Development of analog solid-state photo-detectors for Positron Emission Tomography

Maria Giuseppina Bisogni[a*], Matteo Morrocchi[a]

[a]Department of Physics, University of Pisa and INFN – Pisa, Largo Bruno Pontecorvo 3, I-56127, Pisa, Italy

---

Abstract

Solid-state photo-detectors are one of the main innovations of past century in the field of sensors. First produced in the early forties with the invention of the p-n junction in silicon and the study of its optical properties, photo-detectors received a major boost in the sixties when the p-i-n (PIN) photodiode was developed and successfully used in several applications.

The development of devices with internal gain, avalanche photodiodes (APD) first and then Geiger-mode avalanche photodiodes, named single photon avalanche diode (SPAD), lead to a substantial improvement in sensitivity and allowed single photon detection. Later on, thousands of SPADs have been assembled in arrays of few millimeters squared (named SiPM, silicon photo-multiplier) with single photon resolution.

The high internal gain of SiPMs, together with other features peculiar of the silicon technology like compactness, speed and compatibility with magnetic fields, promoted SiPMs as the principal photo-detector competitor of photomultipliers in many applications from radiation detection to medical imaging.

This paper provides a review of the properties of analog solid-state photo-detectors. Particular emphasis is given to latest advances on Positron Emission Tomography instrumentation boosted by the adoption of the silicon photo-detectors as an alternative to photomultiplier tubes (PMTs). Special attention is dedicated to the SiPMs, which are playing a key role in the development of innovative scanners.

Keywords: solid-state photo-detectors, pin photodiode, avalanche photodiode, silicon photo-multipliers, medical imaging, positron emission tomography

---

* *Corresponding author. Tel: +39 050 2214 240; Fax: +39 0502214 460; e_mail: giuseppina.bisogni@pi.infn.it*

1. Introduction

In the last few decades, the development of solid-state photo-detectors, mainly for fundamental research, has quickly generated a great interest in medical applications. The peculiarities of these detectors, such as compactness, fast response and insensitivity to the magnetic field, allowed the development of new imaging instrumentation. Silicon photo-detectors are used as light sensors in several imaging and diagnostic tools, from optical imaging, computed tomography (coupled to CsI(Tl) scintillating screens), to digital radiography and nuclear medicine (to cite but a few).

The scope of this paper is to review the latest developments of photo-detectors for Positron Emission Tomography (PET) scanners. In PET, silicon photodetectors are optically coupled to inorganic scintillating crystals, which convert the energy of the incident ionizing radiation into optical photons. Silicon photo-detectors are sensitive in a broad range of wavelengths, from UV to NIR, the range where the emission wavelengths of most of the scintillators used in medical imaging fall.

Analog photo-detectors such as avalanche photodiodes (APDs) and silicon photo-multipliers (SiPMs) have demonstrated to be valid candidates to replace the standard photomultiplier tubes (PMTs) in PET. They can have a signal rise-time shorter than one nano-second being suitable for applications requiring good time resolution as TOF-PET. Moreover, silicon detectors can be fabricated in miniaturized sizes (of the order of few mm^3), ideal for applications requiring high spatial resolution (pre-clinical PET) or compactness (intra-operative probes). Finally, APDs (and now SiPMs) enabled the construction of hybrid systems, such as PET combined with magnetic resonance imaging (MRI) scanners (PET/MR). In fact, PMTs cannot be operated in MRI scanners since the electron trajectories are strongly influenced by the magnetic field (higher than 1.5 T). Silicon photo-detectors, instead, are insensitive to the magnetic field and do not require shielding. Moreover, the compactness of these devices has allowed the full integration of the two imaging techniques.

This paper is organized in two main parts. In the first one we describe the basic structure and operation of silicon photodiodes without and with internal gain. A special attention is dedicated to the APDs and the SiPMs, reporting the architecture of these two silicon devices, describing their working principle and the features most relevant for their application to medical imaging systems. In the second part of this paper, we provide a review of the PET applications that have been developed or improved by the adoption of the solid-state photo-detectors. An outlook on the evolution of these devices and their applications is finally provided.

2. Basic structure and operation of the analog silicon photo-detectors

The basic structure of a standard silicon photodiode is the p-n junction. Fig. 1 shows a simplified scheme of this device where a reverse bias voltage is applied to the junction to increase the depletion region. The interaction of a visible photon of suitable energy with silicon creates an electron/hole (hereafter called *e/h*) pair. The two carriers drift in opposite directions inducing a signal on the collecting electrodes. Since the electric field is present only in the depletion region, most of the *e/h* pairs created outside of it recombine and no signal will be induced at the electrodes. The collection time depends on the velocity of the charge carriers in the depletion region and on the interaction depth of the photon. The time resolution is therefore related to the depleted thickness and the time performance can be improved to a certain extent by increasing the bias voltage.

The probability of photogenerating and collecting an *e/h* pair is called quantum efficiency (QE). It depends on: the fraction of photons that are not reflected at the surface of the detector, the fraction of photons that are absorbed in the depletion region, and the probability that an *e/h* pair does not recombine before collection. An anti-reflective coating is typically used to maximize the fraction of photons transmitted through the surface. The absorption length of a photon in silicon depends on its wavelength as shown in Fig. 2 [1].

FIGURE 1

FIGURE 2

Photons with a wavelength lower than around 300 nm are absorbed in few nanometers of silicon therefore the QE at this short wavelength is reduced by the presence of a highly doped non-depleted layer overlying the photo-sensitive depletion region. At longer wavelengths, the QE increases according to the absorption length and to the thickness of the sensitive volume. In this respect, the depth of the depletion region must be optimized as a function of the optical wavelength to be detected. A thin depleted layer limits the sensitivity of the device to short wavelengths. On the other side, in too thick depletion regions the thermally generated noise increases and the time performances degrade.

If an additional layer of intrinsic silicon is placed between the two ends of the junction, a region free of space charge is created thus extending the sensitive volume of the detector. The resulting device is called p-intrinsic-n (PIN) photodiode. The thick layer of “intrinsic” silicon (very low doped silicon with high resistivity) makes the device sensitive to a wide rage of wavelengths. In addition, the low capacitance and the high resistivity of the intrinsic material reduce the serial and the thermal noise. The QE can be made high also at short wavelengths creating a very thin highly doped p front layer. The operation of a PIN photodiode, since it has no internal gain, requires a charge sensitive preamplifier and a shaping amplifier.

Their use make the signal slow (order of few μsec) and the smallest light flash detectable above noise has to be hundred of photons for cm^2 PIN photodiodes [18].

2.1. Avalanche photodiodes

An avalanche photodiode (APD) is a p-n device with internal gain due the high electric field at the junction that gives to a photoelectron enough energy to create an *e/h* pair by impact ionization. The original photoelectron and the additional one can generate further *e/h* pairs providing a charge multiplication. Thus, in the APDs, the signal generated by the incident light is internally amplified, typically by a factor of few hundreds. Several architectures have been proposed for these devices [2] and an example is shown in Fig. 3 together with the electric field as a function of depth (on the right). Three p-layers with different levels of doping and a single highly doped n-layer are used to modulate the electric field through the device. The visible photon interacts in the depleted low doped (p^-) region, generating an *e/h* pair: while the hole is driven to the highly doped (p^+) layer, the electron is drifted towards the n^+ layer through the p region where the electric field is high enough to generate secondary carriers by impact ionization. This triggers the mechanism of charge multiplication, and the resulting amplified signal is then collected at the N-contact. The device shown in figure is based on a n-over-p junction highly sensitive to the red light, but p-over-n APDs are also produced with highest sensitivity in the blue region.

