From 3-D Positron Emission Tomography to 3-D Positron Emission Tomography/Computed Tomography: What Did We Learn?

David W. Townsend, PhD
Departments of Medicine and Radiology, University of Tennessee Medical Center, Knoxville, TN

The recent introduction of combined positron emission tomography (PET)/computed tomography (CT) scanners is having a far-reaching effect on the field of medical imaging by bringing functional imaging to the forefront in radiology, oncology and other specialties. The PET/CT scanner is an evolution in technology combining two well-developed imaging modalities: anatomical imaging with CT and functional imaging with PET. The first prototype PET/CT scanner was a consequence of a succession of steps that, in chronological order, included the development of the High Density Avalanche Chamber (HDAC) PET camera, 3-D PET methodology and the rotating partial-ring tomograph (PRT). The successful completion of each step was a prerequisite to progress to the next phase, and the lessons learned could then be applied to subsequent initiatives. This review will map the milestones from 3-D PET to 3-D PET/CT and assess the role each step played in the development of PET instrumentation over the past two decades. © 2004 Elsevier Inc. All rights reserved.

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Introduction

The past 20 years in particular have seen dramatic advances in the performance of imaging instrumentation for positron emission tomography (PET). From the low resolution, low sensitivity, single slice designs of the early 1980s to the high resolution, multi-slice, scanners of today, key imaging parameters have in most cases improved by at least an order of magnitude. Current high performance clinical PET scanners comprise more than 20,000 individual detector elements, with an axial coverage of 16 cm (or greater), a 4.5 ns coincidence time window, and 20% (or better) energy resolution. With such specifications, modern PET scanners attain a measured spatial resolution of around 2 mm for brain research studies and 4 mm for clinical whole-body studies, a 3-D scatter fraction of 25% to 30%, and a peak noise equivalent count rate (NECR) for 3-D whole-body imaging that approaches 100 kcps. Also of note is a six-decade increase in active coincidence lines, from a few thousand in the early 1980s to over $10^9$ today. This impressive progress is due to developments in detector construction, new scintillators, better scanner designs, improved reconstruction algorithms, integration of application-specific electronics, and, of course, the vast increase in computer power, all of which have been achieved without a corresponding order-of-magnitude increase in cost.

In the late 1980s, an important advance occurred with the introduction of 3-D PET methodology for brain imaging with a multi-ring scanner. Acquisition of PET data in 3-D makes optimal use of the emitted radiation, improving sensitivity compared to 2-D acquisition by a factor of five even after accounting for the increase in scatter and randoms. However, for whole-body imaging, the successful implementation of 3-D methodology has had to await the appearance of faster scintillators, accurate scatter correction models and improved statistically-based reconstruction algorithms. The recent availability of scintillators such as gadolinium oxyorthosilicate (GSO) and lutetium oxyorthosilicate (LSO) with short decay times, accurately modelled scatter distributions, and attenuation-weighted ordered-subset EM reconstruction algorithms have all helped to bring 3-D
whole-body imaging into the clinical arena. More recently, the importance of routinely imaging function in conjunction with high resolution anatomy has been recognized and within the past three years, the combined PET/CT scanner has been introduced into clinical practice. The device acquires accurately-aligned anatomical (CT) and functional (PET) images in the same scanner during a single imaging session, overcoming many of the disadvantages of retrospective software fusion. The combined PET/CT scanner thus provides physicians with a powerful tool to diagnose and stage disease, monitor the effects of treatment, and potentially design better, patient-specific therapies.

This paper maps the milestones from the early PET scanner designs and development of 3-D methodology to the advanced combined PET/CT scanners of today. The topics will include 3-D reconstruction algorithms developed for the High Density Avalanche Chamber (HIDAC) positron camera, the application of 3-D techniques to multi-ring tomographs, the first multi-ring scanners with retractable septa, and the development of the first partial-ring rotating tomograph (PRT). The PRT design in turn helped to launch the development of the PET/CT scanner, the combination of anatomical and functional imaging in the same scanner. From the acquisition of the first images in 1998, there are now more than 350 combined PET/CT devices installed worldwide and they represent up to 80% of new PET scanner sales.

The past two decades of progress in PET instrumentation have not been achieved without considerable effort, dedication and investment, both intellectual and financial. While mapping the milestones of instrumentation advances it is worth surmising whether such progress, impressive though it undoubtedly is, has enabled PET to really achieve its full promise and potential. The lessons thus learned may help guide future directions and identify opportunities that are worthy of further attention.

The HIDAC Camera and 3-D PET

Since the very early development of nuclear medicine instrumentation, scintillators such as sodium iodide (NaI) have formed the basis for the detector systems. Thallium-activated NaI is an ideal scintillator to convert the 140 keV photons from the decay of technetium (99mTc) into light of a wavelength matched to a photomultiplier tube (PMT). The combination of scintillator and PMT, such as found in the conventional gamma camera, has dominated nuclear medicine instrumentation since the 1950s. The challenge presented by positron tomography is the detection of the higher energy, 511 keV photons from the annihilation of positrons in tissue. Early PET scanner designs, however, were based on NaI (TI) even though a typical thickness (3/8”) used in a gamma camera resulted in a very low efficiency at 511 keV. To improve sensitivity, an increased depth of scintillator was adopted in some early PET scanners based on individual crystal arrays. An alternative approach that was explored in the mid 1970s comprised a pair of rotating gamma cameras in either a standard configuration or with thicker, 1” crystals for better sensitivity. Curiously, the rotating dual-head gamma camera experienced a short-lived revival for PET imaging in the mid 1990s.

