State of the art and challenges of time-of-flight PET

Maurizio Conti

Molecular Imaging, Siemens Healthcare, 810 Innovation Drive, Knoxville, TN 37932, USA

Received 19 June 2008; received in revised form 1 October 2008; accepted 5 October 2008
Available online 19 December 2008

Abstract  After a brief review of the history of time-of-flight (TOF) positron emission tomography (PET) instrumentation from the 1980s to present, the principles of TOF PET are introduced, the concept of time resolution and its effect on TOF gain in signal-to-noise ratio (SNR) are discussed. The factors influencing the time resolution of a TOF PET scanner are presented, with focus on the intrinsic properties of scintillators of particular interest for TOF PET. Finally, some open issues, challenges and achievements of today’s TOF PET reconstruction are reviewed: the structure of the data organization, the choice of analytical or iterative method, the recent experimental assessment of TOF image quality, and the most promising applications of TOF PET.

© 2008 Associazione Italiana di Fisica Medica. Published by Elsevier Ltd. All rights reserved.

A brief history of TOF PET instrumentation

The feasibility and advantages of time-of-flight (TOF) positron emission tomography (PET) were identified in the early 1980s [1–3], when the idea of using the time-of-flight information in positron emission tomography was implemented in the first generation of the TOF PET scanner. These scanners were mainly developed by three leading groups: at CEA-LETI in Grenoble with support and evaluation in Orsay, France [4,5]; at Washington University in St. Louis [6,7], Missouri, USA; and at the University of Texas, Houston, Texas, USA [8,9]. But other groups such as the National Institute for Radiological Sciences in Chiba, Japan [10,11] and the University of Washington in Seattle, Washington, USA [12] contributed with instrumentation research and development of reconstruction methods.

This first generation of TOF PET scanners was based on CsF and BaF2 scintillators [13–15]. Laval and colleagues [14] reported a best resolution for BaF2 as low as 156 ps and 212 ps for CsF, for 511 keV. On the system level, however, time resolutions between 470 and 750 ps were reached [15–17]. Low density, low photoelectric fraction and low light output resulted in poor spatial resolution and sensitivity. Moreover, the ultraviolet emission of BaF2 made light collection difficult and required the use of more expensive photomultipliers (PMT) with quartz windows. Thus, the first generation of TOF PET scanners was limited to the research environment.

In a parallel development of non-TOF PET systems during the late 1970s and early 1980s, bismuth germanate (Bi4Ge3O12 or BGO) [18] began to be used for PET. This scintillator has high detection efficiency, acceptable light...
output, and a light emission wavelength of around 480 nm. BGO became the standard in positron emission tomography. Its long decay time and low light output, however, made it unusable in TOF PET. With the success of BGO based PET systems and the low sensitivity of BaF₂, TOF PET development came to a halt.

The discovery of new scintillators in the 1990s prepared the way to a new phase of TOF PET research and development. Cerium-doped lutetium orthosilicate or LSO (Lu₂SiO₅) [19] has a relatively high light yield (about 30,000 photons/MeV⁻¹), high effective Z (Zₑff = 66), and high density (7.4 g cm⁻³). These characteristics alone pushed LSO to become the standard PET detector for one of the major PET scanner manufacturers [20,21]. Another key parameter of LSO is its short decay time (40 ns). The short decay time was immediately used to reduce the coincidence window from the 12 µs typical of BGO scanners to 6 ns and it was later reduced to 4.5 µs with the development of faster electronics. The short time coincidence window reduced the random coincidences in the acquired data.

It became clear that LSO could also be used as a detector for a new generation of TOF PET scanners. Time resolution down to 300 ps has been reported with two single LSO crystals in coincidence, making TOF PET a viable solution [22]. First attempts to perform TOF reconstruction on a commercial LSO PET scanner showed a measurable gain in signal-to-noise ratio due to the TOF reconstruction [23,24], even with a poor 1.2 ns time resolution.