Even though the signal of an APD is amplified by the multiplication process, it is not high enough to be used without an external amplification.

FIGURE 3

The noise (σ_{APD}^2) of an APD connected to a charge preamplifier, for a number N of primary *e/h* pairs generated by the incident radiation, can be expressed as [3],[4]:

$$\sigma_{APD}^2 = (F-1) * N * A^2 + \frac{A^2 * ENC^2}{e^2} \quad (1)$$

where F is the excess noise factor, A is the amplification factor of the APD, ENC is the Equivalent Noise Charge of the preamplifier, and e is the electron charge. The first term in Eq. (1) is due to the fluctuations in the multiplication process and the second one is the electrical noise. F describes the amplitude of the oscillations of the signal due to statistical generation of secondary charges and, for high gain (A>10) it is mainly determined by the contribution of the holes to the multiplication process [5]. ENC is used to convert the electrical noise amplitude in an equivalent number of primary *e/h* pairs due to noise at the input of the preamplifier. Both the pre-amplifier noise and the dark current of the junction are considered in this term. A more detailed description of the *ENC* can be found in [6]. In Eq. (1), only the contributions of the photo-detector and of the front-end electronics are considered. If the photo-detector is coupled to a scintillating crystal (like in PET) the fluctuations in the generation and transport of optical photons in the crystals must be also considered.

The noise level of the device is dependent on the bias voltage and on the temperature. APDs are usually connected to a cooling system to stabilize the signal thus improving the signal-to-noise ratio.

APDs have been also designed to collect the charge at different anodes, typically placed at the four corners of a squared device, to obtain information on the position of the interaction of the detected photon. Using this kind of device, called position sensitive – APD (PS-APD), a matrix of scintillating crystals has been decoded [7].

The time resolution (σ_t) of an APD depends on the statistical fluctuations in the multiplication process, on the electrical noise of the pre-amplifier (see eq. 1) and on the variation in the collection time of the charge generated in the depletion region. The dependence on the signal fluctuation (σ_q) and on the derivative of the signal (dQ/dt) at the trigger level is given by equation (2) [8]:

$$\sigma_t = \frac{\sigma_Q}{dQ/dt} \tag{2}$$

If the APD is coupled to a scintillator, the slope of the rising edge depends both on the response of the APD and on the crystal properties (mainly decay time and light transport). Sub-nanosecond coincidence time resolutions can be achieved with APDs coupled to LSO crystals [9].

2.2. Silicon photo-multipliers

If the bias voltage of an APD is greater than the junction breakdown voltage[1]2, the charge multiplication is a diverging self-sustaining process (Geiger regime). A quenching resistor, connected in series with the junction, is used to interrupt the avalanche: when the current in the junction is high enough to generate a voltage drop across the resistor close to the applied overvoltage (i.e. the difference between the bias voltage and the breakdown voltage), the current flowing becomes low enough that statistically the avalanche can be quenched and the junction is recharged. The device based on this working mechanism is called Single Photon Avalanche Diodes (SPADs) [10].

---

[1]2 The maximum bias that can be applied to a p-n junction is limited by breakdown that is characterized by a rapid increase of the reverse current.

A SiPM (also known as Geiger-mode avalanche photodiode, G-APD) is a device obtained by connecting in parallel several miniaturized SPADs (few tens of μm^2) belonging to the same silicon substrate so that the output signal of the SiPM is the sum of the SPADs outputs. The small SPADs in the SiPM are named microcells. An electrical scheme of the SiPM (left) and the structure of a single micro-cell (right) are shown in Fig. 4.

FIGURE 4

The gain of a SPAD is expressed as the ratio between the charge produced by the avalanche and the primary charge produced by the interaction of the optical photon within the device. Since the avalanche is interrupted when the voltage at the two sides of the micro-cell goes down to the breakdown voltage, the gain G can be expressed as [11]:

$$G = \frac{C * (V_{bias} - V_{BD})}{e} \qquad (3)$$

where C is the total micro-cell capacitance, given by the sum of the diode capacitance and the parasitic capacitance (mainly due to the quenching resistor with respect to the substrate), V_{bias} is the bias voltage, V_{BD} is the breakdown voltage and e is the electron charge. The gain of the device ranges from 10^6 to 10^7 (comparable to PMTs), allowing SiPMs to be used for single photon counting. As it can be noted in Eq. (3), the gain has a linear dependence on the bias voltage. A linear dependence of the gain on the working temperature has been also observed [12].

The SiPMs represent an effective alternative to the current detectors used in PET scanners, since they have a very fast rise time due to the Geiger mechanism [13], are insensitive to magnetic fields [14] and show high gain at few tens of bias voltage. Furthermore, arrays of SiPMs composed of single sensors as small as 1 mm^2 can be produced, either by assembling several devices in a matrix or by fabricating replicas of the same sensor on a common silicon substrate [15]. Both approaches have allowed the development of high spatial resolution detectors (see later discussion).

A single photon time resolution close to 80 ps FWHM [16] has been obtained irradiating in coincidence two SiPMs with a laser source, while a standard deviation of about 20 ps has been achieved by increasing the number of micro-cells triggered simultaneously. This demonstrates that such photo-sensors can be applied in high timing resolution PET detectors.

The noise in SiPM devices is mainly due to the dark count rate: an *e/h* pair can be thermally generated, triggering an avalanche in a micro-cell without an optical photon impinging on it. The dark noise rate depends on the working temperature and on the overvoltage, and it is directly proportional to the active area of the device. Newest SiPM technologies guarantee a dark count rate of about 100 kHz/mm^2 at room temperature [17].

Other noise sources are correlated to other primary events triggered in one cell. Trapping of the carriers and their delayed release in the avalanche region can cause a second avalanche in the junction, named afterpulse: trapped carriers can have a lifetime from tens to hundreds of nanoseconds and the second avalanche can be triggered also after the complete micro-cell recharge [18], increasing artificially the number of counted events.

During the avalanche in a micro-cell optical photons can be produced, whose interactions in adjacent micro-cells of the SiPM can generate optical cross-talk, introducing an additional noise component. The effect of cross-talk can be prevented with trenches (grooves surrounding each micro-cell), which can have metal-coated sidewalls [19] or can be filled with optically dense material to increase the photon absorption probability [20]. The cross-talk can be also increased by the optical coupling with a scintillating crystal: if a high refractive index material is coupled to a SiPM, there is a high probability that an optical photon generated in an avalanche towards the interface will be reflected back to another micro-cell [21].

After a single micro-cell has fired and before the avalanche is quenched, this micro-cell is blind to other optical photons impinging on its active area. Therefore the number of micro-cells connected in parallel in the SiPM represents an upper limit to the number of photons that can be detected at the same time (dynamic range). To avoid saturation effects, the number of micro-cells have to be chosen depending on the expected number of photons that have to be detected (for instance on the light yield of the scintillator). For a given surface of the SiPM (usually 3 x 3 mm^2 or 4 x 4 mm^2 for clinical PET applications), the dynamic range is directly correlated to the size of the micro-cell. Different sizes are available, starting from 15 x 15 μm^2 to 100 x 100 μm^2. The size of the micro-cell affects also other characteristics of the SiPM. The ratio between the active area and the total area (the so called fill factor) of a microcell is higher for large microcells: small micro-cells in fact sacrifice a larger fraction of their area for guard rings at the expenses of sensitivity. The best cell size depends on the fill factor that can be reached with a certain technology and the maximum bias applicable. With the scintillating crystals mostly used in PET applications, it has been shown that a 50 μm micro-cell pitch is the best trade-off between sensitivity and dynamic range for some producers [22, 23], whereas smaller cells are the optimum for others.

