Clinical applications

**Clinical benefits of Time-of-Flight in PET imaging**

J.S. Karp  
S. Surti  
M.E. Daube-Witherspoon  
C.R. Divgi  
A.E. Perkins

University of Pennsylvania, Department of Radiology, Philadelphia, PA, USA.  
Philips Research, Briarcliff, NY, USA.

Figure 1. Time-of-Flight information is used in the data reconstruction to more accurately localize the origin of the annihilation.

In PET imaging, coincident gamma rays are emitted from the annihilation of a positron-labeled radiopharmaceutical injected into the patient. The gamma rays are detected by the PET scanner and tomographic images are created through traditional filtered back-projection, or through an iterative series of back- and forward-projection steps.

In a Time-of-Flight (TOF) PET scanner, the arrival times of each coincident pair of photons are more precisely known, and the (extremely small) difference between them is used to localize the annihilation event along the line between the two detected photons as shown in Figure 1a.

This additional TOF information helps to improve the image by reducing the length over which the coincident events are back-projected (Figure 1b). Instead of being back-projected over the entire distance through the body, the events are back-projected over a smaller distance, determined by the timing resolution of the scanner.

For a coincidence timing resolution of 600 picoseconds (ps) the positional uncertainty is 9 cm Full Width at Half Maximum along the line pair. The average diameter of a typical patient (torso) is 25 - 30 cm, or approximately three times the TOF positional uncertainty. The ratio of patient diameter (D) to the positional uncertainty (Δx) has been shown to be representative of the noise reduction, or the sensitivity gain, with TOF. This benefit in TOF increases as the PET system timing resolution improves but, perhaps more importantly, TOF provides more benefit in the case of heavy patients whose PET images are often of poorer image quality in conventional PET, due to increased attenuation and scatter.
To achieve comparable image quality between slim and heavy patients, the heavy patient would have to be scanned for an unreasonably long period. Consequently, TOF-PET has the potential to improve the image quality of heavy patients within a reasonable scan time.

The idea of using TOF information was originally proposed in the very early stages of PET scanner development [1-3], and the first TOF PET systems were developed in the 1980s [4-8]. A good summary of this early work is given in the publications by Lewellen [9] and Moses [10].

The early TOF systems were capable of meeting the high count rate demands of research brain and heart studies using short-lived isotopes, but they could not match the spatial resolution or the sensitivity of the conventional PET scanners available at that time, and interest in TOF-PET declined.

Recently, TOF has made a comeback with the development of new scintillators that combine fast timing performance with high light output and high stopping power [11, 12]. Improvements have also been made to the performance and reliability of fast photomultiplier tubes (PMTs), as well as to the stability of electronics. In addition, advances in image reconstruction have made TOF-PET achievable for routine clinical operation.

Early reconstruction methods were developed in the 1980s that made use of the TOF information [13-17], but these algorithms were for 2D systems. In the last decade there have been notable developments in list-mode reconstruction methods [18-20] and, more recently, inclusion of both TOF and other physical effects in the system model [21-23].

Although list-mode reconstruction is a computationally intensive method, fast computers and parallelization make a practical implementation feasible today [24].

**Aim of this study**

The benefit of TOF using simulated data has been described in previous publications by our group [25, 26]. It was reported that as the timing resolution improves, similar contrast to that of conventional PET can be achieved with fewer iterations of the TOF reconstruction algorithm. For small lesions in larger objects, it was possible to obtain higher contrast at a similar noise level to conventional PET. Lesion detectability increased nonlinearly with the number of counts in the image and the timing resolution.

In this study, the aim was to investigate the benefits of TOF experimentally using a commercially available TOF-PET system. Phantom studies were performed and the image quality of clinical patient data were assessed. A more detailed description and analysis of the phantom and clinical data can be found in a previous publication [27].

**Commercial introduction of TOF PET**

A commercially available TOF PET/CT scanner (Gemini TF) was introduced by Philips Medical Systems (now Philips Healthcare) in June 2006, although pre-production testing had already begun in November 2005 when the first system was installed at the University of Pennsylvania.

The Gemini TF is a fully 3D scanner and utilizes the scintillator LYSO. The new scanner has very good intrinsic performance, including spatial resolution and sensitivity (as specified by NEMA NU-2 standard [28]), and the TOF capability provides an improvement in image quality of the reconstructed images [29].

The intrinsic system timing resolution is ~ 600 ps, and our experience with this scanner demonstrates that the timing resolution remains very stable over a period of many months without the need for recalibration. While a new timing calibration method was developed for this scanner, and an additional measure has been added to our daily quality control, these new procedures add only a little time compared to that required by a conventional PET scanner.
Although other manufacturers use LSO and/or LYSO, no other manufacturer has announced a TOF-PET scanner as a commercially available product to date.