The recent discovery of cerium-doped lanthanum bromide (LaBr₃) [25] opened another avenue for TOF instrumentation. While lanthanum bromide showed lower stopping power than LSO, it had shorter decay time (16 ns), excellent energy resolution (about 3% at 662 keV), and twice as much light output, making it an attractive candidate for TOF PET [26]. The first LaBr₃ time-of-flight scanner was developed at the University of Pennsylvania [27]. It was based on 4×4×30 mm³ LaBr₃ crystals, assembled in 24 detector modules each of about 10×25 cm², covering 25 cm axial FOV. A continuous light guide coupled each detector array to 24 PMTs. A 7.5% energy resolution allowed for a reduced scatter fraction. A 460 ps time resolution was measured. Recent improvements in triggering technique brought the time resolution to 420 ps, and there is evidence that time resolution could be brought down to 315–330 ps [28].

A first commercial time-of-flight PET scanner, the Gemini TF PET/CT, was recently introduced by Philips in 2006 [29], and uses a LYSO scintillator crystal. LYSO is a material with a structure very similar to LSO: a fraction of the lutetium atoms in the crystal are replaced with yttrium. LYSO properties are also very similar to those of LSO, the main difference being the lower density due to yttrium’s lower weight. Gemini TF uses 28 flat modules made of 4×4×22 mm² LYSO crystals, and covers an area of about 10×18 cm² (18 cm axial coverage). A total of 420 PMTs are coupled to the 28 detector modules in an Anger logic architecture. Time resolution of the Gemini TF is 585 ps if measured with a low activity source.

Recently, clinical results from a Siemens prototype TOF PET scanner have been presented [30]. The new TOF scanner has a time resolution of 550 ps. It comprises 192 independent detector blocks assembled in four rings around the patient on a cylindrical barrel configuration. The axial coverage is about 22 cm. Each block is made of 13×13 LSO crystals (4×4×20 mm³), coupled to a set of four photomultiplier tubes.

Additional valuable sources of information on TOF PET history and research can be found in some recent review papers available in the literature [17,31,32].

Introduction to the principles of TOF PET

Principles of TOF PET

Time-of-flight information is used in conventional (or non-TOF) positron emission tomography to determine if two detected photons are in “time coincidence” and therefore belong to the same positron annihilation event.

Each detected photon is tagged with a detector position and detection time: if the detection time difference between two photons is smaller than a set coincidence window (traditionally 5–10 ns), the two events are considered physically correlated to the same annihilation event. Such measured difference in detection time is directly related to the actual photon time-of-flight difference, blurred by a measurement uncertainty named “time resolution”, which depends on several instrumental factors.

Conventional PET reconstruction uses the time-of-flight information only to identify the line along which the annihilation occurred. It is unable, though, to determine which voxel along the line is the source of the two photons; therefore all the voxels along the line are given the same probability of emission. Analytical or iterative reconstruction algorithms are used to estimate the activity distribution most consistent with the measured projection data.

TOF PET uses the time-of-flight difference to better locate the annihilation position of the emitted positron. The time-of-flight difference t is directly related to the distance x of the annihilation point from the center of the field of view (FOV) (x = ct/2), along the line of response (LOR) identified by the two detectors in coincidence, as shown in Fig. 1. In Fig. 1, TOF_A is proportional to the distance between the source and detector A, and TOF_B is proportional to the distance between the source and detector B. The limitation in our ability to localize the annihilation point is mainly due to uncertainty in the measured time difference t, or time resolution Δt of the coincidence system. The time resolution is used in the reconstruction algorithm as a kernel for a localization probability function. The events are located along the LOR identified by the two detectors; its most probable position is set to the position corresponding to the measured TOF difference t. The FWHM of the probability function is the localization uncertainty Δx (FWHM) = ct/2.

In Figs. 2–4, the difference between conventional and TOF reconstruction is illustrated with a simulation. A simulated uniform disk of activity with an internal hot spot is placed inside a ring of detectors (Fig. 2). A Maximum Likelihood Expectation Maximization (MLEM) iterative algorithm is used for image reconstruction for both TOF and non-TOF. Iterative algorithms are based on repeated updates of an estimated image based on a comparison of
A second more general (common to iterative and analytical reconstruction) characteristic is that the additional information provided by TOF also results in a final image that is characterized by lower noise than the corresponding non-TOF image, as is visible when comparing Figs. 3c and 4c.

**The TOF gain**

In fact, the TOF reconstruction reduces the noise propagation along the LOR during back projection of the data in the reconstruction. The reduction is related to the width of the kernel used, or to the time resolution of the system. This noise reduction was studied during the early years of TOF PET, mainly via modeling the noise propagation through analytical reconstruction processes in TOF and non-TOF reconstruction [2,7,10,33,34].