The number of detected photons (N_{DET}) in a SiPM depends both on the probability that an impinging photon triggers the avalanche, called photon detection efficiency (PDE), and on the number of micro-cells (N_{cell}) with respect to the number of incident optical photons (N_{ph}):

$$N_{DET} = N_{cell}\left(1 - e^{-PDE * \frac{N_{ph}}{N_{cell}}}\right) \tag{4}$$

With a high number of optical photons a saturation effect is visible and the dependence of the collected signal on the energy released in the crystal is no longer linear. As a consequence, the achievable energy resolution depends on the number of micro-cells and on the scintillation energy [24].

The *PDE* in a silicon photomultiplier can be expressed as [25]:

$$PDE = QE * \varepsilon_G * \frac{A_{sens}}{A_{tot}} \tag{5}$$

where *QE* is the quantum efficiency, which can be higher than 90% at the sensitivity peak (usually in the blue region for n-over-p devices), ε_G is the probability that a charge carrier activates the Geiger process, A_{sens} / A_{tot} is the ratio between the sensitive area of the device and its total area (the *fill factor*). The *PDE* is a function of the wavelength of the photon impinging on the detector and it is strictly dependent on the overvoltage. In fact, the higher is the overvoltage, the higher is the probability that a photoelectron triggers the avalanche in the depletion region (ε_G). However, increasing overvoltage has several consequences also on the other parameters previously described: higher afterpulse, higher cross talk, higher DCR, and lower single photon time jitter. The impact of all these parameters depends on the application. Electrons have a higher probability with respect to holes to trigger an avalanche, so the p-layer has the highest sensitivity. Depending on the architecture of the junction (p-over-n or n-over-p), the PDE peak of the device is closer to the blue region or to the red one. In p-over-n devices, the most sensitive layer is at the photon entrance, where blue light has a greater interaction probability; in n-over-p device, instead, blue light is attenuated on the n layer and photons with a higher wavelength are more likely detected. Fig. 5 shows the PDE of two SiPMs with different spectral sensitivity (dashed lines) produced by the vendor reported in [26], [27]. The emission spectra of three inorganic scintillators (Bismuth Germanate - BGO, Lutetium Ortho-Silicate – LSO/LYSO and Lanthanium Bromide - $LaBr_3$:Ce [28]) are also shown (solid lines).

FIGURE 5

The fraction of scintillation light detected by the SiPM depends also on the transmission probability of the photon from the scintillating crystal to the sensitive area. Most of the scintillators used in PET applications have a high refractive index, hence an optical coupling with epoxy resins, silicon glues or silicon grease is usually used to match the refractive index of the silicon oxide.

Digital versions of SiPMs have also been produced [29], [30]. The output of such devices is the time stamp of the trigger and the number of micro-cells fired in the scintillation. A comprehensive review of these devices is given in [31].

2.3. Read-out of multi-channel systems based on SiPMs

The adoption of pixelated sensors with a fine pitch requires a high number of read-out channels to collect the signal of each pixel independently. For example in PET, the number of photo-detectors increases of about two orders of magnitude passing from the block detector [32], composed of a semi-pixelated array of scintillators coupled to four PMTs and decoded using the Anger logic method, to the one-to-one coupling of scintillators and SiPMs. A multiplexing read-out based on charge division circuit has been proposed to minimize the amount of analog read-out channels [33].

The high density of channels can be also addressed with the adoption of integrated front-end circuits (also named application specific integrated circuits, ASIC). ASICs able to manage up to 64 channels have been developed [34],[35],[36]. The front-end should have a high bandwidth to exploit the high timing performance of the detector, it has to sustain the data rate of a PET scan, and it should preserve the energy resolution of the signal. Additional requirements depend also on the applications: a low power consumption is desirable for hybrid PET/MR to avoid large currents inside the bore of the magnet, while a low *ENC* and a validation scheme based on cluster-finding algorithms are useful in SiPMs arrays coupled to monolithic crystals.

It has been demonstrated that front-end ASICs coupled to SiPM detectors can be used in the development of time-of-flight (TOF)-PET systems [37],[38]. The time resolution can be optimized with a low impedance input, with a high bandwidth, and by using a double threshold validation scheme: a lower threshold is used for the timing information (to trigger on one of the first scintillating photons), while a higher threshold is used to validate the event (to discard dark noise).

3. Applications of analog photo-detectors in positron emission tomography

Positron emission tomography is the medical imaging technique that most may profit of the silicon photo-detector technology. PET involves the injection of a tracer labelled with a positron-emitting radionuclide and detection of the 511 keV back-to-back photons produced simultaneously after the positron annihilation with an electron of the tissue. PET has relied on the PMTs technology from its beginning in the sixties of last century. For instance, silicon photo-detectors can be used as a replacement of the PMTs to further compact the size of preclinical scanners or to increase the solid angle coverage of clinical systems. Furthermore, they represent the fundamental components for latest evolutions of the technology like hybrid PET/MR scanners or TOF-PET.

3.1. *Hybrid PET/MR imaging systems*

MRI reveals structure and functions through the interaction of a strong magnetic field with primarily the protons present in water and tissues and their chemical environment. This modality has also a good sensitivity (10^{-3}–10^{-5} mol/l) and an excellent spatial resolution (~1 mm isotropic for clinical systems). The fusion of this anatomical MRI information with the nano-molar functional information given by PET provides a whole spectrum of information that can be used to understand new aspects of the anatomy and the physiology of a disease. The principal applications of the PET/MR hybrid systems are diagnosis, treatment and follow-up of tumours, mainly of head and neck, and of abdomen and prostate, for which the superior imaging capabilities of MRI over computed tomography (CT) are more relevant [39] Furthermore PET/MR opens new fields of neurology research thanks to the capability to provide co-registered images and to monitor time-dependent metabolic processes. The development of new bi-modal tracers can be particularly useful in the study of neurological diseases and in pre-clinical applications for pharmaceutical research.

Hybrid PET/MR scanners have been initially developed using bundles of optical fibres or light-guides to convey the light from the scintillator PET ring positioned inside the bore of the MRI scanner to a region with low magnetic field where photo-multiplier tubes read-out the light without distortion of the signal due to the magnetic field [40],[41]. The main limitations of this method are the signal attenuation in the fibers and the complexity of the optical cabling for a PET system with a large field of view.

Scanners composed of a PET/MR tandem, in which the patient-bed is automatically moved from the MRI to the PET scanner have been also developed using shielded PMT detectors [42]. The main disadvantage of this configuration is that the two images need to be acquired separately and then merged together.

The availability of a new generation of photo-detectors based on semi-conductor materials has allowed the development of PET systems fully integrated inside the MRI bore and of PET inserts that can be employed in existing MRI facilities. The possibility to employ silicon detectors also with ultra-high magnetic fields without worsening the performances has been shown [43].

Large efforts have been invested in the development of a PET/MR scanner, and hybrid systems for simultaneous bi-modal acquisitions are now available both for clinical [44] and pre-clinical applications [45], and they are composed of arrays of APDs coupled to LSO crystals integrated between the MR coils and the gradients of the magnet. The first commercial PET/MR system based on the SiPM technology has been produced by the vendor reported in [46]. The PET is composed of LYSO scintillators coupled to SiPMs and it is fully integrated in a 3T magnet, thus combining the advantages of the TOF technique (see next sub-section) and of the bi-modal PET/MR imaging.

