallapudi MV, Paternoster G, Piemonte C, Lecoq P. State of the art timing in TOF-PET detectors with LuAG, GAGG and L(Y)SO scintillators of various sizes coupled to FBK-SiPMs. *J Instrum.* Aug.2016 11:P08008.

Fig. 1.

Typical search on a likelihood map, showing the first, third and eighth (last) iteration. The algorithm finds the maximum-likelihood of each data vector $\mathbf{g}$. In the first iteration, it computes the likelihood for 16 combinations of $\boldsymbol{\theta} = (A_o, t_o)$ that forms a grid of equally-spaced positions. The grid is then reduced by a factor of two, and the new grid is centered at the maximum-likelihood position of the previous iteration. This process is repeated a fixed number of iterations until the estimates are obtained at a desired precision.

Fig. 2.

Point process $p(t)$ that is convolved with the single-electron response $i_0(t)$ of the PMT to form the current waveform $i(t) = i_0(t) * p(t)$.

Fig. 3.

Simulation of a scintillation pulse. The output of the PMT is modeled as the current waveform $i(t) = i_0(t) * p(t)$ multiplied by a gain G . The result is a random vector with elements $g_{sm} = G \times i(t_m) + n_{\sigma_n}$ where n_{σ_n} is Gaussian electronic noise.

Fig. 4.

Simulated mean pulses are used to compute the likelihood. A least-squares algorithm is used to compute a mean signal based on experimental pulses. Minor oscillations on decay side of pulse result from imperfect impedance matching.

Fig. 5.

Two views of the same scintillation event were observed using a single LaBr₃:Ce(5%) crystal and two photomultiplier tubes. The crystal was thin and the source was collimated in order to reduce variance in position. The signals were acquired with a 50 GS/s oscilloscope and later down sampled.

Fig. 6.

The Cramér-Rao lower bound was computed for 32 segments of simulated scintillation pulses, from sample 1 to sample N (cutoff point). The plot shows that a limit in the detector timing resolution is achieved using the first 10 samples of the pulses past the rising edge, and using more samples does not improve timing resolution.

Fig. 7. Typical 500 MS/s sampling of one experimental pulse from a $\text{LaBr}_3\text{:Ce}(5\%)$ crystal. This is the minimum sampling rate at which there is at least one sample on the rising edge.

Fig. 8.

The coincidence time resolution achieved with the MLE method was 1853.5 ± 45.2 , 400.4 ± 10.8 , 230.6 ± 2.3 and 255.4 ± 4.5 ps FWHM for 250, 500, 1000 and 2000 MS/s, respectively. CFD and LED were derived by finding the intersection of interpolated data with a constant-fraction threshold or a fixed threshold, respectively. 250 MS/s is not fast enough to ensure that there is a sample on the fast rising edge of the $\text{LaBr}_3\text{:Ce}$ scintillator.

Fig. 9.

The timing resolution for different cutoff times was computed using the maximum-likelihood estimator for data sampled at 500 MS/s and 1000 MS/s. Time resolution approaches a limit for lengthening segments of the pulse when we ensure that there is at least one sample at the rising edge. Corresponding pulse segment can be visualized in Figure 7.

TABLE I

Measured decay and rise time constants for a LaBr₃: Ce(5%) crystal and comparison with literature values

	Measured (ns)	Ref. [31] (ns)	Ref. [32] (ns)
τ_{d1}	14.9 ± 0.9 (70%)	15 (70%)	15.4 ± 0.5 (72% $\pm$ 8%)
τ_{d2}	10.2 ± 3.9 (27%)	15 (27%)	15.4 ± 0.5 (26% $\pm$ 8%)
τ_{d3}	54.8 ± 22.9 (3%)	55 (3%)	15.4 ± 0.5 (2% $\pm$ 1%)
τ_{r1}	0.7 ± 0.2 (70%)	0.38 (70%)	0.27 ± 0.07 (72% $\pm$ 8%)
τ_{r2}	1.2 ± 0.7 (27%)	2.2 (27%)	2 ± 0.9 (26% $\pm$ 8%)