Conventional non-TOF signal-to-noise ratio (SNR) has been modeled in a simple case by Strother using an analytical back-projection algorithm [35]. In a cylinder of diameter $D$, with uniform distribution of activity, one can estimate the SNR in an image element of size $d$ starting from the data collected in the projection space:

$$\text{SNR} = \text{SNR}_{\text{non-TOF}} \times \left( \frac{D}{d} \right)^{1/2}$$

where the $T$ represents the total trues in the image, $S$ scatter events, $R$ the random coincidences, and $n$ the number of volume elements influencing the noise in such image element.

In the case of conventional non-TOF PET, all volume elements that contain activity along the same LOR contribute to the same projection data. In reconstruction, each detected event is evenly back-projected in all image elements along the LOR, not only in the image element where it was originated. Therefore, all $n$ elements contribute to the noise in each image element. In this case, $n$ can be estimated as $n_{\text{conv}} = D/d$ (Fig. 5a).

If TOF is implemented, each event is TOF tagged. In reconstruction, each event is back-projected only in the position associated to such TOF information and into few volume elements adjacent to it, with a weight given by a TOF kernel or probability function of width $\Delta x$; $\Delta x$ is the localization uncertainty, related to the time resolution $\Delta t$ by the equation $\Delta x = c \Delta t / d$. In this case, $n$ can be estimated as $n_{\text{TOF}} = \Delta x / d$ (Fig. 5b).

Using the appropriate values of $n$ in Equation (1), one can obtain an estimate of the signal-to-noise gain introduced by TOF reconstruction:

$$\text{SNR}_{\text{TOF}} = \sqrt{\frac{D}{\Delta x}} \text{SNR}_{\text{non-TOF}}$$

Equation (2) is used as a measure of the TOF SNR gain in the literature.

Other researchers estimated a slightly different value [10], or modified the formula for effect of the randoms [36], but Equation (2) is still a reasonable estimate of TOF gain in analytical reconstruction.

Performing a similar analysis for iterative reconstruction is more complex because of the non-linearity of the reconstruction and the complication added by the arbitrary...
choice of the iteration number. If iterative reconstruction is used, Equation (2) can only roughly estimate the SNR gain between a non-TOF and a TOF image which reached similar contrast recovery but at a different iteration number, since TOF has a faster convergence.

The quantity $T^2/(T+S+R)$ in Equation (1) is commonly referred to as the noise equivalent count rate (NEC), which is a measure of the detected counts corrected for the noise contribution of scatter and random coincidences, or a measure of the effective sensitivity of the PET scanner. The NEC can be expressed as the square of the SNR; therefore the SNR gain can be seen as NEC gain or sensitivity gain. TOF reconstruction is equivalent to an amplification of the PET scanner sensitivity, as shown in Equation (3), derived from Equations (1) and (2):

$$\text{NEC}_{\text{TOF}} = \frac{D}{\Delta x} \text{NEC}_{\text{non-TOF}}$$

It can be observed in Equation (3) that the NEC gain is directly proportional to the size of the patient and inversely proportional to the time resolution of the PET scanner. In other words, large patients will particularly benefit from TOF reconstruction.

Equation (3) also indicates that improving the time resolution is the key for better performing TOF PET scanners. The factors influencing the time resolution will be discussed in the Section Time resolution below.

In Table 1, the estimated TOF NEC gain is reported as a function of the time resolution, given a patient size equivalent to a 40-cm diameter cylinder. It shows the tremendous potential of TOF reconstruction as a "sensitivity amplifier".

### Time resolution

The system time resolution is the key parameter that defines a TOF PET scanner. If only two detector elements A and B are considered, the time resolution can be measured by placing a point source between the detectors, and measuring the full width half maximum (FWHM) of the distribution of time of flight difference between detector A and B. The time resolution depends on several factors associated with different components of the detection process in each individual detector. In a more complex system using detector rings or panels, the system time resolution results from the average of the individual time resolution associated with each detector-to-detector pair, and might be also affected by variations in the detector quality and electronics, and by the time alignment procedure.