The three architectures of PET/MR scanners discussed in this section are shown in Fig. 6: a tandem scanner (left), a scintillator ring inside the MRI bore with light-guides to bring the signal to PMTs outside the magnet (center), and a fully integrated PET/MR, feasible only with the adoption of solid-state detectors (right).

FIGURE 6

3.2. *Time-of-Flight PET*

In the standard PET image reconstruction, no assumption is made on the position of annihilation of the positron along the line of response (LOR, the line identified by the two detectors triggered in coincidence), and a uniform distribution of probability is usually assumed over the whole line of response. Ideally, the annihilation position on the line of flight of the two 511 keV photons can be estimated by measuring the delay in the trigger between the two detectors. Taking into account the detector time resolution, a Gaussian bell shaped function can be used to represent the probability of annihilation of the β^+ along the LOR. Considering the typical PET ring geometry, the distance between the Gaussian distribution centre (μ_R) and the PET scanner centre can be evaluated from the delay between the triggers (Δt) : $\mu_R = \frac{c}{2} \Delta t$ (where c is the speed of light). According to the same equation, the width of the Gaussian distribution (σ_R) is related to the coincidence time resolution (CTR) of the pair of triggering detectors: $\sigma_R = \frac{c}{2} CTR$. In practice the annihilation probability distribution is too wide to actually improve the spatial resolution being the time resolution of the detectors the limiting factor. Nevertheless an increase in the Signal-to-Noise Ratio (corresponding to a gain in sensitivity) can be reached using TOF in systems with sub-nanosecond time resolution [47].

Current PET scanners, based on LSO:Ce or LYSO:Ce scintillating crystals read-out by a set of PMTs, can reach a time resolution of 500 – 900 ps [48],[49],[50]. Reconstruction algorithms taking into account the TOF information have been successfully applied to total body PET acquisitions, demonstrating the improvements in terms of Signal-to-Noise ratio.

Limitations in timing performances are mainly due to the speed of response of the PMTs and to the sharing of the scintillation light between multiple photo-detectors. Both issues can be solved with the adoption of fast and compact SiPMs, with a one-to-one coupling between scintillator and photo-sensor. It has been demonstrated that using LYSO scintillators coupled to SiPMs a coincidence time resolution (CTR) close to 200 ps FWHM can be achieved [51], and that a resolution close to 100 ps has been reached using a pair of 3 mm x 3 mm SiPMs coupled to 3 mm x 3 mm x 5 mm $LaBr_3$:Ce crystals [52, 53]. Furthermore, in the last years SiPMs with sensitivity peak in the near-UV range [54] have been developed to match the emission peak of new very fast scintillators. For these reasons, SiPMs are the most suitable candidates in the development of next generation high performances PET systems. The high time performances of SiPMs coupled one-to-one to fast scintillating crystals have been deeply investigated and proven, but the development of PET detectors with TOF capability is still challenging in systems that adopt light sharing or read-out multiplexing to minimize the number of photo-detectors and read-out channels.

3.3. *Pre-clinical imaging systems*

The capability of PS-APD to give continuous information about the position of interaction of the optical photons and the high granularity of APDs and SiPMs make these devices particularly attractive for applications requiring high spatial resolution. In pre-clinical imaging, due to the different dimension of the anatomical structures of small animals with respect to humans, a spatial resolution below the millimeter is needed to obtain in small animals the same functional information that is provided by clinical scanners based on pixellated crystals of 4 mm pitch.

To achieve a high spatial resolution, the capabilities of both pixellated (with pitch of 2 mm or smaller) and continuous crystals have been investigated, showing the advantages and limitations of both solutions.

Arrays of SiPMs with a pitch of 1.5 mm or less [15] have been produced and tested to decode arrays of scintillators with the same pitch. As mentioned in par 2.2, monolithic arrays of SiPMs have been produced with minimal dead area among photo-sensors. An array of thin crystals (as small as 0.7 mm in size) has been decoded using an array of SiPMs with a 3 x 3 mm^2 active area and using light sharing between pixels [55]. However, a degradation of the energy resolution has been observed when using thin crystals coupled to SiPMs, due to the limited light output efficiency of crystals with high aspect ratio and to the saturation effect in SiPMs with a small number of micro-cells facing each scintillator. Results show an energy resolution between 15% and 17% for crystals of 1.5 mm x 1.5 mm section coupled to a SiPM array [56]. PS-APDs have been used to decode arrays of thin crystals with a pitch of 1 mm [57], reading out the scintillator from both sides to maximize the light collection and to identify the depth of interaction position of the photon in the crystal. A spatial resolution close to the millimetre at the centre of the field of view has been reached in pre-clinical PET, using arrays of thin scintillating crystals [58]. Furthermore, position-sensitive SiPMs have been developed. These devices collect the signal of the SPADs in four anodes, and the SPADs connections are such that an array of scintillators can be decoded with a single device using the centre of gravity algorithm [59].

The adoption of monolithic scintillating crystals coupled to photo-detectors for high spatial resolution in pre-clinical systems [60],[61] had already been proposed using PMTs, but the availability of the compact solid-state photo-detectors with small pitch allows to increase the spatial resolution thanks to a finer sampling of the light distribution. With monolithic crystals, the light response depends also on the depth of interaction of the photon, so this information can be obtained as well. PET detectors composed of a slab of LYSO scintillator coupled to an array of SiPMs or APDs have been developed [62],[63]. In this configuration, the scintillating photons are shared between several detectors. Therefore the light collection needs to be maximized using a white coating on the top surface of the crystal and adopting arrays of photo-detectors with a high fill-factor. The lateral sides of the scintillator, instead, are usually painted black to minimize edge effects. Furthermore, new bright crystals like $LaBr_3$: Ce [64] has been investigated [65]. The partial sampling of the light distribution close to the edges of monolithic crystals usually does not allow to reconstruct the interaction position of the 511 keV photon using an Anger-logic scheme. Many methods have been studied to reach a high three-dimensional spatial resolution in the entire volume of the crystal, using statistic-based methods [66],[67], non-linear least square methods based on empirical models of light distribution [68],[69] and artificial neural networks [70].

Even if a spatial resolution close to the millimetre has been reached in monolithic detectors, their application to commercial systems is still limited by the complexity of the calibration process. The development of a fast and handy calibration method could represent a breakthrough in the use of monolithic crystals in pre-clinical systems.

3.4. *New PET detectors with depth of interaction capabilities*

PET scanners with small ring diameters (for pre-clinical or organ-specific applications) show a non-homogeneous spatial resolution across the FOV due to the parallax error. The spatial resolution degrades rapidly with distance from the centre of the FOV. To avoid this detrimental effect, the depth of interaction (DOI) of the 511 keV photon in the crystal must be incorporated into the detector.

The interaction probability of 511 keV photons in silicon photo-detectors is extremely low and the so-called nuclear counter effect is negligible. This allows to explore new geometrical configurations to measure the DOI in the scintillator. With respect to PMTs, in fact, silicon detectors can be placed between the FOV and the crystals without a significant degradation of the photon flux.

A stack of detectors, each composed of a thin scintillator coupled to a SiPMs array, has been proposed [71], allowing a discrete quantization of the depth of interaction with an easy decoding of the crystal in which the 511 keV photon interacts. On the other hand, this method requires a higher number of photo-detectors (proportional to the number of layers) to cover the same solid angle.