A real breakthrough for PET came with the introduction of bismuth germanate (BGO) as an alternative scintillator to sodium iodide. BGO has only 15% of the light output of sodium iodide but is much denser and has a greater stopping power and photofraction. The first PET scanner designs based on BGO appeared in the late 1970s, and the scintillator eventually became the most widely-used detector material for PET, a situation that has continued for more than 20 years. Even so, PET scanner designs based on sodium iodide continued to be developed until recently and at one point a significant fraction of PET scanners in clinical operation were sodium iodide based.

The late 1970s and early 1980s was a period of considerable innovation in PET instrumentation with a number of different scanner designs under development. While the majority were scintillator-based, some groups explored a completely different technology, such as the HIDAC, a detector that originated from the field of high energy particle physics as the brainchild of Dr. Alan Jeavons, a physicist working at the European Center for Nuclear Research (CERN) in Geneva, Switzerland. The HIDAC detector is a multi-wire proportional chamber (MWPC) that incorporates novel lead converters to improve sensitivity for the detection of 511 keV photons. The standard MWPC was originally developed to detect high energy charged particles (> 1 GeV) with high spatial resolution and such devices are relatively insensitive to neutral gamma rays. The addition of perforated lead converters within the chamber significantly increases the intrinsic sensitivity due to the photoelectric conversion in the lead of the incoming gamma. The photoelectron is ejected from the lead into one of the perforations (holes) and, being charged, ionises the gas within the chamber allowing the event to be detected and accurately localized. Groups at the Lawrence Berkeley Laboratory, Queens University in Kingston, Ontario, University of Pisa in Italy, Massachusetts Institute of Technology (MIT) in Boston and the Royal Marsden Hospital in London, England also explored the use of MWPC-based designs for PET, each with a different approach to increasing sensitivity; the drilled lead converter was unique to the HIDAC detector. Figure 1A shows the first HIDAC camera built for
medical imaging around 1980 and Figure 1B is the first $^{18}$F-fluoride bone scan of a mouse imaged with the HIDAC; only 5 µCi of $^{18}$F were injected into the mouse.

Even with the lead converters, a HIDAC detector at that time was, at best, only 10% sensitive to 511 keV photons compared to an efficiency in excess of 80% for BGO. The advantage of the HIDAC approach is the potential to achieve high spatial resolution in a wire chamber with closely-spaced wires. An intrinsic resolution of 1.5 mm was measured with a radioactive line source in air. A PET camera comprising a pair of 20 cm × 20 cm HIDAC modules mounted on a rotating support was assembled and the performance evaluated with some limited clinical imaging \(^{25}\) at Geneva University Hospital, Geneva, Switzerland. Owing to the low intrinsic sensitivity of the HIDAC modules, it was essential to operate the camera in 3-D acquisition mode to make maximum use of the available photon flux. The development of fully 3-D image reconstruction algorithms was, therefore, an important aspect of this work. Since the BGO scanners in the early 1980s consisted of only one or two rings of small crystals with an axial coverage of 1 cm, acquisition and reconstruction were intrinsically 2-D. The 3-D acquisition demands of the HIDAC camera therefore provided an early impetus to the development of fully 3-D reconstruction algorithms. A first step was to derive an appropriate filter to be used in 3-D filtered backprojection to reconstruct data acquired at a number of discrete positions of the HIDAC camera\(^{26}\). Independently, Colsher, working on 3-D filtered backprojection for a dual head rotating gamma camera for PET, derived the general reconstruction filter for continuously rotating area detectors\(^{26}\). The result was also applicable to a continuously rotating HIDAC camera (where continuous in this context means a large number of small steps), with the condition that the system point response function is spatially invariant and appears the same for all points within the imaging field-of-view (FOV). To satisfy this condition for the HIDAC camera, the acceptance angle for annihilation events was limited to a value less than the maximum, thus defining a smaller imaging volume within which the point response function is spatially invariant\(^{27}\). The algorithm was implemented as 3-D backprojection followed by a 3-D filtering step, unlike the mathematically-equivalent but more conventional implementation where the 2-D projections are first filtered and then backprojected in 3-D\(^{28}\).

In the early 1980s, a key advantage of the rotating HIDAC camera was that the reconstructed spatial resolution at the center of the FOV was isotropic and around 3.5 mm, considerably better than the 8 mm to 10 mm for scintillator-based scanners at that time; the corresponding volume resolution was 27 ml for the HIDAC compared with around 1000 ml for the scintillator-based scanner. However, one lesson learned from this device is that very high spatial resolution does not compensate for low efficiency, except when imaging small animals or small organs such as the thyroid. A coincidence time window ($\Delta t$) of 30 ns and the lack of effective energy resolution results in high background levels due to randoms and scatter that, combined with a low 511 keV sensitivity, is a challenging environment in which to
image patients. Some limited clinical imaging was nevertheless attempted successfully, including $^{18}$F-fluoride for bone, $^{123}$I for thyroid, $^{58}$Ga-colloid for liver, and $^{55}$Co-bleomycin for brain tumors. While the original HIDAC camera design never achieved prominence as a clinical scanner, improvements in the technology have established the quad-HIDAC camera as a serious contender for animal imaging (Figure 1C). The most recent version achieves sub-millimetre resolution at sensitivities adequate for imaging small animals; the image of a 27 g mouse scanned on a quad-HIDAC after injection of 320 $\mu$Ci of $^{18}$F-fluoride is shown in Figure 1D. The quantitative imaging potential of the quad-HIDAC has also recently been demonstrated$^{29}$. The HIDAC-related efforts in 3-D reconstruction and the concept of a dual detector rotating scanner were seminal to subsequent work on 3-D reconstruction for multi-ring scanners, the low-cost partial ring rotating scanner and, ultimately, the combined PET/CT. The HIDAC approach highlighted the necessity, in high quality clinical imaging, of achieving both good resolution and high sensitivity while minimizing the acquisition of randoms and scatter. Nevertheless, despite the low sensitivity and high background levels, the HIDAC camera demonstrated the feasibility of fully 3-D imaging with an area detector rotating scanner, including both acquisition and reconstruction.

