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Latest achievements in PET techniques

Alberto Del Guerra[a,*], Nicola Belcari[a], Alfonso Motta[a], Giovanni Di Domenico[b], Nicola Sabba[b], Guido Zavattini[b]

[a] *Dipartimento di Fisica, Università di Pisa and INFN, Sezione di Pisa, Via F. Buonarotti 2, Pisa I-56127, Italy*
[b] *Dipartimento di Fisica, Università di Ferrara e INFN Sezione di Ferrara, Ferrara I-44100, Italy*

Abstract

Positron emission tomography (PET) has moved from a distinguished research tool in physiology, cardiology and neurology to become a major tool for clinical investigation in oncology, in cardiac applications and in neurological disorders. Much of the PET accomplishments is due to the remarkable improvements in the last 10 years both in hardware and software aspects. Nowadays a similar effort is made by many research groups towards the construction of dedicated PET apparatus in new emerging fields such as molecular medicine, gene therapy, breast cancer imaging and combined modalities. This paper reports on some recent results we have obtained in small animal imaging and positron emission mammography, based on the use of advanced technology in the field of scintillators and photodetectors, such as Position-Sensitive Detectors coupled to crystal matrices, combined use of scintillating fibers and Hybrid-Photo-Diodes readout, and Hamamatsu flat panels. New ideas and future developments are discussed.

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1. Introduction

Clinical-performance positron emission tomography (PET) is a well-established technology, but the features of clinical scanners do not fulfill the requirements needed for PET investigation of small animals. In particular, the relatively poor spatial resolution and the disadvantageous geometry (which strongly limits the sensitivity) make the development of dedicated high-performance scanners absolutely necessary.

Functional imaging of small animals, such as mice and rats, using high PET and single-photon emission tomography (SPECT), is becoming a valuable tool for studying animal models of human disease [1–3]. Over the last decade, the use of mouse as a "laboratory" for genetic research shows a dramatic increase due to the ability of modifying the genotype of this animal rapidly. The mouse has long been used by molecular biologists to study fundamental cellular events in vivo but the relatively small size of the mouse (weight ~ 20 g) makes difficult the use of imaging instruments developed for human

*Corresponding author. Tel.: +39-050-2214942; fax: +39-050-2214333.
E-mail address: alberto.delguerra@df.unipi.it (A. Del Guerra).

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subjects, i.e., the sensitivity and spatial resolution of the available PET scanners are not satisfactory for the quantitative and qualitative assessment of in vivo gene expression. Moreover, a further improvement in sensitivity is needed for molecular biology studies that aim to image the expression of genes that are translated in only a few copies per cell (1 pM).

In the last few years the scientific community has shown a growing interest in breast imaging performed by PET as a secondary screening technique for breast cancer, especially when X-ray mammography is not diagnostic. The PET systems actually used in clinical scanning do not fulfill the spatial resolution and sensitivity requirements for the detection and staging of breast cancers. For this specific application an "ad hoc" technique has been developed, called Positron Emission Mammography (PEM) [4–6]. PEM tries to overcome the limitations introduced by the complexity and relatively poor performance of PET systems, still maintaining the advantage of this diagnostic method.

In this paper we present some recent results we have obtained in small animal imaging and positron emission mammography, based on the use of advanced technology in the field of scintillators and photodetectors, such as Position-Sensitive Detectors coupled to crystal matrices, combined use of scintillating fibers and Hybrid-Photo-Diodes readout, and Hamamatsu flat panels. New ideas and future developments are discussed.

2. Photo-detectors for small animal PET

Early PET detector elements were made by a single crystal read by a single PMT. This configuration allows a very simple coding but requires a large number of components, and that means a large number of independent channels to be acquired and processed. By using Anger-type methods, a system of four PMTs is used for the readout of a large number of segmented crystals, thus allowing a more efficient packing and a reduction of acquisition channels.

