The DRAGO Gamma Camera

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Abstract – **In this work, we present the results of the experimental characterization of the DRAGO gamma camera, a detection system developed for high-spatial resolution gamma-ray imaging. This camera is based on a monolithic array of 77 Silicon Drift Detectors (SDDs), with a total active area of 6.7 cm^2, coupled to a single 5 mm thick CsI(Tl) scintillator crystal. The use of an array of SDDs provides a high quantum efficiency for the detection of the scintillation light together with a very low electronics noise. A very compact detection module based on the use of integrated readout circuits was developed. The performances achieved in gamma-ray imaging using this camera are reported here. When imaging a 0.2 mm collimated ^{57}Co source (122keV) over different points of the active area, a spatial resolution ranging between 0.25mm to 0.5mm was measured. The depth-of-interaction capability of the detector, thanks to the use of a maximum likelihood reconstruction algorithm, was also investigated by imaging a collimated beam tilted to an angle of 45° with respect to the scintillator surface. Finally, the imager was characterized with *in-vivo* measurements on mice, in a real pre-clinical environment.**

I. Introduction

The development of scintillation cameras with millimeter or sub-millimeter spatial resolution is of potential interest for several applications ranging from nuclear medicine, e.g. [1-4], to hard X-ray and γ-ray astronomy, e.g. [5-6]. Research activity has been dedicated both to the study of new scintillators and to the development of new photodetectors. Silicon Drift Detectors (SDDs) have recently shown to be competitive devices for the readout of scintillators [7,8]. With respect to conventional photomultiplier tubes (PMTs), they have a higher quantum efficiency. With respect to both PMTs and Avalanche Photodiodes, they have a low intrinsic electronic noise without the need of multiplication, a process that introduces its own statistical contribution to the overall resolution and is quite sensitive to both temperature and bias shifts.

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A position sensitive detector based on SDDs can be designed according to the Anger Camera principle [9]: a scintillator crystal covers the pixels of the detector and, when a gamma event is detected, the scintillation light is shared among several pixels. The position of interaction is obtained subsequently via a centroid identification algorithm, which provides a spatial resolution much smaller than the pixel size, roughly one order of magnitude. Consequently, this solution allows a significant reduction in the number of readout channels, by a factor of one hundred, when compared with pixellated detectors (e.g. CdTe – Cadmium Telluride - or CZT – Cadmium Zinc Telluride - detectors) providing the same spatial resolution. As a disadvantage with respect to pixellated detectors, on the other side, the energy resolution is usually worsened by the addition of the electronic noise of more units reading the same scintillation event. A first small prototype of an SDD-based Anger camera (1 cm^2 total area) using a 3 mm thick CsI(Tl) scintillator achieved an intrinsic spatial resolution of less than 200 um [10].

In this work, we present the DRAGO (Drift detector Array-based Gamma camera for Oncology) camera, which is a high-resolution Anger camera based on a larger photodetector array and a thicker crystal with respect to the previous prototype. This camera was designed to reach sub-millimeter spatial resolution, with potential applications in the field of small animal imaging and intra-operative probes. In addition, the camera could have an application in hard X-ray astronomy. Thanks to the low sensitivity to magnetic fields of the SDD photodetector [11], the imager could also be operated in integration with an MRI system, for performing simultaneous multi-modality imaging.

The imager is based on a monolithic array of SDDs of 6.7 cm^2 total active area, coupled to a single CsI(Tl) scintillator crystal. The detection system is composed of the detector module, equipped with custom front-end ASICs (Application Specific Integrated Circuits), a data acquisition board and a host PC, where data processing and event reconstruction are implemented with a Maximum Likelihood algorithm.

The architecture of the DRAGO camera is described in the first part of this paper while, in the second part we discuss the imaging performances as well as the Depth-of-Interaction (DOI) capabilities of the imager. Finally, we report few examples of *in-vivo* measurements on mice carried out with the system.