Different couples of detectors have been also adopted to read-out the two sides of a pixelated scintillator array. A non fully reflective wrapping is used to make the amplitude of the signals collected on the two sides dependent on the DOI. In fact, due to multiple interactions at the lateral sides of the crystal, the light is attenuated in the path from the scintillation point to the sensor surface and the DOI is related to the asymmetry in the magnitude of the collected energies. Moses and Derenzo proposed a scintillator matrix coupled to a PIN photodiode array on one side and to a single PMT on the other side [72]. The PMT collects the energy on one side while the PIN array identifies the crystals and the energy on the other face.

The principle of the two sides read-out of a crystal array has been proposed also using a couple of PS-APDs [73] and two silicon photomultiplier arrays [74]. The DOI is reconstructed comparing the energy collected on the two sides.

As mentioned previously, the DOI can be reconstructed from a single monolithic crystal coupled to an array of photo-detectors, and the method of the double side read-out has been proposed also for monolithic crystals [75],[76]. The information on the DOI can be reconstructed easily and with a higher resolution by using arrays of detectors on the top and bottom sides of the scintillator as a trade-off. A larger amount of detectors are required and the signal-to-noise ratio in each device is lower because only direct light is collected.

Four detector architectures with depth of interaction capabilities implemented using silicon photo-detectors are represented in Fig. 7: a double side read-out of a scintillator array (top - left), a stack of layers composed of photo-detectors coupled to scintillators (top - right), a monolithic crystal read-out by photo-detectors on a single side (bottom - left) and on top and bottom sides (bottom – right).

FIGURE 7

3.5. *Application-specific PET scanners*

Light and thin sensors allow the development of PET detectors for new specific applications. RatCAP (Rat Conscious Animal PET) [77], the EndoTOFPET-US (Endoscopic TOFPET & Ultrasound) [78] and INSIDE (Innovative Solutions for In-beam DosimEtry in Hadrontherapy) are some examples described in the following.

In RatCAP, a miniaturized PET ring is fixed on the head of the mouse and the image is acquired without the adoption of anesthesia, letting the mouse partially free to move. The size of the detector ring allows imaging the whole brain with a spatial resolution below 2 mm of full width at half maximum, while the total weight of the detector ring is only 250 g [79]. A set of brackets fixes the scanner to the mouse skull to avoid motion artifacts during the scan.

In EndoTOFPET-US, one of the two detection heads is composed of a scintillator array coupled to a SiPM matrix integrated in an endoscopic probe: this allows to minimize the distance between the region of interest and the detector, thus increasing the sensitivity. The miniaturized detector installed in the endoscopic probe is composed of an array of 0.7 x 0.7 x 10 mm^3 LYSO crystals optically coupled to a digital SiPM array, while the external detector plate is composed of 3 x 3 x 15 mm^3 scintillators read-out by analog SiPMs The asymmetric configuration of the detectors, with the probe very close to the region of interest, requires a high time resolution to employ TOF in the reconstruction algorithm and to remove the background of the surrounding tissue [80].

The compactness and the flexibility in the design of SiPMs and APDs make them particularly appealing for custom systems that have to be fitted in narrow spaces (as in the PET/MR systems) or in complex geometries. An example of this is definitely the in-beam monitoring of particle therapy treatment. In this case, the PET scanner needs to stay as close as possible to the patient, without hampering the patient-bed motion and the particle beam path. As an example of in-beam PET scanner, the one developed in the framework of the INSIDE project [81] is composed of two planar detectors, 10 cm wide (transaxially) x 25 cm long (axially, along the beam direction), each to be placed at 25 cm from the isocenter. The PET heads are composed of 2x5 detection units, each made of arrays of 256 Lutetium Fine Silicate (LFS) pixel crystals, 3x3x20 mm^3 each, and coupled one to one to SiPMs. A custom designed electronics system is being developed to cope with the prompt particle rates typical of a therapeutic beam (~10 Mhz/cm^2).

4. Conclusions

The unique features of solid-state photo-detectors like compactness, fast response and insensitivity to the magnetic field open new frontiers for the next generation of medical imaging systems. Concerning PET applications, the high granularity of APDs and SiPMs allows to reach a spatial resolution of one millimetre or less. These detectors can be employed to decode arrays of small scintillating crystal pixels or in the read-out of monolithic crystals. Furthermore the compactness and the high transparency to the 511 keV energy radiation used in PET allow to place these detectors between the patient and the crystal without causing a significant perturbation of the photon flux. Thanks to these features, new detectors with depth of interaction capabilities can be developed, thus improving the spatial resolution at the periphery of the field of view. Fast photo-detectors like SiPMs, coupled one-to-one to scintillators, can overtake the time resolution of current PET scanners, reaching a coincidence time resolution of about 100 ps using $LaBr_3$: Ce crystals. This results are particularly relevant for the new generation of TOF-PET scanners where a higher timing resolution provides a significant improvement in the image quality. The insensitivity of the silicon photo-detectors to the magnetic field and their compactness were key features to produce hybrid fully-integrated PET/MR scanners, now commercially available for clinical and pre-clinical applications.

SiPM technology has reached such a level of maturity that a large-scale industrial production is now possible at prices below 1 $\$/mm^2$. The high cost was one of the major limits to the massive use of the SiPMs, especially in medical and pre-clinical devices. But as the prices have dropped below the PMTs, it is likely that SiPMs for PET and especially PET/MR applications will dominate the market.

Further improvements of the SiPM technology are focused on the integration of the electronic read-out on the same silicon die of the detector to obtain a digital output from the photo-sensor [82]. Furthermore, solutions for a direct connection of analog SiPMs to read-out integrated electronics are under way. In this case, the read-out of the detector is performed from the back side by means of Through Silicon Vias (TSV) and Vertical Integration technologies [83]. The latter solution is potentially preferable with respect to the monolithic approach since allows optimizing the sensor and the electronics tiers separately.

References

[1] M. A. Green, Self-Consistent optical parameters of intrinsic silicon at 300K including temperature coefficients, Solar Energy Materials & Solar Cells 92 (2008), pp. 1305-1310.

[2] D. Renker, Geiger-mode avalanche photodiodes, history, properties and problems, Nuclear Instruments and Methods in Physics Research A 567 (2006), pp. 48-56.

[3] R. Chen, A. Fremout, S. Tavernier, P. Bruyndonckx, D. Clement, J. F. Loude, C. Morel, Readout of scintillator light with avalanche photodiodes for positron emission tomography, Nuclear Instruments and Methods in Physics Research A 433 (1999), pp. 637-645.

[4] R. Lecomte, C. Pepin, D. Rouleau, A. Saoudi, M. S. Andreaco, M. Casey, R. Nutt, H. Dautet, P. P. Webb, Investigation of GSO, LSO, YSO scintillators using reverse avalanche photodiodes, IEEE Transaction on Nuclear Science 1998, Vol. 45, No. 3, pp. 478-482.

[5] R. J. McIntyre, The distribution of gains in uniformly multiplying avalanche photodiodes: Theory, IEEE Transaction on Electron Devices 1972, Vol. 19, Issue 6, pp. 703-713.

[6] V. Radeka, Optimum signal-processing for pulse amplitude spectrometry in the presence of high-rate effects and noise, IEEE Transaction on Nuclear Science 1968, Vol. 15, pp. 455-470.

[7] K. S. Shah, R. Grazioso, R. Farrell, J. Glodo, M. A. McClish, G. Entine, P. A. Dokhale, S. Cherry, Position sensitive APDs for small animal PET imaging, IEEE Nuclear Science Symposium Conference Record, 2002, Vol. 3, pp. 1411-1415.