The advent of novel high-resolution Position-Sensitive Photo-Detectors has dramatically expanded the possibilities for the construction of more simple and flexible systems with improved performances. Nowadays detectors based on a matrix of scintillating crystals coupled to a position-sensitive photo-detector are a well-established technology and represent the state of the art. Usually, a Position-Sensitive Photomultiplier Tube (PS-PMT) is used for the identification of the crystal element in which the interaction occurs. Many different combinations of scintillator pixellization and PS-PMT are actually used depending on the specific application and on the required FoV size. A first solution is represented by a crystal matrix coupled to a single large area PS-PMT. This solution is very simple to implement, but it is limited by the dimension of the active area (up to 100 mm $\varnothing$) and by the circular shape of the photo-cathode that forbids the close packing of more PMTs in a matrix configuration. A commonly adopted one is the use of novel Multi-Anode Photo-Multiplier Tubes (MA-PMT) that offer in a small package (up to $22 \times 22\,\mathrm{mm}^2$ active area) performances similar to larger PS-PMTs. These PMTs can be easily arranged in matrices so as to cover the whole area of larger scintillator matrices with a relatively low dead area. Furthermore, the possibility to readout these tubes with a resistive chain makes the acquisition circuitry very simple. New flat panel MA-PMTs by Hamamatsu will be soon available. These devices will be characterized by a larger active area ($5 \times 5\,\mathrm{cm}^2$) and by a very high packing fraction (up to 96% active area) for building very large cameras.

As an alternative method for the readout of matrices of scintillators, solutions based on semiconductor photo-detector are also used. For example, matrices of small area Avalanche Photo-Diodes (APDs) are used for the parallel readout of the crystals (each one is coupled to a single APD) [7,8]. This method, similar to those used in early PET, allows a very simple, "perfect" coding at a very high count rate. On the other hand, these devices still suffer from some limitations; e.g. the gain depends on bias voltage and temperature (that means tricky tuning) and they are rather expensive.

Solutions based on Hybrid PhotoDiodes (HPD) have been suggested as a valid alternative. Once again, the relatively small active area and rather high dead area of the commercially available devices make their use impractical for direct coupling to large matrices. Multi-Pixel HPDs have been proposed in combination with Wavelength Shifting Fibers for the readout of matrices of scintillating crystals [9,10]. However, this method is limited in sensitivity due to the very low light yield that can be achieved at the end of the fiber [11]. Highly pixellated large area HPD are now being developed [12]; HPD can then become a realistic alternative to PS-PMT for the direct readout of matrices of crystals in the near future.

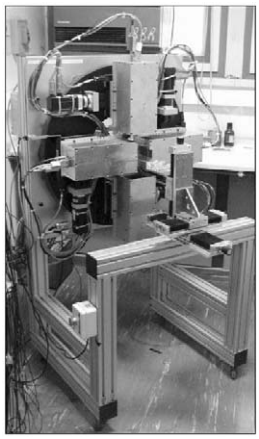

Fig. 1. The YAP-(S)PET scanner installed at the Department of Nuclear Medicine of the University of Ferrara.

3. Small animal PET scanners

Despite the high complexity of current small animal PET scanners, the remarkable possibilities offered by these techniques justify the growing interest of many research groups all over the world for the development of better and better instruments. Dedicated instruments, characterized by high performance have been produced but most of those have been built as research prototypes [13]. Two are commercially available: microPET®4, designed and developed at UCLA, Los Angeles, and distributed by Concorde Microsystems Inc. (Concorde Microsystems, Inc., 10427 Cogdill Rd, Suite 500 Knoxville, TN 37932, USA) and HIDAC PET produced by Oxford Positron Systems Ltd. (Oxford Positron Systems Ltd., 5 Landscape Close, Weston Business Park, Weston-on-the-Green, Oxon OX25 3SX, UK). Also in Italy, a high-performance tomograph, able to perform both PET and SPECT animal studies, has been built at the University of Ferrara. The technical characteristics and performance of this scanner is described in the following paragraph. A commercial version of this tomograph is now under development by I.S.E. (I.S.E. Via Nuova 128, 56010 Vecchiano (Pisa), Italy).

3.1. YAP-(S)PET

This experimental prototype (Fig. 1), built at University of Ferrara (Italy), is a dedicated small animal 3-D PET scanner (called YAP-(S)PET) with a very high spatial resolution and sensitivity as required for radiopharmaceutical studies on rats and mice [14].