In the present and past generations of TOF scanner, the detector is based on an inorganic crystal that converts the high energy photon into light photons, a light sensor and amplifier such as the photomultiplier tube (PMT), and the associated electronics for shaping, amplification, time and energy discrimination. We will focus on this present architecture and describe the factors that influence the time resolution.
Crystal material

The intrinsic material characteristics are the first and often main limitations to the time resolution. In particular, it has been shown that the time resolution is controlled by rise time, decay time and absolute light output. If rise time is negligible compared to the decay time, only decay time and light output determine the intrinsic limits of the time resolution; in particular, faster decay time and higher light output reduce, i.e. improve, time resolution. Materials with high light output and fast decay time, for example LaBr₃ and LSO, are good candidates for TOF PET. The Section **Scintillators for TOF** presents a review and a discussion of these scintillators.

Crystal shape and surface

The crystal geometry and surface finish have a direct and indirect effect on the time resolution. A surface finish with smaller reflectivity decreases the light output of the crystal, with an indirect effect on time resolution. A long crystal implies a path length dispersion and consequently a transit time dispersion of light in the detector on the order of 50 ps/cm for a material with a refractive index of 1.7.

Crystal arrays and light guides

In most PET scanners, scintillator crystals are assembled in arrays and mounted on a light guide that is coupled with a group of PMTs that shares the light coming from the crystals. Reflective material is placed between the crystals to reduce crosstalk. Due to light sharing between several PMTs and the light guide design and optical properties, the time resolution of the crystal array is significantly worse than the time resolution of a single crystal [37,38].

Photomultipliers

There are two groups of phenomena that originate in the PMTs: phenomena that affect the number of photoelectrons produced for each light photon, and phenomena that affect the dispersion of electron transit time in the PMT [39].

The number of photoelectrons produced for each light photon, or quantum efficiency (QE), is related to the photocathode sensitivity and the photoelectron collection efficiency of the first dynode.

The dispersion of electron transit time is mainly related to the variation of electron transit time from the photocathode to the first dynode, which is due to the different positions of the emitted electrons in the photocathode (center or edge, for example) and to the different initial velocity (both direction and modulus) of the emitted electrons. Such dispersion can also be reduced by increasing the high voltage between the cathode and the first dynode.

A TOF-grade PMT needs an optimization of the uniformity of the electric field and of the mechanical assembly in order to reduce transit path dispersions. Finally, a complete TOF PET system requires a large set of PMTs with consistent or uniform response in terms of time jitter and electron transit time.

Electronics

The signal from the PMT or similar light sensor is fed into the electronic chain for time triggering and stamping, which usually comprises a discriminator and a time to digital converter (TDC). Both constant fraction discriminators (CFD) and leading edge discriminators (LED) have been considered for TOF PET. Time jitter from electronics components, time slewing due to pick up of smaller amplitude signals and non optimal TDC design can contribute to degrade the time resolution of a PET scanner.

While the electronics could be a major limitation for time resolution, it has been shown that proper design can reduce its contribution to a negligible fraction [28,38].

Scintillators for TOF

If several factors contribute to the overall performance of a TOF PET scanner, the fundamental limits to the
performance itself are rooted in the intrinsic properties of the scintillating material used as the photon detector. In this section we will overview some of the scintillators presently being investigated for their TOF capabilities.

A good PET detector must have high density and high Z to increase the interaction probability of 511 keV photons and the probability of photoelectric interaction (over Compton and coherent scattering). These parameters have a direct effect on sensitivity and spatial resolution.

In addition, a TOF detector must offer a good time resolution. If all the other contributors (Section Time resolution) to time resolution are minimized or optimized, the time resolution $\Delta t$ decreases with shorter decay time $\tau$ and with higher absolute light output $N$ (number of light photons emitted per MeV of interacting high energy photon). More specifically, a theoretical model and experimental data are available that directly relate time resolution to the decay time and the inverse of the square root of the number of photoelectrons emitted by the PMT’s photocathode [39–43]. This model assumes a rise time that is negligible compared to the decay time; it is an accurate model for materials such as LSO [39], and it is less than accurate if such approximation is not valid [44,45]. Even for materials in which the rise time is not negligible, this model provides at least a lower limit for the time resolution, but more complex modeling is needed for a more accurate description of the data.