TOF gains in phantom studies

The benefit of TOF can be leveraged either to decrease the scan time or to improve the image quality. However, it is important to recognize that TOF is a local effect which depends on a number of parameters. Consequently, the benefit cannot be adequately characterized by a simple ratio of the object size to the positional uncertainty arising from the finite timing resolution.

Experimental studies of cylindrical phantoms with hot and cold spheres in a warm background were performed to quantify the TOF gain, taking into account data corrections and reconstruction. The sizes of the cylindrical phantoms (27 cm and 35 cm diameter) were chosen to represent average (~65 kg) and heavy (~100 kg) patients according to the correlation of count-rate vs. weight presented in one of our previous publications [29].

The contrast recovery coefficients (CRC) of the spheres were calculated according to the NEMA standard [28] and noise was calculated as the average pixel-to-pixel percent standard deviation (SD) in the background regions of interest.

Figure 2 shows the benefit with TOF in images from the 35-cm phantom study for a five-minute scan reconstructed without (Figure 2a) and with (Figure 2b) TOF information for different iterations of the ML-EM reconstruction with 20 chronologically ordered subsets. The smallest 10 mm sphere is very difficult to detect in the non-TOF images, even after 20 iterations, while it is observed even after only one iteration of the TOF reconstruction. It can also be seen that the images converge significantly faster with TOF reconstruction.

The effect of decreasing the imaging time is shown in Figure 2c (non-TOF) and 2d (TOF). The same phantom was reconstructed for different scan times from five minutes to one minute. All spheres can be clearly detected in the TOF images down to two minutes and all but the smallest 10-mm sphere are visible in the one-minute image. However, for the non-TOF images, the image quality degrades much more quickly with a reduction in scan time. The 10 mm sphere is not visible in any of the images and it becomes very difficult to detect the 13 mm sphere in the noisy two-minute image.

The CRC as a function of noise for the 13 mm sphere in the 35 cm phantom is shown in Figure 3. The curves demonstrate that the convergence is faster with TOF and the results are less sensitive to the different scan durations with TOF. There is evidence that the contrast at which the curves converge is also higher for TOF, perhaps indicating that the local behavior of the reconstruction is more independent of inconsistencies in the data. Results for the other spheres were similar although the differences between TOF and non-TOF become smaller as the sphere size increases.

The results from all the spheres and from both phantoms show that convergence is reached faster with:
- TOF
- a smaller diameter phantom
- a larger lesion
- increased statistics or longer scan time.

Clinical benefits of TOF

Clinical data from the Gemini TF were investigated to determine if these phantom results help us to understand, and ultimately optimize, the TOF gain in patients, bearing in mind that the distribution of activity in a patient is much more complex than that in a phantom.

The average prompt rate for patients is 220 - 550 kcps, which leads to approximately 40 - 100 Mcts (prompts) for a single bed position in a typical study. The singles rate for clinical studies range between 15 - 25 Mcps. These patient rates are close to the rates in the phantom experiment. The initial patient studies were acquired with a 15 mCi FDG injection followed by a three minute per bed position (3 min/bed position) scan one hour post injection.

A low-dose CT acquisition was used for PET attenuation correction. The data were reconstructed for three iterations with 33 subsets, using a patient-specific TOF resolution.
Figure 4. Representative transverse sections of two different patients; low dose CT (left), non-TOF LM-EM (middle), and TOF LM-EM (right).

Patient 1 (above) with colon cancer (119 kg, BMI 46.5). The lesion in the abdomen (arrow) is shown much more clearly in the TOF image than in the non-TOF image.

Patient 2 (below) with abdominal cancer (115 kg, BMI 38). The structure in the aorta (arrow) is shown much more clearly in the TOF image than in the non-TOF image.

Figure 5. Patient with non-Hodgkin’s lymphoma (140 kg, BMI = 46). The top row shows representative transverse, sagittal, and coronal images (not triangulated) with non-TOF reconstruction, while the bottom row shows corresponding cross-sectional images with TOF reconstruction. In each of these images the different lesions are seen more clearly in the TOF reconstruction than in the non-TOF reconstruction.

(average TOF resolution = 660 ps), since the TOF resolution has been shown to depend on the singles count-rate of the study [29].