[8] C. Fiorini, A. Gola, A. Longoni, F. Perotti, L. Struder, Timing properties of silicon drift detectors for scintillation detection, IEEE Transactions on Nuclear Science 2004, Vol. 51, Issue 3, pp. 1091-1097.

[9] M. Moszynski, M. Szawlowski, M. Kapusta, M.Balcerzyk, Avalanche photodiodes in scintillation detection, Nuclear Instruments and Methods in Physics Research A 497 (2003), pp. 226-233.

[10] S. Cova, A. Longoni, A. Andreoni, R. Cubeddu, A semiconductor detector for measuring ultraweak fluorescence decays with 70 ps FWHM resolution, IEEE Journal of Quantum Electronics (1983), Volume 19, Issue 4, pp. 630 – 634.

[11] C. Piemonte, R. Battiston, M. Boscardin, G. Dalla Betta, A. Del Guerra, N. Dinu, A. Pozza, N. Zorzi, Characterization of the first prototypes of silicon photo-multiplier fabricated at ITC-irst, IEEE Transactions on Nuclear Science 2007, Vol. 54, Issue 1, pp. 236-244.

[12] M. Ramilli, Characterization of SiPM: Temperature dependencies, IEEE Nuclear Science Symposium Conference Record, 2008, pp. 2467-2470.

[13] G. Collazuol, G. Ambrosi, M. Boscardin, F. Corsi, G.F. Dalla Betta, A. Del Guerra, N. Dinu, M. Galimberti, D. Giulietti, L.A. Gizzi, L. Labate, G. Llosa, S. Marcatili, F. Morsani, C. Piemonte, A. Pozza, L. Zaccarelli, N. Zorzi, Single photon timing resolution and detection efficiency of the IRST silicon photo-multipliers, Nuclear Instruments and Methods in Physics Research A 581 (2007), pp. 461-464.

[14] S. Espana, L. M. Fraile, J. L. Herraiz, J. M. and Udaas, M. Desco, J. J. Vaquero, "Performance evaluation of SiPM photo-detectors for PET imaging in the presence of magnetic fields, Nuclear Instruments and Methods in Physics Research A 613(2) (2010), pp. 308-316.

[15] G. Llosa, N. Belcari, M. G. Bisogni, G. Collazuol, S. Marcatili, P. Barrillon, C. de la Taille, S. Bondil-Blin, N. Dinu, M. Melchiorri, A. Tarolli, C. Piemonte, A. Del Guerra, Energy, Timing and position Resolution Studies with 16-Pixel silicon Photomultiplier matrices for small animal PET, IEEE Transaction on Nuclear Science 2009, Vol. 56, No. 5, pp. 2586-2593.

[16] S. Gundacker, E. Auffray, N. Di Vara, B. Frisch, H. Hillemanns, P. Jarron, B. Lang, T. Meyer, SiPM time resolution: From single photon to saturation, Nuclear Instruments and Methods in Physics Research A 718 (2013), pp. 569-572.

[17] F. Acerbi, A. Ferri, G. Zappala, G. Paternoster, A. Picciotto, A. Gola, N. Zorzi, C. Piemonte, NUV silicon Photomultipliers with high detection efficiency and reduced delayed, IEEE Transaction on Nuclear Science 2015, in press.

[18] D. Renker, E. Lorenz, Advances in solid-state photon detectors, Journal of Instrumentation, 2009, Vol. 4, article N. P04004.

[19] W. J. Kindt, H. W. van Zeijl, S. Middelhoek, Optical Cross Talk in Geiger mode Avalanche Photodiode Arrays: Modeling, Prevention and Measurement, Proceedings of 28th European Solid-State Device Research Conference, 1998, pp. 192-195.

[20] D. McNally, V. Golovin, Review of solid-state photo-multiplier developments by CPTA and Photonique SA, Nuclear Instruments and Methods in Physics Research A, Vol. 610, Issue 1 (2009), pp. 150-153.

[21] A Gola, A Tarolli, C. Piemonte, SiPM Cross-talk Amplification due to the Scintillator Crystal: Effects on Timing Performance, IEEE Nuclear Science Symposium Conference Record, 2012, pp. 421-423.

[22] D. Henseler, R. Grazioso, N. Zhang, M. Schmand, SiPM performance in PET application: an experimental and theoretical analysis, IEEE Nuclear Science Symposium Conference Record, 2009, pp. 1941-1948.

[23] S. Gundacker, E. Auffray, B. Frisch, H. Hillemanns, P. Jarron, T. Meyer, K. Pauwels, P. Lecoq, A systematic study to optimize SiPM Photodetectors for Highest Time Resolution in PET, IEEE Transaction on Nuclear Science 2012, Vol. 59, Issue 5, pp. 1798-1804.

[24] A. Stoykov, Y. Musienko, A. Kuznetsov, S. Reucroft, J. Swain, On the limited amplitude resolution of multipixel Geiger-Mode APDs, Journal of Instrumentation, 2007, Vol. 2, Issue 6, , article N. P06005.

[25] P. Buzhan, B. Dolgoshein, L. Filatov, A. Ilyin, V. Kantzerov, V. Kaplin, A. Karakash, F. Kayumov, S. Klemin, A. Pleshko, E. Popova, S. Smirnov, Yu. Volkov, The advanced study of silicon photo-multiplier, in: Proceedings of the Seventh International Conference on Advance Technology & Particle Physics, 2002, pp. 717-728.

[26] AdvanSiD, http://advansid.com/attachment/get/up_53_1432731710.pdf, access on the website on 27/05/2015.

[27] AdvanSiD, http://advansid.com/attachment/get/up_53_1432741078.pdf access on the website on 27/05/2015.

[28] L. Zhang, R. Mao, R. Zhu, Emission Spectra of LSO and LYSO crystals excited by UV light, X-ray and gamma-ray, IEEE Nuclear Science Symposium Conference Record (2007), pp. 4574-4581.

[29] T. Frach, G. Prescher, G. Degenhardt, R. de Gruyter, A Schmitz, R. Ballizany, The digital silicon photo-multiplier – principle of operation and intrinsic detector performance, IEEE Nuclear Science Symposium Conference Record 2009, pp. 1959-1965

[30] S. Seifert, G. van der Lei, H. T. van Dam, D. Schaart, First characterization od a digital SiPM based time-of-flight PET detector with 1 mm spatial resolution, Physics in Medicine and Biology 58 (2013), pp. 3061-3074.

[31] D.R.Schaart, E. Charbon, T. Frach, V. Schulz, Advances in Digital SiPMs and their Application in Biomedical Imaging, to be published in NIMA Special Issue "Advances in detectors and applications for medicine".

[32] M.E. Casey, R. Nutt. A Multi-crystal Two Dimensional BGO Detector System for Positron Emission Tomography. IEEE Transactions on Nuclear Science 1986, Vol. 33, No. 1, pp. 460-463.

[33] A. L. Goertzen, Z. Xuezhu, M. M. McClarty, E. J. Berg, C. Y. Liu, P. Kozlowski, F. Retiere, L Ryner, V. Sossi, G. Stortz, C. J. Thompson, Design and performance of a resistor multiplexing readout circuit for a SiPM detector, IEEE Transaction on Nuclear Science 2013, Vol 60, Issue 3, pp. 1541-1549.