Most of the materials currently being studied and considered for TOF PET are Ce-doped. These have a fast decay time related to 5d–4f transition of Ce$^{3+}$ ions [43,46]. Halides or other compounds that contain heavy Lu or La are generally used, in order to reach high density and effective Z. Pr$^{3+}$ has similar characteristics as a dopant and has been recently considered for use instead of Ce$^{3+}$. The emission light wavelength of all these materials ranges between 300 and 450 nm.

A first group of scintillators is in the class of lutetium oxyorthosilicate, Ce-doped, such as Lu$_2$SiO$_5$ (LSO) [19,47] and its modifications such as Lu$_3$Y$_2$O$_{12}$-SiO$_3$ (LYSO), where part of the lutetium atoms have been replaced by the lighter yttrium [48,49]. These scintillators are dense (up to 7.4 g/cm$^3$) and are characterized by a decay time of around 40 ns and by a fairly high light output (up to 40,000 photons/MeV).

A second group of scintillators is also in the class of lutetium compounds: lutetium aluminum perovskite LuAlO$_3$ (LuAP) and modifications such as Lu$_3$Y$_2$O$_{12}$-AlO$_3$ (LuYAP), which are all Ce-doped [50–53]. The growth of pure lutetium aluminum perovskite is a critical process that can terminate into formation of garnets. On the other end, a lutetium aluminum garnet, Lu$_2$Al$_5$O$_{12}$ (LuAG), Pr-doped, is by itself an interesting scintillator [54–58]. This class of materials can be as dense as 8.3 g/cm$^3$, with decay times around 20 ns, but light output is usually below 20,000 photons/MeV.

A third group is the lutetium or lanthanum halides, Ce-doped, particularly LaCl$_3$ [59,60], LaBr$_3$ [44,61,62], and LuI$_3$ [63–66]. They are lighter materials (less than 6 g/cm$^3$), but have very high light output (up to 100,000 photons/MeV) and decay times between 20 and 40 ns. They are hygroscopic.

As historical reference, BaF$_2$ was one of the first scintillators to be used for TOF PET in the 1980s. It has an exceptionally short decay time (0.8 ns) but low density (4.9 g/cm$^3$) and very poor light output in the fast component (1800 photons/MeV). The low light output worsens energy resolution and the ability to identify individual crystals in crystal arrays. The very short emission wavelength (220 nm) caused additional light collection problems.

In Table 2 the main performance parameters of some materials considered for TOF PET are reported. A good candidate for TOF PET must have high density and photoelectric interaction probability for 511 keV photons [67], high light output and short decay time. It is worth mentioning that the decay time reported in Table 2 is the fast component of the decay time, if more than one component participates in the scintillation mechanism. The light yield is usually the total light yield integrated over a long enough time to include all components. Scintillators with one decay component like LSO release all light in the useful fast component. Two component scintillators such as LuAG or LuI$_3$ release only a fraction of the light in the fast component, for example around 50% in LuI$_3$ [65]. The fraction of the light emitted in the fast component is also reported in Table 2.

A quantitative method to compare possible TOF-grade scintillators has been recently presented [58]: it defines a figure of merit that is computed using conventional efficiency parameters such as absorption coefficient and photopeak fraction, and TOF-relevant parameters such as decay time and absolute light yield. This and other figures of merit, based on quantitative intrinsic material characteristics, point in the right direction, but do not provide a unique and definitive answer to the question of which scintillator can offer the best performance in a TOF PET scanner.

In general, as can be seen in Table 2, there is no such a thing as a best TOF PET scintillator. Sensible choices must be made to optimize the performance of the chosen material in terms of architecture, photomultiplier or other light sensor, and electronics. Also, other parameters not discussed here could determine the choice, such as fabrication complexity, hygroscopicity, cost and availability. For example, is the technology mature enough as to be able to deliver hundreds of thousands of crystals identical in terms of these key parameters, particularly light output? If not, large contribution to time resolution will simply come from components’ non-uniformity. Is the production cost competitive? Can other technical issues be properly addressed, hygroscopicity for example? In addition, one exceptionally good parameter cannot compensate for another extremely poor parameter: for example, BaF$_2$ has exceptionally fast light, but the light output is so poor that crystal positions cannot be properly separated if light is shared in a typical block structure.

**TOF reconstruction: questions and challenges**

TOF PET faces challenges not only in terms of instrumentation, but also in the field of image reconstruction algorithms. We will briefly discuss some of these challenges in this section.