The YAP-(S)PET scanner is made up of four modules: each one is composed of 20×20 $YAlO_3$:Ce (Yttrium Aluminum Perovskite activated by Cerium or YAP:Ce) finger crystals ($2 \times 2 \times 30\,mm^3$) glued together. Each element being optically isolated from an adjacent one by a 5 μm insulating layer. The matrix is directly coupled to a 3″ PS-PMT (Hamamatsu R2486-06). The modules are positioned on a rotating gantry; the opposite detectors are in time coincident and can be set at a distance ranging from 10 to 25 cm so as to give the possibility of choosing the maximum spatial resolution (larger distance) or maximum sensitivity (smaller distance) configuration. The system operates in 3-D data acquisition mode and an Expectation Maximization (EM) algorithm is used for image reconstruction [15], thus permitting the utilization of all the acquired data. The scanner has an axial field of view of 4 cm and the diameter of the transaxial FoV is 4 cm; these dimensions permit the use of YAP-PET for rat and mice studies. The spatial resolution is constant over the whole FoV and is better than 1.8 mm FWHM; the volume resolution at the center of the tomograph is 5.8 mm^3. The sensitivity at the center of the FoV

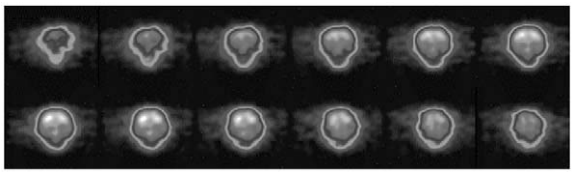

Fig. 2. Example of PET images obtained with the YAP-(S)PET scanner: ex vivo transaxials section of a rat brain injected with ^{18}F-FESP.

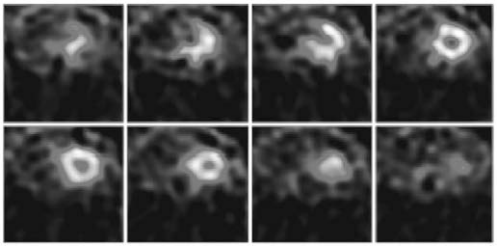

Fig. 3. Example of SPECT images obtained with the YAP-(S)PET scanner [18]: transaxial sections of a rat heart injected with 170 MBq of TcN-PNP5-DBODC.

is 17.3 cps/kBq (640 cps/μCi) with the detectors 15 cm apart [16].

YAP-(S)PET is not only suitable for PET imaging (Fig. 2), but also for SPECT studies on small animals [17]. The scanner can be switched between these modalities without any change in the detector configuration or in the acquisition system, but simply mounting a high-resolution parallel hole collimator in front of each crystal. The collimator we used has 0.6 mm diameter holes with a 0.15 mm thick lead septum. With these parameters the geometrical efficiency of the collimator is 4×10^{-5}. The YAP-(S)PET scanner running in SPECT modality has the same FoV as in PET mode. The spatial resolution, measured on phantoms, is 3.5 mm (FWHM); the sensitivity with all of the detectors (four heads) equipped with collimator is 114 cps/MBq (3 cps/μCi).

The YAP-(S)PET tomograph was used in SPECT mode to study the dynamic uptake of various technetiated radiotracers and to obtain quantitative measurements of the activity in the heart of a rat (Fig. 3). A comparison of in vivo measurements with the standard measurement of activity, as obtained by sacrificing the rat and putting the heart in a gamma counter, shows that quantitative measurements of activity in vivo can be performed with the YAP-(S)PET at better than 5% [18].

4. Positron emission mammography scanners

The latest advances in animal PET scanners can greatly favor the development of systems dedicated to Positron Emission Mammography. In fact, the requirements of PEM are partially fulfilled by PET scanners dedicated to small animal imaging which are characterized by similar spatial resolution, FoV and sensitivity. On the other hand, there are different design requirements for PEM systems, mainly due to the fact that the breast is attached to the thorax. This implies that no detector rotation around the breast is possible. Moreover, a compression is needed to reduce the scattering in the breast and this adds a time limit because of patient discomfort.

