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newsletter

PET COE Board Meets with Industry Advisory Group to Map Out Goals

By James W. Fletcher, MD
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An inaugural meeting was held recently in Chicago between the PET Center of Excellence Board of Directors (BOD) and the Industry Advisory Group (IAG). The meeting was very well attended with representation from a large cross-section of industry.

The interaction and discussion at the conjoint morning meeting was lively and informative, with little disagreement on the issues that need to be addressed. Not surprisingly, these included reimbursement, standardization/clinical trials, demonstrating the value of PET to referring physicians, education, the need for collaboration, and government regulation—the later dealing mostly with PET radiopharmaceutical development.

In the afternoon the board met to create, based on the morning's discussion, an agenda of specific goals that the PET COE plans to accomplish in the next 12 to 18 months.

Standardization/Clinical Trials

The BOD agreed to convene a workshop on standardization to be held in early 2007. The focus of the meeting will be to optimize PET/CT by identifying minimum standards of acceptable performance, with a goal of presenting a working draft of the standards at the 2007 SNM Mid-Winter Meeting, then presenting the final workshop proceedings at the Annual Meeting in June, 2007. The workshop will cover multiple issues from quality assurance to standardized methods of performance.

Attendees at the workshop should include industry, instrument manufacturers, the National Electrical Manufactures Association, and invited experts who have published on this topic.

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Time-of-Flight PET

By Joel S. Karp, PhD

The idea to use time-of-flight (TOF) information in PET image reconstruction was originally proposed in the 1960's at a very early stage in the development of positron imaging. By the early 1980s, fully functional TOF PET systems had been built, not long after the first conventional PET systems were completed. Why then did it take so long to introduce a clinical TOF PET scanner, and how does it compare to the first TOF PET instruments built 25 years ago?

Time of Flight Theory

The concept of time-of-flight means simply that for each annihilation event, we note the precise time that each of the coincident photons is detected and calculate the difference. Since the closer photon will arrive at its detector first, the difference in arrival times helps pin down the location of the annihilation event along the line between the two detectors.

To understand why this information is useful, we need to recall that normally in PET we collect line pair data at many angles and create tomographic images through traditional filtered back-projection or through an iterative series of back- and forward-projection steps. While tomographic reconstruction leads to superior contrast compared to planar imaging, the drawback is that it leads to higher noise although iterative reconstruction techniques help reduce this effect. Hypothetically, if we had perfect TOF information then we wouldn't need to reconstruct the image at all—we could identify the location of each annihilation event based only on TOF information and crystal identification and create an image by adding events into an image matrix. Unfortunately, this is not the case.

However, even imperfect timing information helps to improve the image by approximately localizing the event. For example, a coincidence timing resolution of 600 picoseconds (ps) (FWHM) translates to a positional uncertainty of 9 cm (FWHM) along the line pair. At first glance it seems that this can't possibly help, since this is much greater than the spatial resolution of a state-of-the-art PET scanner (4–6 mm). However, we can appreciate the significance of this information by considering that without TOF we would back-project the data for each line pair through a length D that is the distance across the patient, which for adults is considerably larger than 9 cm; with TOF PET the data are back-projected through a smaller distance, related to the positional uncertainty. For a typical patient, D is about 27 cm, which is 3 times larger than TOF positional uncertainty at 600 ps. We, therefore, expect the benefit of TOF to be proportional, though not necessarily equal, to this ratio.

The ratio between positional uncertainty and distance across the patient is also representative of the noise reduction or, conversely, the sensitivity gain, to be expected with TOF. This simple measure is useful since it provides an estimate of the relative importance of increasing timing resolution through improvements in the detector, calibra-

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tions, and electronics. This metric argues that TOF gain increases not only as timing resolution improves but also as patient girth increases. This is fortuitous, since conventional PET image quality degrades noticeably for large patients due to increased attenuation, which leads to the loss of true counts and increase of scatter counts. In fact, the difference in the noise-equivalent count-rate for a heavy patient (e.g., 120 kg) compared to a slim patient (e.g., 50 kg) is about a factor of six. Thus, to achieve comparable image quality for the heavy patient, we would need to scan for six times longer, which is clinically impractical. The promise of TOF PET is that it has the potential to improve the image quality in heavy patients, precisely where it is needed most.