**Multi-ring PET Scanners and 3-D Imaging**

With the exception of the dual-head rotating gamma camera$^{16,30}$ and the HIDAC camera$^{11}$, most PET scanner designs in the 1980s were single or dual rings of crystals covering an axial extent of 1 cm to 2 cm$^{31}$. Such a small axial coverage was especially a limitation for PET studies in neuroscience research where ideally the whole brain should be imaged at the same time rather than with multiple bed positions at different times. The architectural and financial difficulties of increased axial coverage were largely solved by a breakthrough invention of Drs. Ron Nutt and Mike Casey at CTI in Knoxville, Tennessee – the block detector in which a 5 cm $\times$ 5 cm block of scintillator (BGO) is bonded to four 1” photomultiplier tubes (PMTs)$^{32}$. The first blocks were cut into 8 $\times$ 4 smaller crystals and the four PMTs localized the incident photon to one of the 32 crystals based on the light sharing between the PMTs. The coupling of 32 crystals to four PMTs significantly reduced cost (by reducing the number of PMTs relative to a 1-1 coupling) and a single ring of blocks covered 5 cm axially, subdivided into four rings of crystals. The first multi-ring scanners based on the block design appeared in the mid-1980s, and by 1987 scanners incorporating two rings of blocks covering 10 cm axially with eight rings of crystals were starting to appear at a small number of research institutions$^{34}$. With that coverage, much of the brain could be imaged in a single scan.

PET was originally conceived in the 1950s as a 3-D imaging modality with the physical collimation of conventional single-photon emitters replaced by the electronic collimation of coincidence imaging. However, concerns over the high level of scattered photons and the perceived absence of an effective fully 3-D reconstruction algorithm resulted in the first multi-ring PET scanners being equipped with lead annuli, or septa, between each ring of crystals (Figure 2A). Septa shield the detectors from out-of-plane scatter, effectively subdividing the 3-D imaging volume into a set of independent 2-D slices analogous to multiple CT sections (Figure 2B). Each slice was reconstructed with a 2-D algorithm such as filtered backprojection that had been exhaustively validated for CT and single photon emission computed tomography (SPECT). The first multi-ring scanners therefore imaged a 3-D positron-emitting distribution as a set of contiguous 2-D sections, a procedure that continues to this day some two decades later even though it makes poor use of the available photon flux.

Following the installation of one of the early eight-ring PET scanners, the ECAT 931/08-12$^{35}$ at Hammersmith Hospital, London in 1987, Dr. Terry Jones was among the first to propose removing the septa and operating the scanner fully in 3-D. With foresight, the eight-ring ECAT had actually been designed to acquire all possible coincidence lines-of-response (LORs) and collect a full 3-D data set of 8 $\times$ 8 sinograms. After physically removing the septa, the first 3-D data sets were acquired for a multi-ring BGO PET scanner in early 1988 and reconstructed using a backproject and filter algorithm$^{34}$. This algorithm satisfies the condition that the point response function must be spatially invariant by subdividing the reconstruction volume into smaller sub-volumes within each of which invariance is preserved. The filter used in this algorithm is that derived by Golshe$^{26}$, the same as used with the rotating area detectors. However, the algorithm is different to that for the HIDAC camera where spatial invariance was achieved by restricting the acceptance angle to a value less than the maximum possible, ensuring a central volume of uniform response. This procedure could not be applied to the multi-ring scanner without restricting the acceptance angle to a small value equivalent to the acceptance angle in 2-D (Figure 2B), eliminating all the benefits of 3-D acquisition.

In general, a more efficient implementation of filtered backprojection, particularly in 3-D, is to filter the 2-D projection data and then backproject in 3-D. The requirement that the point response function is spatially invariant is equivalent to a requirement that all projections are fully measured. For a scanner of limited axial extent, this is obviously not the case since projections
at oblique angles are incompletely measured. A solution to the problem of incompletely-measured projections, the reprojection algorithm was proposed by Kinahan and Rogers in 1989 while investigating image reconstruction for a volume PET scanner design. Instead of restricting the acceptance angle, all angles are allowed and the partially measured parallel projections are completed by re-projecting the missing projection data through an initial estimate of the volume image. The initial estimate is obtained by reconstructing the complete set of 2-D sections and stacking them to form the volume through which the missing LORs can be re-projected. Volume images reconstructed with the reprojection algorithm typically incorporated more than 90% of the full 3-D data set.

The results from these preliminary studies with the septa removed were encouraging, particularly for the brain, where a factor of 8 increase in count rate was observed. Although the random and scattered coincidence rates also increased, there was still a net gain of at least a factor of 2 in signal-to-noise for the 3-D acquisition, particularly at low activity concentrations. In addition, for the brain, the peak signal-to-noise in 3-D was achieved at an activity concentration of about 10% that required to achieve a similar signal-to-noise with 2-D acquisition. The lessons learned from this work clearly highlighted some of the advantages of 3-D PET imaging with a multi-ring scanner, at least for brain-sized distributions. However, physical removal of the septa from this first multi-ring scanner was impractical on a routine basis and a more efficient procedure to offer both 2-D and 3-D acquisition capability was required.