The first challenge is to make reconstruction time clinically viable, since TOF brings a non-negligible additional computation burden. The choice of algorithm (analytical or
iterative) and the choice of data organization (sinogram or listmode) are only parts of this equation, together with other elements, such as computer architecture or software optimization.

A second issue is the "correctness" of the reconstruction in terms of validating the individual components that must now properly include the TOF information; for example, the scatter correction.

Finally, we must consider the clinical impact of TOF PET reconstruction in terms of better diagnosis or treatment of patients and where we expect to see the largest improvements. Even if it is too early to fully answer these questions, the first clinical studies show encouraging results and indicate some directions.

Analytical or iterative reconstruction?

Analytical reconstruction methods were the only reconstruction methods available at the beginning of TOF PET development. A variation of filtered back projection (FBP) with a time-of-flight one dimensional weight along the time-of-flight line was the natural extension of non TOF reconstruction [10]. This method, also known as confidence weighting (CW) time of flight reconstruction, performed better than non-TOF and better than other analytical TOF methods, in terms of signal-to-noise [34].

The introduction of maximum likelihood iterative reconstruction [68] prompted an extension of this method to TOF PET [11,69]: a point spread function along the line of flight is applied in the projector, with a width corresponding to the system time resolution of the scanner. Iterative reconstruction methods are generally slower than analytical methods and in particular compared to FBP, but outperform FBP from the point of view of image noise [70]. In the early 1980s the authors admitted that computational speed constituted a problem, but they forecast that future generations of computers would close the gap and make iterative reconstruction viable [69].

In fact, today iterative reconstruction methods are the standard in clinical PET, and also appear to be the natural choice for TOF PET in both present and future clinical TOF scanners [71].

But there is still interest in developing analytical methods for TOF reconstruction, and a new adaptive CW kernel has been proposed for TOF analytical reconstruction, together with a method to improve the noise performance of FBP through a locally adaptive filter [72,73]. Fast analytical methods such as TOF-FBP might be viable solutions for some applications where speed and accurate quantification are preferred to low image noise.

Sinogram or listmode reconstruction?

Each pair of detector elements in coincidence in a PET scanner identifies a line-of-response (LOR), and a fully "correct" data organization should preserve the spatial information carried by each LOR.

The first natural approach is a "listmode" reconstruction, in which data are stored as a list of detected events. Typically, an iterative reconstruction algorithm processes each event and correspondingly updates the image array. Reconstruction methods based on listmode organization of the data are usually slower, since back- and forward-projection is independently executed for each event of the list and the reconstruction time depends on the length on the list, thus on the acquisition time.

Recent publications [74–76] showed ways to efficiently incorporate new information such as TOF or local spatial resolution in listmode reconstruction.

A second approach to PET data organization is to bin the acquired data into projection representation of the data or sinograms. Events are accumulated into a 3D sinogram array, where each element is identified by a radial position, a transaxial angle, and an axial position (with polar angle). The size of the sinogram array grows with the number of independent detector elements. The large axial coverage and fine spatial resolution of today's PET scanners requires $10^4–10^5$ detectors. Different methods, commonly called "rebinning", can be used to reduce the size of the sinogram array. Rebinning techniques, by grouping LORs, reduce the number of transaxial angles (transaxial mashing) or polar angles (axial rebinning): some information is lost in this process and axial or transaxial blurring is possible and must be evaluated.

TOF PET adds complexity to data organization and computation time to the reconstruction algorithm. If the reconstruction is sinogram based, TOF information adds a 4th dimension to the 3D sinogram representation,