II. The Gamma Camera Architecture

A. The Detection module

The detection module is based on a monolithic array of SDDs made up of 77 hexagonal elements, each one with an area of 8.7 mm^2 (internal diameter of 3.16 mm) and with an on-chip JFET (Junction Field Effect Transistor) [12]. They are arranged in a honeycomb configuration, as can be seen in Fig.1, where the front side of the chip (opposite to the scintillation entrance window) is shown. The chip size is 36×32 mm^2, while the useful field of view for Gamma detection, taking into account also the border effects, related to the position reconstruction algorithm, is approximately restricted to a rectangle connecting the centers of the SDDs at the four corners of the array, i.e. 25×22 mm^2.

Thanks to the availability of two interconnecting layers (polysilicon and aluminum) in the fabrication technology, in the present detector all signal and bias lines have been extracted from the centre of each unit to the external regions of the chip and fed to a series of bonding pads, facilitating the connection to the ceramic carrier. The back-side of the detector consists of a homogeneous entrance window for the radiation, with bonding pads placed at the corners outside the active area in order to couple the scintillator without interfering with the bonding wire. A suitable anti-reflective coating was implemented on the backside, achieving a QE higher than 80% between 400 nm and 650 nm with a peak transmission of 95% at 550 nm.

The DRAGO detection module, whose structure is shown in Fig.2, was designed minimizing the cross section as possible, being limited only by the dimensions of the photodetector chip. It contains the photodetector, the scintillator, the Peltier cooler, the heat sink and two analog front-end electronics boards.

The scintillator was sized to cover the whole SDD chip, with its lateral surfaces well outside the sensitive area of the photodetector. This choice, together with the blackening of the lateral surfaces reduced the effect of light reflections at the borders of the crystal. The crystal has been cut at one corner only, giving space for the electrical bonding of the back contact. On the top side of the scintillator, a diffusive Millipore paper was applied, for improving light collection by the photodetector. The thickness of the crystal, 5 mm, was chosen large enough to provide good detection efficiency (80% at 140keV) and to minimize possible artifacts due to the pattern of the photodetector array. Depending on the depth of interaction of the gamma-rays inside the crystal, the number of SDD units contributing significantly to the reconstruction of a single Gamma event (122keV in our tests with a ^{57}Co source) ranges between 3 and 14.

B. The electronics readout system

The DRAGO electronics readout system is composed of two front-end readout boards (depicted in Fig.2) and a data acquisition (DAQ) system [13]. A scheme of the complete system is shown in Fig.3. The front end electronics is based on a custom designed ASIC [14], whose architecture is reported in Fig.4. The ASIC was processed with the AMS CMOS 0.35 μm technology and contains 8 analog readout channels, so that a total of 10 ASICs is needed for the readout of the whole photodetector array. Each analog channel of the circuit includes a low-noise preamplifier, a 6^{th} order semigaussian shaping amplifier with four selectable peaking times from 1.8 μs up to 6 μs, a peak stretcher and a baseline holder. The 8 analog channels of the chip are multiplexed to a single, differential analog output. A suitable digital section provides self-resetting of the channels, trigger output and the programming of an independent threshold for each analog channel. The ASICs are directly wire bonded on a multi layer PCB, each one hosting 5 ASICs, as shown in Fig.5. Two identical PCBs are connected to the DAQ unit by multi-coaxial cables.

The acquisition system is based on a modular structure, with a “motherboard” and five two-channel ADC boards. Each ADC has a differential input buffer, with level translation functions, and is directly connected to one ASIC chip, so that its task is the A/D conversion of 8 analog channels. The motherboard features a 10:1 digital multiplexer, a 1 Mbit FIFO for buffering and a USB 2.0 link to the host PC. The control signals are provided by three CPLDs (Complex Programmable Logic Devices) and the system is designed to guarantee a burst conversion rate of 50 Ms/s, in order to minimize the dead time. The USB interface, implemented with an integrated microcontroller-transceiver IC, has enough bandwidth to support the event rate required by the application, up to 10.000 counts/s.

Finally, the converted data are sent to a PC, where they are processed using a Maximum Likelihood (ML) reconstruction algorithm to calculate the position of interaction of the gamma ray with the crystal. The ML algorithm determines all three coordinates (X,Y,Z) of the interaction in the scintillator, basing on an optical model of the detector response, obtained using the SCIDRA Monte Carlo simulator [15]. This procedure was adopted with the aim to measure also the Depth-of-Interaction (DOI) of the events in the scintillator which is useful to improve the precision in the determination of the X,Y coordinates and to correct parallax effects when tilted beams (e.g. from pinholes or coded apertures collimators) interact with the scintillator.