**Scanners with Retractable Septa**

The results from these preliminary 3-D studies were promising and in 1989 CTI PET Systems in Knoxville, Tennessee embarked on the design and construction of the first multi-ring PET scanner with retractable septa, the ECAT 953B. With a patient port of 35 cm, the scanner was designed specifically for imaging the brain. Push-button control was provided to extend or retract the septa within two minutes. The ECAT 953B was also the first 16-ring PET scanner comprising two rings of 5 cm × 5 cm BGO blocks cut into 8 × 8 small crystals. The first scanner of this design was installed in Hammersmith Hospital London in early 1990. With septa retracted (Figure 2C), many more LORs are active and a total of 256 (16 × 16) sinograms are acquired.

The capability of this system to acquire data in either 2-D or 3-D offered an excellent environment in which to assess the advantages and challenges of 3-D PET. Exhaustive phantom studies were conducted to compare the 2-D and 3-D performance of the ECAT 953B. Studies with a 20 cm diameter uniform cylinder showed that the system count rate increased by a factor of 7.8 when the septa were retracted, reducing to a factor of 4.7 after scatter subtraction. Other results confirmed those found previously during the preliminary studies, such as a factor of 2 to 3 improvement in NECR at low activity concentrations despite a factor 3 increase in scatter fraction. Similar NECR improvement factors of 3 to 5 were found for flow and ligand studies in the brain.

Procedures for 3-D normalization, attenuation and scatter correction were developed and image reconstruction was based on an implementation of the reprojection algorithm with the Colsher filter. At that time...
a drawback to the adoption of 3-D methodology was that the reconstruction of a $128 \times 128 \times 31$ voxel matrix took several hours on a standard workstation. Accurate scatter correction was also a concern for quantitative studies especially for receptor measurements. Despite these and other concerns, by the early 1990s, 3-D PET methodology for the brain had been developed to a point where it was being applied in practice for activation studies. Accurate quantitation was not essential and 12 mCi of $^{15}$O-water could be injected in 3-D rather than the 50 mCi required in 2-D. Some brain receptor studies were also performed in 3-D since the high sensitivity was of benefit for measurements of low receptor populations, but here accurate quantitation is required. Other PET scanner designs with retractable septa followed the ECAT 953B and retractable septa quickly became standard on all scanners that were not already intrinsically 3-D. Whole-body designs with retractable septa appeared in the early 1990s for cardiac and tumor imaging although valid concerns about high levels of random and scattered events limited the use of 3-D outside the brain. The lessons learned from this work firmly established 3-D PET methodology for brain studies capitalizing on the increased sensitivity essential for ligand studies and enabling the injected activity level for activation studies to be significantly reduced.

The latest septa-retractable LSO-based PET scanner designs show a similar trend in 3-D (Figure 2D) as the earlier designs. The measurements of NECR in Figure 2D are for the NEMA NU-2001 phantom in the ECAT ACCEL with septa extended (2-D) and septa retracted (3-D); the advantages of 3-D methodology at low activity concentrations can clearly be seen. The success of 3-D methodology such as demonstrated in Figure 2D suggested a possible design for a low-cost or entry-level PET scanner. The design, completed in 1990 and commercially available even today, is based on dual rotating arrays of block detectors, and the first prototype was the partial ring rotating tomograph (PRT-1)

The PRT

PET tomographs based on the rotation of a pair of opposing 2-D area detectors were thoroughly explored during the late 1970s and early 1980s. As described, most of these approaches had low sensitivity or poor count rate performance and generated little clinical interest. With few exceptions, by 1988, rotating designs had been abandoned for PET imaging in favor of the stationary multi-ring BGO scanners. In the late 1980s, the capital outlay for the imaging equipment was perceived as a major impediment to the wider acceptance of PET and efforts to limit the financial investment required to establish a PET center were considered important. For a typical BGO scanner, more than half the cost lies in the detectors – scintillator and PMTs – and eliminating a significant number of detectors can have a major impact on cost. Thus, increasing sensitivity by acquiring data in 3-D presented an opportunity to design and build a lower cost scanner by removing over half the detector blocks from a multi-ring scanner and rotating the remaining partial rings of detectors to acquire the full set of 3-D projection data (Figure 3A). This design, with two banks of block detectors, achieves a clinically-acceptable sensitivity by acquiring data fully in 3-D. In fact, for a fixed number of detectors, it can be shown that a higher sensitivity (a greater number of active LORs) is achieved by arranging the detectors as two rotating arrays rather than a continuous stationary ring due to the greater axial coverage of the arrays.

The first design of this type (Figure 3B, top), the PRT-1 consisted of two arrays of 48 (transaxial) $\times$ 2 (axial) blocks, each block cut into 8 $\times$ 8 crystals. The blocks in this prototype were identical to those of the 953B and the PRT-1 contained one third of the number of detectors in the full-ring scanner. The absolute sensitivity of the prototype was 0.51 %c, slightly less than the 0.63% of the ECAT 953B with septa extended. The data were acquired in step-and-shoot mode at six positions of the detectors for a 20 cm transverse FOV and a 10.8 cm axial FOV. The minimum scan time including rotation was 60 seconds and the prototype included both static and dynamic imaging capability. The transmission source for attenuation correction in 3-D was a 6 mm thick solid germanium plane source containing 0.9 mCi of $^{68}$Ge; the source was 10.8 cm wide to cover the axial FOV and it could be attached to the front of one detector array. Scatter correction was based on an iterative deconvolution approach. Excellent results were obtained for imaging brain (Figure 3B, bottom) and heart with 2-deoxy-2-$^{18}$F]fluoro-D-glucose (FDG), including a 13-frame dynamic acquisition for the brain. The device was also capable of imaging $^{82}$Rb in the heart for myocardial flow studies, an impressive achievement with a rotating scanner considering the 75 seconds half-life of the tracer.