Many research groups worldwide are working on the development of dedicated PET systems for breast cancer investigation. These prototypes have different geometries and technology. Basically, two different detectors geometries have been proposed: *Parallel Plane* and *Rectangular Box*. In the Parallel Plane geometry [19], two plane detectors are placed on opposite sides with respect to the breast. This configuration offers a good solid angle coverage but the angular sampling is incomplete (nearly planar reconstruction); moreover, it permits many positioning options (Top/Bottom–Left/Right) and an easy compression of the breast (mild or strong). In fact, it is compatible with existing X-ray mammography compression systems, thus also allowing for image fusion (Multi-Modality). In the Rectangular Box geometry [20], four detectors are arranged around the breast so as to fully encircle the organ. This configuration is characterized by a higher and more uniform solid angle coverage (efficiency up to 15%) and by an almost complete angular sampling (proto-tomografic reconstruction). As a drawback it permits fewer positioning options and a mild compression of the breast, even if possible, is difficult.

4.1. YAP-PEM

We are developing a dedicated device based on YAP scintillator and PSPMTs, to detect breast lesions, with a dimension of 5.0 mm (and possibly below) in diameter and a specific activity ratio of 10:1 between cancer and breast tissue [21]. The device will be composed of two opposite detectors (parallel plane geometry) whose technology derives from the YAP-(S)PET scanner. The proposed dimensions of crystals are 3 cm thick with a detection area of $6 \times 6\,cm^2$; each detector has 30×30 finger crystals, each of size $2 \times 2 \times 30\,mm^3$. The distance between the detectors can range from 5 to 10 cm, depending on compression status.

We have used the EGS4 code [22] for our simulation, implemented to our purpose. The simulated object is a "hot" (1.0 μCi/cc) spherical tumor of variable size positioned inside an active (0.1 μCi/cc) region of breast tissue; the simulated sources were always ^{18}F. The lower-energy threshold for detection of the γ in the YAP crystal was fixed to 50 keV. We adapted the EM algorithm developed for the YAP-(S)PET tomograph to our PEM prototype. All the performed studies simulate acquisitions of 10 min. Tumors of diameter of 9.8 mm (0.5 cc) and 5.0 mm (0.065 cc) were considered and the SNR evaluated.

An experiment was performed [22], with the YAP-(S)PET tomograph in planar geometry (one pair of detectors only), to produce images of a specially designed ^{68}Ge solid breast phantom. Three tumors, of different size, are mimicked by cylinders with diameters of 0.3, 0.5 and 1.0 cm, and height equal to its diameter, with activities 10 nCi, 44 nCi and 350 nCi, respectively. The breast tissue is mimicked by a ^{68}Ge planar source with a specific activity 10 times lower than that of tumors. Fig. 4 shows a comparison between the image of the 0.5 cm tumor obtained with the YAP-(S)PET scanner (left) and the Monte Carlo image (right) produced simulating the YAP-PET geometry.

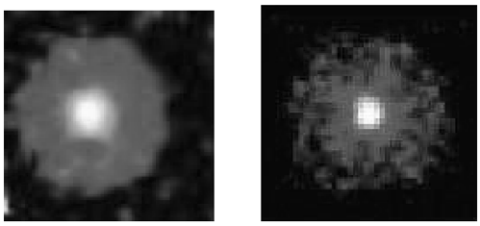

Fig. 4. (Left) Image of a the 0.5 height × 0.5 cm ∅ "cylindrical tumor" (volume 0.1 cc, with an activity of 44 nCi) embedded in an active "breast tissue" obtained with the YAP-(S)PET scanner. Acquisition time: ~10 min. (Right) Corresponding image obtained via Monte Carlo simulation.

5. Conclusions

Dedicated PET scanners for small animal study are now commercially available. Further improvements are needed in terms of spatial resolution and sensitivity for various research applications, especially in genetic research for the development and monitoring of gene therapies.

Dedicated scanners for Positron Emission Mammography could be valuable tools for breast cancer diagnosis. However, this technique is still under scrutiny in clinical investigation and too few research prototypes are actually available.

Due to their similarities, small animal PET and PEM can be based on the same technology. We have shown that a high density/medium Z scintillator (such as YAP) could be very useful for both these apparatuses (e.g. YAP-(S)PET and YAP-PEM).

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