### Table 2

<table>
<thead>
<tr>
<th>Material</th>
<th>Density (g/cm³)</th>
<th>Photoelectric absorption (cm²/g)</th>
<th>Decay time (ns)</th>
<th>Total light output (photons/MeV)</th>
<th>Fast component fraction (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSO(Ce)</td>
<td>7.4</td>
<td>0.0379</td>
<td>40</td>
<td>32000</td>
<td>100</td>
<td>[19,47]</td>
</tr>
<tr>
<td>LYSO(Ce) (Lu₁.₈, Y₀.₂)</td>
<td>7.1</td>
<td>0.0345</td>
<td>41</td>
<td>32000</td>
<td>100</td>
<td>[48,49]</td>
</tr>
<tr>
<td>LuAP(Ce)</td>
<td>8.3</td>
<td>0.0347</td>
<td>17</td>
<td>11000</td>
<td>90</td>
<td>[51]</td>
</tr>
<tr>
<td>LuYAP(Ce) (Lu₀.₇, Y₀.₃)</td>
<td>7.1</td>
<td>0.0255</td>
<td>20</td>
<td>13000</td>
<td>65</td>
<td>[52,53]</td>
</tr>
<tr>
<td>LuAG(Pr)</td>
<td>6.7</td>
<td>0.0306</td>
<td>21</td>
<td>18000</td>
<td>63</td>
<td>[57,58]</td>
</tr>
<tr>
<td>LaBr₃(Ce)</td>
<td>5.1</td>
<td>0.0116</td>
<td>16</td>
<td>63000</td>
<td>97</td>
<td>[62,63]</td>
</tr>
<tr>
<td>LaCl₃(Ce)</td>
<td>3.8</td>
<td>0.0136</td>
<td>28</td>
<td>49000</td>
<td>65</td>
<td>[59,60]</td>
</tr>
<tr>
<td>LuI₃(Ce)</td>
<td>5.6</td>
<td>0.0285</td>
<td>36</td>
<td>76000</td>
<td>57</td>
<td>[66,67]</td>
</tr>
<tr>
<td>BaF₂</td>
<td>4.9</td>
<td>0.0174</td>
<td>0.8</td>
<td>12000</td>
<td>15</td>
<td>[13,17]</td>
</tr>
</tbody>
</table>

The data were taken from the references listed in the last column.
changing data storage and dynamic memory requirements. If the reconstruction is listmode based, more computation time is added to the already slower method.

However, TOF information can be used to actually improve present axial rebinning methods such as single slice rebinnings (SSRB) and Fourier rebinning (FORE), and allows reduction of the transaxial angular sampling with minimal resolution degradation [77,78].

**Emission data corrections for TOF PET**

In non-TOF PET the coincidence emission data acquired in a PET scanner usually undergo a pre-reconstruction phase in which several corrections are applied in order to recover the "true" emission data. Random coincidences are estimated and subtracted; normalization is applied to equalize the response of single detectors or line-of-response; the scatter events contribution is estimated and subtracted; and an attenuation correction is applied to account for the photons' self-absorption in the patient body or any other medium present in the scanner's FOV.

The introduction of the TOF dimension requires a revision of the whole process and an accurate analysis in order to identify how the different elements change in the presence of TOF.

It appears the randoms do not have a TOF structure and there is no reason to expect the attenuation to have TOF dependence. The current approach is therefore to apply conventional non-TOF corrections to the new TOF data.

Similarly, a non-TOF normalization is usually applied to TOF data, a reasonable approximation that probably requires some further study.

On the contrary, scatter correction is clearly identified as the component that definitely has a TOF structure and requires an appropriate TOF computation. Recent papers provided a TOF extension of conventional scatter estimate [79–81].

While work is necessary to refine and confirm the present form of TOF corrections, it appears that TOF reconstruction is much less sensitive to errors and improper approximations. The "redundant" information present in TOF data naturally corrects the data inconsistencies during the iterative reconstruction. It has been observed that TOF reconstruction reduces artifacts due to incorrect normalization, approximated scatter correction, truncated CT attenuation map, and metal and contrast agent artifacts in the PET image.

**Can we measure an image quality improvement due to TOF reconstruction?**

A TOF sensitivity gain was estimated and measured even in the early 1980s, using phantoms and analytical reconstruction. Making a quantitative and solid assessment on clinical patient images reconstructed with today's iterative methods is a more complex problem. First, clinical iterative reconstruction is usually stopped before convergence to a "true" solution. Second, the "true" solution might not be the same if different reconstruction methods are used, particularly in the presence of a high noise level. Third, this is complicated by a faster convergence of TOF reconstruction relative to non-TOF, which makes it improper to compare TOF and non-TOF images obtained with the same iteration number. Finally, the "true" solution in a patient image is in fact unknown.

Nevertheless, attempts to quantify the TOF sensitivity gain in today's iterative reconstruction have been made and some results are available in the literature.