Advancements in TOF Technology

The potential benefits of TOF were understood in the early 1980s, and this motivated the development of the first TOF PET scanners. These early systems—developed at Washington University, CEA LETI, and University of Texas—used either cesium fluoride (CsF) or barium fluoride (BaF_2) scintillators, which were the best scintillators available at the time for TOF PET. These scanners were capable of meeting the high count-rate demands of research brain and heart studies using short-lived isotopes (such as ^{15}O-water), but they could match neither the spatial resolution nor the sensitivity of conventional PET scanners that used bismuth germanate (BGO) scintillators. The system coincidence timing resolution of these TOF scanners was between 500 and 750 ps; however, it was reported to be very challenging to achieve this performance on a daily basis due to difficulties with reliability and stabilization of electronics and calibrations. By the early 1990s, these early TOF PET scanners had been retired—just before whole-body oncology studies with ^{18}F-FDG became prevalent.

There are a number of reasons why TOF is making a resurgence in PET today. First, new scintillators are available that combine fast timing with high light output. The low light output of CsF and BaF_2 did not allow much choice for light-sharing and decoding crystals, as is commonly done today. This led to poor packing fraction in the detector (and low scanner sensitivity) and poor spatial resolution, since the crystals were necessarily large. Newer scintillators, such as lutetium orthosilicate (LSO), lutetium orthosilicate with a yttrium impurity (LYSO), and lanthanum bromide ($LaBr_3$), all combine fast timing and high light output, leading to very good timing resolution. Overall, the characteristics of these scintillators are superior to the original TOF scintillators and enable us to incorporate them in a TOF PET system with spatial resolution and sensitivity comparable to current state-of-the-art conventional (non-TOF) PET scanners. Where the original TOF PET scanners in the 1980s needed TOF to match the performance of conventional PET scanners, today, we can use TOF to leapfrog over the performance of conventional PET scanners.

In addition to new scintillators, continued improvements in the performance and reliability of photo-multiplier tubes and electronics are making TOF more practical today than in the past. Fast-timing electronics were available 25 years ago, but stability was difficult to achieve with early TOF PET scanners.

Finally, there has been a steady stream of progress in image reconstruction algorithms, although it is only recently that a 3D list-mode iterative algorithm for TOF PET data has been developed with all physical effects included in the system model. Including TOF information in the data leads naturally to list-mode acquisition, since the TOF information requires only a modest increase in data storage while still preserving the full spatial and temporal information of the data. However, a list-mode image reconstruction algorithm, particularly for 3D, is computationally intensive and requires computers that are orders of magnitude more powerful than those available two decades ago. Although list-mode reconstruction has been put into clinical practice for TOF, work continues to develop a faster TOF PET image reconstruction algorithm that, hopefully, won't require such expensive hardware yet still achieves comparable image quality.

Commercial Introduction of TOF PET

Philips Medical Systems introduced a TOF PET/CT scanner (GEMINI TF) in June 2006, although pre-production testing began in November 2005 when the first system was installed at the University of Pennsylvania. The GEMINI TF is a fully 3D scanner using the LYSO scintillator. In contrast to early TOF scanners, this new scanner has very good intrinsic performance, including spatial resolution and sensitivity (as specified by NEMA NU-2 standards), and the TOF capability improves the quality of the reconstructed images. The system timing resolution is 600 ps, and our experience with this scanner demonstrates that the timing resolution is 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 quality control for a conventional PET scanner. Although Siemens uses LSO in all of their clinical PET scanners, and GE uses LYSO in their research PET scanner, neither manufacturer has announced a TOF PET scanner as a product.

TOF Gains in the Clinic

The earlier discussion of the benefit of TOF information was characterized in terms of noise reduction and was based on a uniform activity distribution. This benefit should translate to either a reduction in scan time or improvement in image quality that is comparable to imaging with a more sensitive scanner. However, we should recognize that it is simplistic to characterize the TOF gain as a single value because TOF is inherently a local effect that depends on the method of data correction and image reconstruction as well as the activity distribution. We have, therefore, performed a series of phantom studies with hot and cold spheres in a warm background to simulate lesions in an oncology study because the task at hand for FDG whole-body imaging is often lesion uptake quantification (i.e., semi-quantitative SUV measurement) or lesion delectability. Using these phantom studies, we have found that the TOF PET reconstruction converges faster and with higher lesion contrast for similar image noise, compared to a non-TOF reconstruction. Alternatively, if we stop the TOF PET reconstruction earlier (fewer iterations), we can achieve similar contrast with lower noise, compared to a non-TOF reconstruction. This conclusion is consistent with our prediction that TOF information would reduce image noise.