[34] M. Rolo, R. Bugalho, F. Goncalves, A. Rivetti, G. Mazza, J. Silva, R. Silva, J. Varela, A 64-channel ASIC for TOFPET applications, Proceedings of IEEE Nuclear Science Symposium and Medical Imaging Conference 2012, pp. 1460-1464.

[35] V. Stankova, W. Shen, K. Briggl, H. Chen, P. Fisher, A. Gil, T. Harion, V. Kiworra, Y. Munwes, M. Ritzert, H.-C. Schultz-Coulon, STIC3 – silicon photo-multiplier timing chip with picosecond resolution, Nuclear Instruments and Methods in Physics Research A, 787 (2014), pp. 284-287.

[36] S. Ahmad, J. fleury, C. de la Taille, N. Seuin-Moreau, F. Dulucq, G. Martin-Chassard, S. Callier, D. Thienpont, L. Raux, Triroc: A Multi-Channel SiPM Read-Out ASIC for PET/PET-TOF Application, IEEE Transaction on nuclear science 2014, IN PRESS.

[37] M. Morrocchi, S. Marcatili, N. Belcari, M. G. Bisogni, G. Collazuol, G. Ambrosi, F. Corsi, M. Foresta, C. Marzocca, G. Matarrese, G. Sportelli, P. Guerra, A. Santos, Timing performances of a data acquisition system for Time Of Flight PET, A. Del Guerra, Nuclear Instruments and Methods in Physics Research A, 695 (2012), pp. 210-212.

[38] M. D. Rolo, R. Bugalho, F. Gonçalves, G. Mazza, A. Rivetti, J. C. Silva, R. Silva, J. Varela, TOFPET ASIC for PET applications, journal of Instrumentation 2013, Vol 8, article N. C02050.

[39] D. A. Torigian, H. Zaidi, T. C. Kwee, B. Saboury, J. K. Udupa, Z. H. Cho, A. Alavi, PET/MR imaging: technical aspects and potential clinical applications, Radiology 2013, 267(1) pp. 26-44.

[40] N. L. Christensen, B. E. Hammer, B. G. Heil, K. Fetterly, Positron Emission Tomography within a magnetic field using photo-multiplier tubes and lightguides, Phys Med Biol. 1995; 40(4) pp. 691-697.

[41] J. A. Disselhorst, M. Brom, P. Laverman, C. H. Slump, O. C. Boerman, W. J. G. Oyen, M. Gotthardt, E. P. Visser, Image-Quality Assessment for Several Positron Emitters Using The NEMA NU 4-2008 Standards in the Siemens Inveon Small-Animal PET Scanner Journal of Nuclear Medicine , Vol 51, Issue. 4 (2010) pp. 610-617.

[42] H. Zaidi, N. Ojha, M. Morich, J. Griesmer, Z. Hu, P. Maniawski, O. Ratib, D. Izquierdo-Garcia, Z. A. Fayad, L. Shao, Design and performance evaluation of a whole-body Ingenuity TF PET-MRI system, 2011, Physics in Medicine and Biology, Vol. 56, pp. 3091-3106.

[43] B. j. Pichler, H. F. Wehrl, A. Kolb, M. S. Judenhofer, Positron Emission Tomography/ Magnetic Resonance Imaging: The next Generation of Multimodality Imaging?, Sem. Nucl. Med. 2008; 38 (3), pp. 199-208.

[44] G. Delso, S. Fürst, B. Jakoby, R. Ladebeck, C. Ganter, S. G. Nekolla, M. Schwaiger, S. I. Ziegler, Performance measurements of the Siemens mMR integrated whole-body PET/MR scanner, Journal of Nuclear Medicine 2011; pp. 1914-1922.

[45] S. H. Maramraju, S. D. Smith, S. S. Junnarkar, D. Schulz, S. Stoll, B. Ravindranath, M. L. Purschke, S. Rescia, S. Southekal, J. F. Pratte, P. Vaska, C. L. Woody, D. J. Schlyer, Small animal simultaneous PET/MR: initial experiences in a 9.4 T microMRI, Physics in Medicine and Biology 56 (2011), pp. 2459-2480.

[46] GE healthcare, SIGMA PET/MR, http://www3.gehealthcare.com, Document ID: JB26282XX, website accessed on 3/7/2015.

[47] J. S. Karp, S. Surti, M. E. Daube-Witherspoon, G. Muehllehner, Benefit of Time-of-Flight in PET: Experimental and Clinical Results, Journal of Nuclear Medicine 2008, Vol 49, No. 3, pp. 462-470.

[48] S. Surti, A. Kuhn, M. E. Werner, A. E. Perkins, J. Kolthammer, J. S. Karp, Performance of Philips Gemini TF PET/CT Scanner with Special Consideration for Its Time-of-Flight Imaging Capabilities. J. Nucl. Med. 2007, 48, 471-480.

[49] B. Jacoby, Y. Bercier, M. Conti, M. Casey, T. Gremillion, C. Hayden, B. Bendriem, D. W. Townsend, Performance Investigation of a Time-of-Flight PET/CT Scanner. Proceedings of nuclear Science Symposium Conference Record, 2008, pp. 3738-3743.

[50] J. Wilson, T. Turkington, TOF-PET Small-Lesion Image Quality measured Over a Range of Phantom Sizes. Proceedings of nuclear Science Symposium Conference Record, 2009, pp. 3710-3714.

[51] E. Auffray, B. Frisch, F. Geraci, A. Ghezzi, S. Gundacker, H. Hillemanns, P. Jarron, T. Meyer, M. Paganoni, K. Pauwels, M. Pizzichemi, P. Lecoq, A Comprehensive & Systematic Study of Coincidence Time Resolution and Light Yield Using Scintillators of Different Size, Wrapping and Doping. IEEE Transation on Nuclear Science 2013, Vol. 60, Issue 5, pp. 3163-3171.

[52] D. R. Shaart, S. Seifert, R. Vinke, H. T. van Dam, P. Dendooven, H. Löhner, F. J. Beekman, $LaBr_3$:Ce and SiPMs for time-of-flight PET: achieving 100 ps coincidence resolving time, Physics in Medicine and Biology 2010, Vol. 55, No. 7, pp. 179-189.

[53] M. Varun Nemallapudi, S. Gundacker, P. Lecoq, E. Auffray, A. Ferri, A. Gola , C. Piemonte, Sub-100 ps coincidence time resolution for positron emission tomography with LSO:Ce codoped with Ca, Physics in Medicine and Biology 2011, Vol. 60, No. 12, pp. 4635-4649.

[54] T. Pro, A. Ferri, A. Gola, N. Serra, A. Tarolli, N. Zorzi, C. Piemonte, New Developments of near-UV SiPMs at FBK, IEEE Transaction on Nuclear Science 2013, Vol. 60, No. 3, pp. 2247-2253.

[55] S. Yamamoto, H. Watabe, J. Hatazawa, Performance comparison of SiPM-based block detectors with different pixel sizes for an ultrahigh

resolution small-animal PET system, Physics in Medicine and Biology 2011, Vol. 56, No. 20, pp. 227-236.

[56] A. V. Stolin, S. Majewski, G. Jaliparthi, R. R. Raylman, J. Proffitt, Evaluation of Imaging Modules Based on SensL Array SB-8 for Nuclear Medicine Applications, IEEE Transaction on Nuclear Science 2014, Vol. 61, No. 5, pp. 2433-2438.

[57] K. S. Shah, R. Grazioso, R. Farrell, J. Glodo, M. McClish, G. Entine, P. Dokhale, S. R. Cherry, Position Sensitive APDs for Small Animal PET Imaging, IEEE Transaction on Nuclear Science 2004, Vol. 50, Issue 1, pp. 91-95.