The SNR improvement was measured in a simulation study of a LaBr₃ TOF scanner at the University of Pennsylvania [82]. The images were reconstructed using listmode iterative reconstruction and evaluated using a Non-PreWhitening Matched Filter (NPWMF) SNR observer. Time resolutions from 1000 ps to 300 ps were simulated. SNR in TOF images was consistently better than in non TOF images, and the improvement was larger if time resolution was better, i.e. smaller. Also, contrast recovery was observed to be better in TOF images, and the convergence of the iterative algorithm was faster if TOF reconstruction was used.

A study published in 2005 [24] plotted image noise versus cold spot residuals for different counts statistics in a simulation study of a 40 cm diameter water phantom, for a PET scanner with 1.2 ns time resolution. The study showed that the TOF data lay on a curve that was consistently better (for any iteration number) than the non-TOF data acquired with twice as many statistics. Also, a criterion was proposed for comparing TOF and non-TOF images in iterative reconstruction: a TOF and a non-TOF image can be selected with matched contrast recovery, even if produced with different iterations. This approach compensates for the faster convergence of TOF reconstruction. It was demonstrated that at matched contrast the SNR was higher in TOF reconstruction.

A recent paper [83] presented the first quantitative analysis of TOF gain on oncology patient studies, for a 600 ps time resolution TOF scanner. In this paper, TOF and non-TOF images of the same noise level were matched, and TOF contrast gain for small lesions (1—2 cm size) was demonstrated to be correlated with the patient mass. Also, SNR versus noise level curves were presented for different patients and different small lesions, and TOF consistently outperformed non-TOF. Even though the authors admitted that it was difficult to quantify a single sensitivity gain factor for TOF, the results showed a significant impact of TOF reconstruction on image quality.

A study on a large set of oncology patients was recently presented [30], confirming that human observers prefer TOF images from the point of view of contrast recovery, noise level and clarity of detail in anatomical structure. In this phase, still more clinical studies are needed to determine how this improved image quality affects clinical diagnosis and subsequent patient therapy.

**Who benefits from TOF PET?**

In the literature, recent and past, it has been pointed out that TOF images, compared to "equivalent" non-TOF images, in general show a lower level of noise and better resolution. But there are particular cases in which the improvement in image quality carried by TOF information is more significant.

First, there is a correlation between patient size and TOF gain in signal-to-noise, and this correlation has been
demonstrated in recent papers [30,83]. The TOF gain in large patients, due to the better localization of coincidence events along the line-of-response as discussed in the subsection The TOF gain, may be even more significant when limited acquisition time and high attenuation reduce the total counts in the image.

Second, another set of patients might find TOF PET beneficial; those whose PET scans have a low number of counts because of the chosen PET protocol. For example, in dynamic studies short frames are acquired with very low statistics. It has been observed that, using iterative reconstruction algorithms, scans with different levels of counts do not necessarily converge to the same image. This is due to a bias introduced by high noise level. TOF reconstruction, operating as a "statistics booster", might reduce the initial image bias due to limited statistics and help the reconstruction to converge to a "truer" and less noisy answer, regardless of the patient size.

Third, any PET application where there is a partial coverage of the patient can take advantage of TOF reconstruction, most commonly in limited transaxial angle coverage. Incomplete coverage of all angles creates image artifacts in conventional PET reconstruction. The additional TOF information can recover some of the missing information and reduce or eliminate the artifacts, as has been shown in two simulation studies: a dedicated breast TOF PET scanner and an in-beam PET system for hadron-therapy treatment facilities [84,85].

A fourth opportunity, related to the better performance of TOF in low statistics cases, is for high resolution studies. The limited acquisition time and noise level in the images favor a preference for a low resolution and low-pass-filtered image, in particular for oncology imaging. The full spatial resolution of today’s PET scanners is usually not sufficiently exploited. The lower noise and amplified sensitivity of TOF reconstruction could favor a better use of the full resolution potentiality of PET scanners, if computation speed allows it.

Finally, the image quality might be kept at the same level as non-TOF PET, but the TOF gain can be used to reduce acquisition time, improving the hospital workflow and patient comfort, and reducing costs.

Acknowledgments

I would like to thank Lars Eriksson, Mike Casey, Bernard Bendriem and David Townsend for providing experimental data, valuable references and deeper understanding through useful discussions.

References