A second prototype, PRT-2, was built in 1993 incorporating dual arrays of ECAT EXACT block detectors covering 16.2 cm axially (Figure 4A). Each array comprised 10 (transaxial) $\times$ 3 (axial) blocks representing 40% of the detectors in the equivalent full-ring scanner, the ECAT EXACT. Data acquisition was again in step-and-shoot mode with the number of angular steps depending on the transaxial imaging FOV required, typically 18 positions for a 47 cm FOV. Similar to the PRT-1, the transmission source was a rectangular planar source covering the 16.2 cm axial FOV; for this prototype, the source was shaped to follow the curvature of the detectors. The sensitivity of PRT-2 was approximately double that of PRT-1 due to the additional axial coverage and was actually 25% higher than that of the EXACT.
with septa extended; with septa retracted, the 3-D sensitivity of the EXACT was a factor 3.5 higher than that of the PRT-2. The scanner was evaluated clinically, showing promise for imaging FDG in brain and heart (Figure 4C, right), $^{13}$N-ammonia for myocardial flow (Figure 4C, left), and even $^{15}$O-water for blood flow activation studies (Figure 4B). Whole-body FDG-PET studies of oncology patients were also acquired in step-and-shoot mode.$^{14}$

The success of the two prototypes stimulated the development of a commercial version of the partial ring tomograph, announced in 1995 (Figure 5A). The design of the advanced rotating tomograph (ART) (CPS Innovations, Knoxville, TN), was based on dual arrays of 11 (transaxial) × 3 (axial) ECAT EXACT blocks corresponding to 46% of the detectors in the ECAT EXACT. The sensitivity was therefore similar to that of the PRT-2. The design eliminated cables by incorporating slip-ring technology, both mechanical for power and serial communications and optical for high-speed data transfer, and rotated constantly at 30 rpm. The early ART

**Figure 3.** (A) a more cost effective design of PET scanner was developed by removing detectors from a full-ring scanner (top) and then rotating the dual partial ring arrays (bottom) to acquire a full 3-D data set, (B) the first partial ring rotating PET scanner PRT-1 built at the University of Geneva Hospital in collaboration with CTI PET Systems (top) and (bottom) the first FDG brain scan acquired with the prototype in May, 1991.

**Figure 4.** (A) a second prototype partial ring tomograph PRT-2 still requiring the use of cables, (B) cerebral blood flow imaged with $^{15}$O-water in the PRT-2; the images are summed over 12 injections each of 12 mCi of $^{15}$O-water and the scan time is 90 s, and (C) a cardiac viability study with (left) 8 mCi of $^{13}$N-ammonia to image myocardial blood flow, and (right) 10 mCi of FDG to image myocardial metabolism. Data courtesy of the University of Pittsburgh.
designs incorporated dual $^{68}\text{Ge}$ rod transmission sources mounted at one end of each detector array, later replaced by collimated $^{137}\text{Cs}$ point sources that scanned axially during rotation; transmission acquisition was in singles mode. A number of these low-cost scanners, the first dedicated PET scanner to be sold for under $1$ million, appeared at clinical installations from the mid to late 1990s and were used effectively for FDG imaging of brain, heart and whole-body. The ART was also used for brain activation studies with $^{17}\text{O}$-water, blood flow measurements in peripheral muscle, and $^{82}\text{Rb}$ for gated cardiac studies. Figure 5B shows the experimental set-up for brain activation studies with laser pain stimulation, and summed flow images in a normal volunteer subjected to pain stimulation are shown in Figure 5C. The ART played a particularly important role in clinical whole-body imaging at several institutions.

The second and more significant impact of the PRT-1 design was the realization that, with dual arrays of detectors, there was potentially enough void between the arrays (Figure 6A, arrowed) to mount an X-ray tube and detectors and acquire anatomical images in addition to the functional images from PET, the two data sets being accurately co-registered. Such a concept (Figure 6B), first envisaged in 1991, would address many of the difficulties of software registration for the whole body where patient positioning differences and internal organ motion are particularly challenging issues. Although the combined PET/CT concept was proposed in 1991, it was another seven years before the first prototype appeared in the clinic, as described in detail below.

**Whole-body PET Imaging for Oncology**

The success of 3-D PET methodology in the brain was not matched by a comparable situation for the rest of the body. Poor whole-body image quality was due to several reasons: randoms and scatter arising from activity outside the imaging FOV could not be effectively shielded as they can for the brain; the uptake in the brain is generally greater than for any other organ and hence in the rest of the body the true coincidence rate decreases while the scatter and randoms increase; patient movement is more difficult to control than for the brain; patient body habitus varies considerably and, for the larger patients, the transmission and emission scans are highly noisy; and the reprojection algorithm, a 3-D version of filtered backprojection does not perform optimally in a high noise situation, introducing streak and other artifacts that interfere with image interpretation (Figure 7A). The situation for whole-body imaging in 3-D was therefore not favorable despite extensive effort to produce an accurate scatter correction.

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![Figure 5](image-url)

**Figure 5.** (A) a commercial ECAT ART scanner with the front cover removed; the data and power cables required in the two prototypes are replaced by mechanical and optical slip rings, (B) the ART scanner being used for brain activations studies; the device to the left of the scanner is a laser for stimulating a response to differing levels of pain, and (C) summed blood flow images acquired with $^{17}\text{O}$-water injections during pain stimulation. (Activation studies performed in collaboration with Drs. Anthony Jones and Stuart Derbyshire, Manchester University, UK.)
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model\textsuperscript{43,44}. At that time, most institutions with retractable septa scanners elected to perform whole-body scanning in 2-D since the septa shielded the detectors from the high level of randoms and scatter and a fast 2-D reconstruction algorithm could be used.