III. The Experimental Characterization

A. Laboratory measurements

In order to estimate the electronic noise added by the SDD array, the photodetector without scintillator was directly irradiated with a ^{55}Fe source. The electronic noise was determined from the energy resolution measured for the 5.9keV Ma-Kα line (with a Gaussian fit of the peak), subtracting the Fano contribution. The SDD chip was cooled, as in all other measurements presented in the paper, down to a temperature of -13°C and a peaking time of 6 μs was used. All units showed spectra with homogeneous performances, despite the fact that all the 77 units were biased with same voltage. The map of the distribution of the electronics noise in the array is shown in Fig.6: the average noise is of 13.4 electrons rms, with maximum and minimum values over the full array of, respectively, 16.0 and 11.0 electrons rms.

With the complete Anger camera, i.e. coupling the SDD array to the scintillator and a collimator, gamma-ray measurements were carried out to evaluate the response over the whole active area and to asses the spatial resolution. A 2 mm thick lead disk, shown in Fig.7, was used to collimate a ^{57}Co gamma-ray source (122 keV main emission line) through a pattern of holes toward the gamma imager. A constellation of 36 holes was drilled in the lead, with a spacing of 2 mm between holes and a hole diameter of about 0.4 mm. In Fig.8, the projection of the ^{57}Co source through the collimator holes is shown, superposed to the SDD photodetector layout. The irradiation points appear well distinguished. The image is obtained by raw data without any geometric correction. Some non-linearity effects, still noticeable in the figure, are partially due to misalignments of the points drilled in the collimator, as visible in Fig.7. Moreover, the model of the detector, used by ML reconstruction algorithm, was based on the simulated detector response, which may differ from the actual one and can finally contribute to non-linarity in the reconstructed image. It has to be mentioned that the XY positions were determined by using also the Z information of the interaction point. Usually, the DOI effects on the determination of the XY coordinates are reduced by adding a light guide between the scintillator and the photodetector to spread the scintillation light over several photodetectors. This procedure introduces intrinsically a worsening of the spatial resolution because of the spread of the light distribution. In our case, we succeeded to reconstruct satisfactorily the XY coordinates by taking into account the DOI of the event without the need of adding a light guide.

In order to determine the spatial resolution achievable by the DRAGO imager, a ^{57}Co source (1 mm size) was collimated by tungsten collimators to reach an irradiation spot on the detector of 0.2 mm (the collimator structure was the same adopted in [10]). The collimated source was shifted in four positions corresponding to the corners of a square of 1 mm side. The image, resulting from the superposition of the four irradiation spots, normalized in amplitude, is shown in Fig.9. The points can be well distinguished. The spatial resolution measured with the four points, including the contribution of the collimator, ranges between 0.25 mm and 0.5 mm FWHM, with an average value of 0.35 mm FWHM. The resolution was estimated with a Gaussian fit of the peaks.

The DOI capability of the detector was also investigated by imaging a ^{57}Co source, collimated with a 1 mm pin-hole and tilted by 45° with respect to the scintillator surface. Fig.12 (upper) shows the XY image of the interaction points. The collimated beam was kept parallel to one side of the array (horizontal direction in Fig.1). Fig.12 (upper) shows clearly the expected spread of the irradiation points in the XY map due to the different DOI inside the scintillator. Fig. 12 (lower) shows the corresponding XZ map of the irradiation points. The tilted irradiation beam looks properly reconstructed and indicates that a satisfactory capability of reconstructing the X,Y,Z coordinates of the interaction points was achieved. The width of the measured distribution is dominated by the collimator hole size (1 mm), while the the Z-dependence of intensity follows the DOI probability inside the crystal.

The energy resolution provided by the DRAGO camera was evaluated from the measurements of the constellation of points reported above in this section. The resolution was measured to be 19% FWHM at 122keV and is most likely limited, in the present configuration of the system, by the relatively high threshold for the channels to be considered valid for processing (about 100e-). This threshold is set common to all channels and is kept high to avoid frequent triggers due to external noise. This issue needs to be improved in the future developments of the Gamma Ccamera.