Figure 4 shows transverse slices from two heavy patients (BMIs of 46.5 and 38); the benefit of TOF is very apparent in the images. BMI is the body mass index (kg/m²) where a value above 25 is considered to be overweight and a value above 30 is obese. The top row shows images from a patient with colon cancer. The arrow points to a lesion seen in CT that can clearly be detected in the TOF image, but is much more difficult to see in the non-TOF image. The lower row of images from a heavy patient with abdominal cancer demonstrate the improved structural detail evident in the TOF images. In this set of images the structure in the aorta is much sharper in the TOF image.

An example of another heavy patient (BMI = 46) with non-Hodgkin’s lymphoma and multiple lesions is shown in Figure 5. The TOF image is sharper and the contrast of the lesions identified by the arrows is higher. In this case, the increase in measured lesion contrast, particularly in the axilla (coronal view), with the TOF reconstruction is significant enough to make a visual impact on lesion detectability. In addition, the shape of the lesion seen in the transverse view in the TOF image is not as blurred as in the non-TOF image.

For this patient, seven lesions (1 - 2 cm diameter) were chosen for analysis. Small circular ROIs (1 cm diameter) were drawn on the lesions and the average count in each ROI was recorded. A larger diameter ROI drawn in a region of the liver that was visually determined to be uniform was used as a background region to normalize out any bias. The ratio of average lesion counts to average background counts (L/B ratio) was calculated for each lesion. Noise was determined as the pixel-to-pixel percent SD in the liver ROI.

The results of the analysis from the non-Hodgkin’s lymphoma patient (Figure 5) are shown in Figure 6 (labeled a through g). The L/B ratio is plotted as a function of the noise in the liver for the non-TOF (middle plot) and TOF (right plot) images. These curves show that the reconstructed lesion contrast is higher with TOF for all of the lesions. The data from all five patients show that the TOF curves have converged, or are very close to convergence, by 10 iterations, while the non-TOF curves show a greater variability in convergence rate. Without TOF, lesions near areas of high uptake are quite slow to converge and have still not reached an asymptotic value by 10 iterations. These results...
suggest that convergence with TOF is more spatially invariant, as noted in a recent study using simulated data [30].

**Practical issues in the clinic**

The axial field of view of the Gemini TF is 18 cm, and a 50% overlap between bed positions is used to maintain high sensitivity and uniform noise through the body scan. A typical patient scan from the base of the skull to the thigh requires 8 to 11 bed positions.

The standard conventional PET imaging protocol at the University of Pennsylvania of a 3 min/bed position scan was initially used with the Gemini TF. To accommodate an increasing clinical demand, a new protocol has since been implemented for patients with a BMI less than 30. For these patients, the scan is reduced to 2 min/bed position. Evaluations using partial patient data sets have shown that the shorter scan time provides the same diagnostic clinical information in these patients.

The fact that the TOF reconstruction converges more quickly has practical significance. In routine clinical iterative reconstruction protocols, the number of iterations must be fixed. The faster and less spatially variant convergence of the TOF reconstruction leads to more stable results at earlier iterations. In routine practice, only three iterations are used to keep reconstruction times clinically practical (i.e. to complete reconstruction within 10-30 minutes after acquisition ends using a cluster of 10 Xeon 3.6 GHz dual-processor computers connected by a Gigabit Ethernet network). The images of the average size patients, as well as those of the heavy patients, are typically close to convergence by three iterations, which leads to more consistency across patients. In addition, the convergence with TOF is more uniform and not as dependent upon nearby regions of activity as without TOF. In contrast, the conventional non-TOF reconstructions demonstrated more variability in convergence with patient size and lesion location, and three iterations were often insufficient to reach convergence.

**Conclusion**

It has been shown that the TOF benefits reported previously for simulations are observed in experimental phantom studies, as well as in clinical patients. TOF leads to a better CRC vs. noise trade-off and faster convergence in both phantoms and patients. As was observed from the phantom data, TOF allows shorter acquisition times while still achieving good image quality (as measured with the CRC/noise analysis and visual impressions). With or without TOF, image noise increases for shorter scans because fewer events are detected; however, TOF reconstruction leads to improved structural detail, so images with fewer counts may still have satisfactory image quality. This implies that TOF can be beneficial in situations where few counts are collected: e.g., dynamic imaging; respiratory gating; and imaging with non-pure positron-emitters, such as $^{124}$I, where the positron branching ratio is markedly lower than that of $^{18}$F and the complex decay scheme of gamma rays leads to additional random and cascade coincidences.

**Acknowledgements**

The authors would like to thank Matthew Werner for implementing the TOF reconstruction and SSS algorithms and for processing much of the data. We would also like to thank Joshua Scheuermann for assistance with the phantom data.
References