Nevertheless, from 1995 onwards an increasing number of 3-D only, dedicated PET scanners, including the ART scanner, appeared in clinical practice even though it was not until 1998 that Medicare approved reimbursement in the US for PET in lung and a few other cancers. In addition to the ECAT ART, designs such as the QUEST (UGM Medical, Philadelphia, PA) based on the PENN-PET\textsuperscript{18}, and later the C-PET\textsuperscript{19} were 3-D only and used the superior energy resolution of sodium iodide to limit the 3-D scatter fraction. Nevertheless, for all but the lighter patients, whole-body image quality in 3-D was poor, further degraded by attenuation correction due to the magnitude of the correction factors. Many physicians insisted on reviewing the less-noisy non-corrected images. Even so, for a typical patient, the NECR averaged over all body positions is about a factor of 2 higher in 3-D than 2-D\textsuperscript{45}. Owing to the success (and low capital outlay) of the sodium iodide-based designs, and with a small contribution from the installed base of ART scanners, by the late 1990s a significant fraction of tomographs in clinical operation for oncology were 3-D only. However, for the larger patients, the image quality was far from optimal and whole-body BGO scanners with septa extended were generally superior. The lesson to be learned is that BGO is not the best scintillator for whole-body imaging in 3-D and filtered back-projection is not the optimal algorithm to reconstruct the images.

The situation began to change with the introduction of new fast scintillators for PET. For the first time in over two decades, an alternative to BGO appeared in the form of lutetium oxyorthosilicate (LSO), a scintillator with five times the light output and seven times faster than BGO. Discovered around 1996\textsuperscript{46}, LSO first appeared in commercial PET scanners some ten years

Figure 6. (A) the proposal for a combined PET/CT scanner arose from the observation of the empty space (arrowed) between the detector arrays in the PET-1, and (B) the initial design envisaged for the combined PET/CT with the X-ray tube and detectors mounted in the gaps between the PET detectors. The final design actually had the PET detectors mounted on the rear of the CT support.

Figure 7. A coronal section from an FDG-PET whole-body scan acquired in 3-D mode with septa retracted and reconstructed using (A) 3-D filtered back-projection algorithm with reprojection, (B) Fourier rebinning (FORE) and attenuation-weighted OSEM (AWOSEM). The noise streaks that are a characteristic feature of filtered backprojection are eliminated by the statistical approach (reconstructions courtesy of Dr David Brasse).
later. LSO offers better positioning accuracy, shorter coincidence time window, better energy resolution, and reduced detector dead time due to the superior physical characteristics. The scintillator was introduced by CTI, Inc (Knoxville, Tennessee) and was incorporated into the ECAT ACCEL, the first LSO-based clinical scanner. Compared to the ECAT EXACT, the BGO-equivalent of the ACCEL, the impact of LSO on performance includes higher spatial resolution, reduced scatter and randoms rates and better count rate performance. The NECR curves for the ACCEL in 2-D and 3-D are shown in Figure 2D. At about the same time, Philips Medical introduced the ALLEGRO, a gadolinium oxyorthosilicate (GSO) based scanner. First described in 1983, GSO is less sensitive than LSO, has about 50% longer decay time, and only 36% of the light output; however, it outperforms BGO in all aspects except stopping power.

In addition to these improvements in detector technology and hardware, significant software advances have taken place over the past decade. The considerable effort invested in scatter correction has converged to an accurate image-based scatter correction model, and with improvements in computing power and algorithm development, a statistically-based reconstruction algorithm has emerged as a successor to filtered backprojection. In order to reduce the computational burden, the 3-D acquired data set is rebinned into an equivalent 2-D set and then reconstructed using the attenuation-weighted ordered-subset EM (AWOSEM) algorithm. Currently, Fourier rebinning (FORE) is performed to reduce the 3-D sinogram set to 2-D for reconstruction by AWOSEM in which a coincidence LOR is assigned a weight related to the attenuation factor of the line – LORs with large factors are assigned the smallest weight. The combination of FORE with AWOSEM has been implemented efficiently and a reconstructed image can be produced within a couple of minutes. The same data set as that used for Figure 7A has been reconstructed with FORE + AWOSEM; the significantly improved image quality is shown in Figure 7B. A fast implementation of 3-D AWOSEM is under evaluation and initial results show improved clinical image quality compared to the 2-D rebinning approach.

The most obvious lesson to be learned from this decade of focussed effort is that it is a challenge to obtain high quality 3-D whole-body images. The combination of BGO, filtered backprojection reconstruction and a simple scatter correction model failed to produce whole-body images of sufficiently high quality that were diagnostically useful and acceptable to physicians, especially in large patients. Fortunately, these lessons have been well-learned and the situation is now very different with 3-D whole-body imaging becoming an established methodology in many institutions.

### The Combined PET/CT Scanner

The significance of anatomical landmarks in functional images has long been recognized, at least since the days of hand-drawn neck outlines on the early nuclear medicine thyroid scans. With the advent of digital imaging, a more rigorous approach to combining anatomy and function became possible by using software to align the two image sets. Nevertheless, most image alignment is still performed visually by physicians with CT and PET images presented together on adjacent displays. Despite receiving little attention clinically, over the past decade or so software registration algorithms for aligning image sets acquired by two different modalities have evolved from simple matching procedures to complex non-linear warping techniques. Motivated by the belief that the combination of anatomical and functional images is beneficial and complementary to both modalities, sophisticated software tools have been developed to perform registration. Outside the brain, however, despite the sophistication, software registration has had only limited success and is still not widely used clinically. Difficulties include allowing for inconsistent patient positioning between the different scanners, and uncontrolled internal organ movement. While reasonably accurate localized alignment is possible for specific regions such as the thorax, co-registration of the whole body remains problematic and validation of the techniques remains a challenge. Nevertheless, limited studies that have been made using software-based registration have highlighted, despite practical difficulties, the intrinsic advantages of combining anatomical and metabolic information.