B. *In-vivo measurements on small animals*

After having characterized the DRAGO imager with phantoms and calibration gamma-ray sources, we carried out a set of *in-vivo* measurements, for testing the system in a real experimental environment, at the research laboratories of the Interdepartmental Centre of Molecular and Cellular Imaging (IMAGO) of the University of Milan. In the following, we will show three sets of measurements: the first two have been performed for the purpose of assessing the imaging performances of the DRAGO Gamma Camera and are not directly related to the study of a biological model. On the contrary, the last measurement is part of a cellular imaging study, aimed at a better understanding of dendritic cell migration kinetics in a tumor immunotherapy protocol. The measurements were carried out by using a parallel holes collimator with hexagonal shaped holes, 0.6mm of diameter, 0.15mm septa and 1cm thickness.

The first measurement is a bone-scintigraphy of a mouse, shown in Fig.11. The mouse was injected intravenously with 5 mCi of ^{99m}Tc-MDP, which is expected to concentrate in the regions of the skeletal system where there is an increase in osteoblastic activity. The image, as shown, is bigger than the FOV of the detector and was obtained merging several single images acquired in sequence, for a total duration of 40 minutes, starting 6h after tracer injection. Many anatomical details are clearly distinguishable. Expected improvements of the image quality would be obtained if the detection system would be used in tomographic configuration (SPECT, Single Photon Emission Computed Tomography).

The second measurement was related to the visualization of the early biodistribution phases of neural stem cells injected into the tail vein in a mouse model. Cells were labeled with 30 μCi of ^{111}In-Oxine per 1×10^6 cells and labeling efficiency was 60%, so that a total activity of 18 μCi was injected into the tail vein of each mouse. The image, shown in Fig.12, was taken 30 minutes after injection for 12 minutes and demonstrates that, in the early phases post-injection, stem cells can be detected within the lungs of the animal. As a confirmation, the same image, taken 1 hour later, failed in showing any detectable signal in the same area (data not shown). This measurement is part of a more complex experiment which is beyond the scope of this paper.

Finally, the measurement related to the tumor immunotherapy was based on Dendritic cells (DCs). DCs are antigen-presenting cells that mediate naïve T cell activation against specific antigens and some active anti-neoplastic immunotherapy clinical protocols are based on use of these cells [16]. However, the efficacy of therapeutic vaccination has recently been questioned because of the limited rates of objective tumor regression observed in some clinical studies. Parameters such as injection route, maturation state and amount of antigen loaded onto administered DCs influence the migration of these cells to the lymph nodes and thus their ability to activate an effective cell-mediated immune response [17-21]. Through cellular imaging we may arrive at an in-depth understanding of the fundamental aspects of tumor immunotherapy and refine therapeutic strategies in humans.

To the purpose of the study, bone marrow DCs were *in vitro* activated and labeled with 30 μCi of ^{111}In-Oxine per 1x 10^6 cells. The labeling efficiency was of about 80% and DC viability was not affected by the labeling procedures, as evaluated by standard Trypan Blue Exclusion Test (data not shown). Two million of DCs were injected into the distal portion of the anterior limb of MMTV-hRas tumor bearing mice, homolateral to the neoplastic lesion.

Migration of DCs to the draining lymph nodes (Fig.13) was observed 4 hours after cell injection and signal remained detectable for the entire observation time, correlating with the anatomical position of the accessory and proper axillary lymph nodes as confirmed by *ex vivo* analysis of the collected organs with a gamma counter, demonstrating presence of radioactivity only in the nodes homolateral to the injection side.

IV. Conclusions

In this work, we have presented the DRAGO gamma camera and the results of its experimental characterization. The DRAGO camera achieves a spatial resolution of 0.35mm FWHM, and uniform imaging capabilities over its field-of-view. DOI capability has been also experimentally verified. First *in-vivo* measurements on small animals have been also carried out successfully. The detector is now ready for applications in the field of nuclear imaging as well as for hard-X astronomy.

A new large FOV camera ($10\times10cm^2$) based on SDDs $1cm^2$ each is also under development for human imaging in the framework of the HICAM project [22].

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