[58] S. I. Kwon, J. S. Lee, H. S. Yoon, M. Ito, G. B. Ko, J. Y. Choi, S. H. Lee, I. C. Song, J. M. Jeong, D. S. Lee, S. J. Hong, Development of Small-Animal PET prototype using silicon Photomultiplier (SiPM): initial results of phantom and animal imaging studies, Journal of Nuclear Medicine 2011; Vol. 52, No. 4, pp. 572-579.

[59] V. Schulz et al., Sensitivity encoded silicon photomultipliers — A new sensor for high-resolution PET-MRI, Phys. Med. Biol. 58 (2013) 4733.

[60] J. Joung, R. S. Miyaoka, T. K. Lewellen, C. Mice: a high resolution animal PET using continuous LSO with a statistics based positioning scheme, Nuclear Instruments and Method in Physics Research Section A 2002, Vol. 489, Issue 1-3, pp. 584-598.

[61] T. E. Peterson, L. R. Furenlid, SPECT detectors: the Anger camera and beyond, Physics in Medicine and Biology 56 (2011), pp. 145-182.

[62] X. Li, C. Lockhart, T.K. Lewellen, R. S. Miyaoka, Study of PET Detector Performance with varying SiPM Parameters and Readout Schemes, IEEE Trans Nucl Sci. 2011; 58(3), pp. 590/596.

[63] G. Llosá, J. Barrio, C. Lacasta, M. G. Bisogni, A. Del Guerra, S. Marcatili, P. Barillon, S. Bondil-Blin, C. de la Taille, C. Piemonte, Characterization of a PET detector head based on continuous LYSO crystals and monolithic, 64-pixel silicon photo-multiplier matrices, Phys Med Biol. 2010; 55(23) pp. 7299-7315.

[64] A. Kuhn, S. Surti, J. S. Karp, G. Muehllehner, F. M. Newcomer, R. VanBerg, Performance assessment of pixelated $LaBr_3$ detector modules for time of-flight PET, IEEE Transaction on Nuclear Science 2006; Vol. 53, Issue 3, pp. 1090-1095.

[65] S. Seifert, H. van Dam, J. Huizenga, R. Vinke, P. Dendooven, H. Löhner, D. R. Schaart, Monolithic $LaBr_3$:Ce crystals on silicon photo-multiplier arrays for time-of-flight positron emission tomography, Physics in Medicine and Biology 2012, Vol. 57, No. 8, pp. 2219-2233.

[66] R. Gray, A. Macovski, Maximum a posteriori estimation of position in scintillation cameras, IEEE Transaction on nuclear science 1976, Vol. 23, No. 1, pp. 849-852.

[67] W. C. Hunter, H. H. Barret, L. R. Furenlid, Calibration method for ML estimation of 3D interaction position in a thick gamma-ray detector, 2009, IEEE Transaction on Nuclear Science, Vol. 56, No. 1, pp. 189-196.

[68] Z. Li, M. Wedrowski, P. Bruyndonckx, G. Vandersteen, Nonlinear least-squares modeling of 3D interaction position in a monolithic scintillator block, , Physics in Medicine and Biology 2010, Vol. 55, No. 21, pp. 6515-6532.

[69] D. A. B. Bonifacio, M. Moralles, Modeling of 3D gamma interaction position in a monolithic scintillator block with a row-column summing readout, Conference Record of the IEEE Nuclear Science Symposium and Medical Imaging Conference 2012, pp. 2606-2613.

[70] Y. Wang, W. Shu, X. Cheng, D. Li, 3D position estimation using an artificial neural network for a continuous scintillator PET detector, Physics in Medicine and Biology 2013, Vol. 58, No. 5, pp. 1375-1390.

[71] D. J. Herbert, S. Moehrs, N. D'Ascenzo, N. Belcari, A. Del Guerra, F. Morsani, V. Saveliev, The silicon Photomultiplier for application to high resolution Positron Emission Tomography, Nuclear Instruments and Methods in Physics Research Section A 2007, A573(1-2), pp. 84-87.

[72] W. W. Moses, S. E. Derenzo, Design studies for a PET detector module using a PIN photodiode to measure depth of interaction, IEEE Transactions on Nuclear Science 1994 41(4), pp. 1441-1445.

[73] Y. Yang, P. A. Dokhale, R. W. Silverman, K. S. Shah, M.A. McClish, R. Farrell, G. Entine, S. E. Cherry, Depth of interaction resolution measurements for a high resolution PET detector using position sensitive avalanche photodiodes, Physics in Medicine and Biology 2006, Vol. 51, N. 9, pp. 1161-1166.

[74] M. Morrocchi, M.G. Bisogni, G. Ambrosi, M. Ionica, R. Wheadon, C. Marzocca, G. Pirrone, M.A. Piliero, A. Del Guerra, A detector module composed of pixellated crystals coupled to SiPM strips 2014, Jinst, Vol 9, Issue 8, article N. P08007.

[75] M. Morrocchi, G. Ambrosi, M. G. Bisogni, P. Cerello, F. Corsi, M. Ionica, N. Marino, C. Marzocca, F. Pennazio, G. Pirrone, C. Santoni, R. Wheadon, A. Del Guerra, Development of a PET Detector Module with Depth of Interaction Capability, Nuclear Instruments and Methods in Physics Research A 732 (2013), pp. 603-606.

[76] M. C. Maas, D. R. Schaart, D. J. van der Laan, H. T. van Dam, J. Huizenga, J. C. Brouwer, P. Bruyndonckx, C. Lemaître, C. W. E. van Eijk, Signal to Noise Ratio of APD-Based Monolithic Scintillator Detectors for High Resolution PET, IEEE Trans Nucl Sci. 2008; 55(3), pp. 842/852.

[77] C. Woody, A. Kriplani, P. O'Connor, J.-K. Pratte, V. Radeka, S. Rescia, D. Schlyer, S. Shokouhi, S. Stoll, P. Vaska, A. Villaneuva, N. Volkow, B. Yu, RatCAP: A small, head-mounted PET tomograph for imaging the brain of an awake rat, Nuclear Instruments and Methods in Physics Research Section A 2004, Vol. 572, pp. 166-170.

[78] B. Frisch, Combining endoscopic ultrasound with Time-Of-Flight PET: The EndoTOFPET-US Project, Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment 2013, vol. 732, pp. 577-580.

[79] D. Schultz, P. Vaska, Integrating PET with behavioral neuroscience using RatCAP tomography, Reviews in Neurosciences, Vol. 22, Issue 6, pp. 647-655.

[80] N. Aubry et al., EndoTOFPET-US: a novel multimodal tool for endoscopy and positron emission tomography, JINST 2013, Vol. 8, Issue 4, art. N. C04002.

[81] M. Marafini et al., The INSIDE project: innovative solutions for In-Beam dosimetry in hadronteraphy, Proceeding of the II Symposium on positron emission Tomography, Krakow (2014), ACTA PHYSICA POLONICA A, Vol. 127, No. 5, pp. 1465-1467.

[82] L. H. C. Braga, A Fully Digital 8 16 SiPM Array for PET Applications With Per-Pixel TDCs and Real-Time Energy Output, Ieee Journal Of Solid-State Circuits 2014, Vol. 49, No. 1, pp. 301-314.

[83] W. S. Choong and S. E. Holland, Back-Side Readout Silicon Photomultiplier, IEEE Transaction on Electron Devices (2012) vol. 59, Issue 8.