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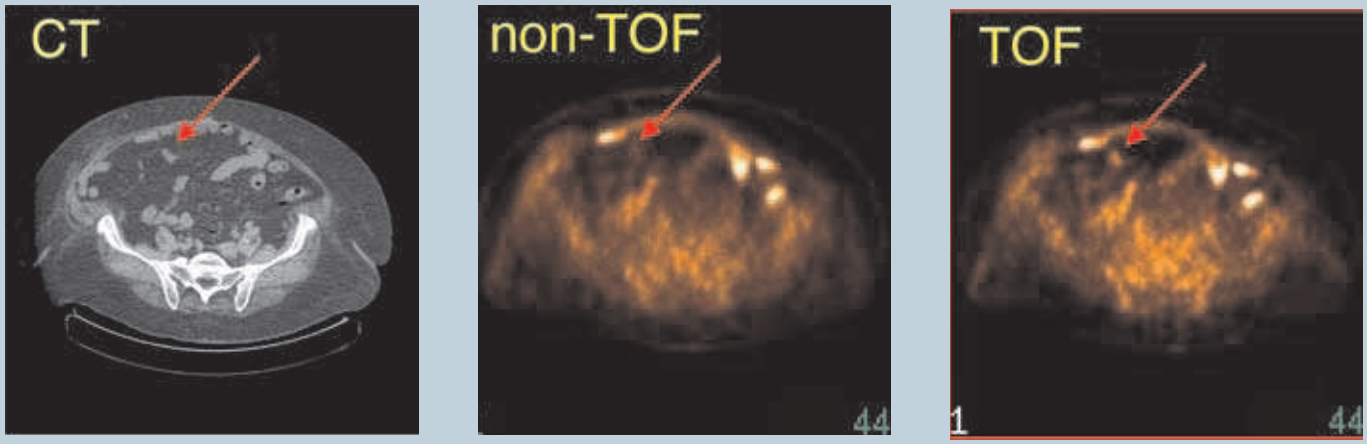

Fig 1: Suspicious lesion, left, is undetectable in an obese patient using standard PET, center. TOF PET, right, dramatically improves lesion detectability and general definition.

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The improvement with TOF PET is dramatically seen in the example of a heavy patient diagnosed with colon cancer (Fig. 1). The patient weighs 119 kg with a BMI of 46.5. The data were reconstructed with and without TOF information and show an obvious improvement with TOF in lesion detectability (at arrow) and overall structural definition in the abdomen.

This patient was scanned for 3 minutes per bed position, about a 30-minute scan (10 bed positions), our default acquisition protocol at Penn. Rather than using TOF to reduce the scan time, we have emphasized the use of TOF to improve image quality or, more specifically, the signal-to-noise ratio. In the case shown here, the difference in lesion contrast is significant enough to make a visual impact on lesion detectability. We have evaluated images of lighter patients with scan times as short as 1 minute per bed position and achieved good image quality, but there is little doubt that additional counts lead to better image quality for both light and heavy patients.

Future directions of TOF PET Technology Research

Our research efforts at Penn on TOF have included scintillators other than LYSO, in particular lanthanum bromide ($LaBr^3$), which was discovered in 2001 at Delft University and further developed at Radiation Monitoring Devices (RMD) and Saint-Gobain Crystals (SGC). Both the energy resolution and timing resolution of this scintillator are remarkable—a detector array built by SGC and suitable for PET (30-mm long crystals with 4x4 mm^2 cross-section) has 5% energy resolution and 300 ps timing resolution. These detectors have been incorporated into a prototype scanner, but further work is needed to improve the system electronics in order to match the scintillator performance that we have measured in the laboratory. When coupled with further refinement of the data correction and image reconstruction algorithms, we believe that the LaBr3 scanner with its superior timing resolution will help us to better understand how to use TOF PET to improve image quality for patients of moderate, as well as large, size.

Developing methods to evaluate image quality, and in particular the influence of TOF on image quality is an active area of research at a number of academic institutions. It is perhaps even more important to understand how to use TOF PET to improve the accuracy of quantification, which is key to the future of nuclear medicine imaging and targeted therapy.

There is experimental evidence that timing resolutions even better than 300 ps can be achieved, perhaps with new scintillators and photomultipliers under development and evaluation at a number of research centers. In the laboratory we have measured a coincidence timing resolution between two cerium bromide ($CeBr^3$) crystals from RMD of 110 ps, albeit in a configuration not designed to achieve the sensitivity and spatial resolution required for a PET detector. While challenging, these results convince us that it is possible to develop a practical detector for PET to surpass the TOF performance achieved to date in commercially available scanners. The Gemini TF scanner is notable in that it gives us clinical evidence that TOF PET is an important technology and should help to motivate research for further improvements in TOF PET.

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