The general concept of fusing anatomy and function in the same device is not new. Historically, one of the first dual modality systems reported in the literature was a combination of CT and SPECT with work in the late 1980s by Hasegawa et al resulting in a device that used the same detector material, high purity germanium, for both modalities. However, to avoid compromising either modality by the choice of a common detector material, Lang, Hasegawa and coworkers later developed a device based on two separate scanners – a CT and a SPECT scanner. In patenting the concept Hasegawa noted that it could equally well apply to CT and PET, although to progress from concept to realization of a functioning PET/CT scanner required funding, adequate engineering facilities, and a motivated team of people. While the PET/CT concept emerged independently in 1991 from a proposal by Townsend and Nutt after observing the void within the PRT-1, the completed prototype did not appear in the clinic until 1998. Funded in part by a grant from the National Cancer Institute in 1995, the final prototype design was a considerable departure from the initial concept.
The prototype design (Figure 8) incorporated a Siemens Somatom AR.SP spiral CT scanner with an ART scanner. The high packing density of components on the CT rotating assembly precluded the mounting of the ART detectors as originally envisaged (Figure 6B). Instead, a second annular support was attached to the rear of the CT assembly, set back from the slip rings, and the PET detectors mounted on the additional support. The complete assembly rotated at 30 rpm and to avoid any cross interaction the imaging components were operated consecutively and not concurrently. The data acquisition systems and image reconstruction computers were not integrated and the CT and PET images were acquired and processed separately (Figure 8). The CT images were imported into the PET environment and used to generate the PET attenuation correction factors to be applied to the PET emission data. The CT, PET and fused images were displayed on the PET console for review and interpretation. The device was installed at the University of Pittsburgh PET Facility in April 1998 for clinical evaluation. During the subsequent three-year evaluation program, more than 300 cancer patients were scanned on the prototype. Some important lessons were learned from the six-year PET/CT development program, covering scientific, engineering and clinical aspects. The scientific and engineering experience influenced the design of the first commercial PET/CT scanners, while the initial clinical experience clarified some of the strengths and challenges of the approach, identified the application areas where PET/CT could bring the greatest benefits, and defined protocols appropriate for these applications.

Following the promising clinical results, the major vendors moved rapidly to bring a commercial design to the marketplace. A common feature of the designs that eventually emerged is the low level of hardware integration – all essentially comprise a CT scanner and a PET scanner in tandem. The integration of the two modalities is more focused on the computer systems in order to present a unified operation for acquisition and image reconstruction with the underlying computational complexity transparent to the user. Interestingly, of the four major distributors, three opted for 3-D-only PET scanners and eliminated the septa and two of them opted not to provide standard PET transmission sources and base the attenuation correction on the CT images. It is less than three years since the first commercial PET/CT scanner was installed and the technology is still evolving, and will doubtless continue to evolve in the future. CT in particular is experiencing a period of rapid change as multi-slice CT scanners, in only three years, have progressed from 2 to 16 slices, with 32 and 64 slices recently announced. There is now a realistic prospect of 2-D area detectors and cone-beam CT. The appropriate configurations for PET/CT have still to be established and may well depend upon the application area targeted: oncology, cardiology or neurology. High performance CT may not be required for imaging cancer, and PET/
Figure 9. (A) the latest high-performance 16-slice LSO PET/CT scanner at the University of Tennessee Medical Center in Knoxville, Tennessee. The unique design of the patient couch eliminates any vertical deflection due to patient weight as the bed moves into the scanner, and (B) a typical PET/CT scan acquired with this system; the patient is a 155 lb, 50 year-old male undergoing treatment for colon cancer with bladder metastases. The PET scan (left) was acquired 148 minutes post-injection of 10 mCi of FDG for four minutes per bed position, and the scan demonstrated a focal area of elevated uptake in the right lower quadrant; the PET/CT scan (right) accurately localizes the uptake anatomically within the abdomen.

CT protocols are still under development, addressing issues such as respiration and the use of CT oral contrast media.68

One of the latest PET/CT designs (Figure 9A) comprises a Sensation 16 CT scanner (Siemens Medical Solutions, Forchheim, Germany) with a high resolution, LSO-based PET scanner (CPS Innovations, Knoxville, TN). This combination is now distributed by Siemens as the biograph 16. The spiral CT with 5 mm slice spacing takes less than 25 s to scan from base of brain to upper thigh, and the combination of fast scintillator and high count rate electronics ensures a PET imaging time that can be as short as six to seven minutes for small patients. This is a significant improvement over the 60-minute imaging times that were the norm just a few years ago. Other commercially-available designs include an open system where the CT and GSO-based PET scanner can be moved apart (Gemini, Philips Medical), and a BGO-based PET scanner with 6 mm detectors and a 4, 8 or 16-slice CT (Discovery ST, GE Medical Systems).

An illustration of the extent of progress in PET instrumentation is demonstrated by the quality of the scans in Figure 9B: the images show a coronal section of a patient scanned recently on the 16-slice LSO PET/CT at the University of Tennessee, Knoxville. The PET scan identified a focal area of increased uptake in the right lower quadrant. To date, many thousands of cancer patients have been imaged in PET/CT scanners installed at more than 400 institutions worldwide. The impact of this evolution in imaging technology has been profound within radiology and nuclear medicine especially, and sales this year are predicted to exceed $1 billion. Many lessons have already been learnt from combined PET/CT imaging, the most important ones being the added confidence in reading PET scans with the co-registered CT anatomy routinely available, the ability to accurately localize focal tracer uptake, and the potential to distinguish between normal accumulation of tracer and pathology. Many more lessons are to be learned as the technology matures and becomes more widely available.

Discussion

In the past two decades, it is evident that there have been dramatic advances in imaging instrumentation for PET. Numerous scientists and engineers have contributed to these advances at universities and corporate institutions worldwide. Much of the pioneering work has been funded through research grants and with financial support from national agencies and private foundations. The unrelenting quest for higher sensitivity, better spatial resolution, improved signal-to-noise and lower cost has resulted in PET scanners that achieve 2 mm spatial resolution throughout the brain, can acquire data at system count rates up to $4 \times 10^7$ singles per second, and attain a peak NECR of up to 100 kcps. To meet these levels of performance, the number of active LORs has increased from a few thousands in 1980 to more than $10^9$ today. Fortunately, the progress in computational and data storage capacity has kept pace with demand and the resources available today largely satisfy clinical needs.

Until reimbursement was approved for a limited number of oncology studies in 1998, PET was primarily a research tool for neuroscience. Consequently, in the decades preceding reimbursement the main driving
force for instrumentation development was brain imaging, specifically for studies of psychiatric and neurodegenerative disorders. These studies demanded high spatial resolution to resolve small brain structures, high sensitivity to measure low receptor populations, dynamic scanning capability to follow rapid tracer kinetics, and accurate quantitation of both specific and nonspecific ligand binding. As the emphasis shifted to oncology in the latter part of the 1990s, the demands on the instrumentation also changed. For clinical oncology imaging, of greater importance are short scan times, high throughput capability, ease of operation, high reliability, fast image reconstruction and application-specific image display and analysis. Obviously, there are some demands that apply equally to clinical and research applications such as high sensitivity and low scatter and randoms rates. Research activities generally require access to the raw data, to scanner operating procedures, detector setup, data acquisition settings, reconstruction parameters and image analysis tools. Clinical operation has a preference for standard protocols with fixed parameter settings to reduce the opportunity for operator error, fast reconstruction times for rapid physician feedback, and efficient display tools for reading and interpreting images. The lessons learned in one domain obviously impact progress in the other domain.

From the early beginnings with HIDAC and other fully 3-D PET scanners, the man-years of effort that has been devoted to 3-D methodology, first in the brain and now for the whole-body, is a major investment. Since PET is intrinsically 3-D, in these days of heightened sensitivity to radiation exposure, it is an obligation to make maximum use of the available photon flux from the patient while ensuring diagnostic image quality. To limit the potentially high skin exposure from CT, considerable effort has been devoted to making efficient use of the X-ray dose. Although radiation exposure from a positron-emitting tracer like FDG is much lower than the CT skin dose, there is nevertheless an increasing trend to reduce the injected dose to levels that will almost obligate the use of 3-D acquisition. Fortunately, the achievements for the past 15 years have finally established the role of 3-D methodology for both brain and whole-body.

The addition of anatomical imaging capability to PET scanners has had a profound effect, particularly on the clinical operation by essentially eliminating the time for the transmission scan, improving image quality and increasing patient throughput. Initially, from the performance of the original prototype where five minutes was required for CT and 45 minutes for PET, the PET/CT approach was often criticized for making inefficient use of the CT scanner. As a consequence of the dramatic advances in both CT and PET technology, the high performance PET/CT scanners of today require 30 seconds for CT and 10 minutes or so for PET. From the viewpoint of the patient, the actual scan time is now a small fraction of the time required for the complete study, including patient preparation, FDG uptake, and positioning in the scanner. Much has been learned and much has been achieved towards improving imaging technology for PET.

From its inception, one of the great strengths of positron tomography was the richness of the compounds that could be labelled with short-lived positron-emitting biomolecules such as $^{15}$O, $^{13}$N and $^{11}$C. The first images of the human brain with FDG, were acquired in 1976 at a time when the HIDAC camera was imaging the first mouse with $^{18}$F-fluoride. Now, 28 years later, FDG is still the only radiopharmaceutical widely used and reimbursed for clinical imaging, with $^{82}$Rb on a much smaller scale for myocardial flow imaging. Whole-body imaging with FDG can hardly be said to challenge the performance of current instrumentation. There are, of course, a much wider range of PET radiopharmaceuticals available in the research domain, primarily for brain studies. It is important for the future of PET that the current situation evolves so that other tracers such as $^{3}$H$[^{18}$F$]fluoro-3^3$-deoxythymidine (FLT), $^{11}$C-acetate, $^{18}$F-choline and maybe a hypoxia imaging agent such as $^{18}$F-misonidazole or $^{68}$Cu-ATSM become available clinically. There are many aspects of tumor physiology more representative of cancer than elevated glucose metabolism that could provide an earlier indication of a primary or recurrent malignancy at a time when effective treatment is still possible. PET is clinically under-utilized and even with FDG has not yet achieved the promise of the 1980s despite these major advances in imaging instrumentation. Progress in tracer development and regulatory approval of PET radiopharmaceuticals is now essential to match the advances described here that have occurred in PET instrumentation over the past two decades.

It is a great honor, although with considerable sadness, to accept this award in memory of my dear friend and colleague Dr. Peter Valk who passed away December 16, 2003. Peter himself made numerous contributions to the advances described here, particularly to the evaluation of PET scanner designs, to 3-D PET methodology, and to clinical applications of PET in which he was instrumental in obtaining the first Medicare reimbursement for PET oncology studies in 1998. He was a great supporter of PET/CT and he will be sadly missed. It is also a privilege to recognize the many individuals, both friends and colleagues, who have contributed to this work over more than two decades. The author is particularly indebted to Dr. Alan Jeavons inventor of the HIDAC camera.

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