A large area CMOS Active Pixel Sensor for imaging in proton therapy

M. Esposito,¹, T. Price,¹ S. Manger,¹ C. Waltham,¹ T. Anaxagoras,¹ D. J. Parker,¹ J. Nieto-Camero and N.M. Allinson

¹Laboratory of Vision Engineering, University of Lincoln, Lincoln, LN6 7TS, U.K.
²School of Physics and Astronomy, University of Birmingham, Birmingham, B15 2TT, U.K.
³Department of Physics, University of Warwick, Coventry CV4 7AL, U.K.
⁴ISDI Ltd (Image Sensor Design and Innovation), London NW5 2QL, U.K.
⁵iThemba LABS, Somerset West, South Africa

E-mail: m.esposito@physics.org

ABSTRACT: There is an increased interest in developing imaging systems in proton therapy, with the aim of reducing range uncertainty in treatment planning, assisting in patient positioning and verifying anatomical changes at the time of the treatment. Recently, the PRAVDA collaboration has developed two different solid-state detector technologies for imaging in proton therapy: Silicon Strip Detectors and CMOS Active Pixel Sensors (APSs). This paper reports on the design and optimisation process of the PRAVDA CMOS APSs. Optimisation of parameters, such as epitaxial thickness and resistivity, and performance for individual proton detection and proton radiography are reported.

KEYWORDS: Instrumentation for hadron therapy; Solid state detectors
1 Introduction

The potential benefits of proton Computed Tomography (pCT) and proton radiography (pRG) to reduce range uncertainty in treatment planning, as well as assisting patient positioning and verifying anatomical changes at the time of treatment [1, 2], have driven a world-wide interest in the development of instrumentation for imaging in proton therapy. Several pCT and pRG prototypes have been developed over the last decade, based on a number of different technologies, including Silicon Strip Detectors (SSDs) [3–5], scintillating fibres [6–9], scintillator-based calorimeters [3–8, 10] and CMOS Active Pixel Sensors (APSs) [11–13]. In this scenario, the PRaVDA collaboration was formed to develop a novel instrument for proton imaging and associated reconstruction algorithms.

The PRaVDA pCT system [14], currently entirely based on Silicon Strip Detectors (SSDs), features two trackers (four sets of $x$-$u$-$v$ SSDs) to measure proton trajectories before and after the patient [15, 16], and a mono-dimensional SSD-based energy-Range Telescope (RT) working as a range counter, to infer the residual proton energy from their range.

Although the final choice for the PRaVDA prototype was SSDs, two different solid-state technologies were developed during the course of this project to be potentially used as a range detector: SSDs and CMOS APSs. APSs and SSDs, as position sensitive detectors, allow for many protons to be reconstructed per frame time, unlike calorimeters or scintillator stack designs, which require only one proton per scintillator element during a readout cycle. Both these technologies offer a number of pros and cons when used as an energy detector for pCT.
While SSDs, measuring 1-D coordinates in each layer, need reconstruction across multiple layers to obtain a 2-D hit position [15], CMOS imagers, being pixelated, have the advantage of providing 2-D coordinates at each detection plane. CMOS imagers, benefiting from advances in lithographic processes and high levels of integration [17], can now be built over large areas (12-inches wafers) by reticule stitching [18, 19]. Larger imaging areas needed in pCT and pRG (i.e. 30×30 cm$^2$ for a head pCT scan) can be easily achieved by mosaic tiling of edge-less CMOS sensors, unlike SSDs. On the other side, SSDs can be designed to sustain radiation damage in very demanding environments (e.g. high luminosity colliders), while CMOS imagers, with appropriate design choices [20–22], can offer a moderate radiation hardness in the clinical environment. Different readout speeds can also be envisaged for these two technologies. In fact, SSD can be readout at MHz frequency while readout speed for large area CMOS imagers tends to be orders of magnitude lower. A low readout speed for CMOS sensors, together with the need to keep pCT scan time at clinically feasible lengths, makes the need for track reconstruction across the RT at high occupancy.

Previous works within the PRaVDA collaboration have demonstrated the capability of CMOS imagers to be used as energy-range detectors for pCT, with respect to individual proton imaging [23], and capability of $dE/dx$ measurements at energies relevant for clinical pCT [24]. A further proof of concept has been provided in [25], demonstrating the capability of detecting correlated events in a stack of two CMOS imagers, a condition necessary to perform track reconstruction across a CMOS RT. Additionally, several other authors have demonstrate the capability for CMOS APSs to be used for (pRG) [11] and pCT [12, 13].

This paper reports on the development of a large area CMOS APS for pCT and, more generally, for imaging in proton therapy. Optimisation of design parameters, such as epitaxial layer and resistivity, as well as performance in individual proton imaging and proton radiography are reported.

2 The PRaVDA CMOS Active Pixel Sensor

The PRaVDA CMOS APS has been manufactured in a 0.18μm commercial CMOS process using reticule stitching technique [18, 26]. Each sensor offers an imaging area of approximately 5×10 cm$^2$ with a 198 μm pixel pitch and it is two-side buttable to allow larger imaging areas. For the PRaVDA experiments, two sensors were tiled together to offer an imaging area of approximately 10×10 cm$^2$, and a synchronised rolling shutter readout of both sensors was implemented.

Each pixel of the PRaVDA sensor is fitted with 5 diodes: 4 placed at the corner of pixel and one in the middle to improve charge collection efficiency (see figure 1(a)). A conventional readout architecture, shown in figure 1(b), is adopted for this sensor. Pixel values are addressed row-wise via a vertical decoder, enabled by a shift register. For each addressed row, pixel values are sampled along Sample and Hold column stages. Analog pixel values are then converted into the digital domain by an internal single-slope column-parallel Analog to Digital Converters (ADCs) programmable over the range 8–16 bits, loaded onto shift registers and finally clocked out through a number of CMOS digital lines.

Full frame readout of the full imaging area (10×10 cm$^2$) can reach 1000 fps (11-bit readout, ADCs clocked at 100 MHz), while higher bit resolution or slower ADC settings lead to lower frame rates, although offering a reduced noise level. A faster readout is achievable when reading out only a fraction of the imaging area (Region of Interest mode).
During the development phase of the PRaVDA sensors, three combinations of epitaxial layer thickness and resistivity were tested in order to reach an optimal trade-off in terms of charge collection efficiency and cluster size, and ultimately image quality.

Specification parameters for the three sensors tested are reported in Table 1, including epitaxial thickness, resistivity and charge carrier lifetime (for both epitaxial layer and substrate). Values of resistivity and carrier lifetime are provided by the foundry. The former results from doping concentration specified in the CMOS process used, while the latter is derived from the Technology Computer Aided Design (TCAD) simulations.

**Table 1.** Epitaxial thickness, resistivity and minority charge carrier lifetime, for the epitaxial layer (epi) and substrate, for each of three sensors under testing. Resistivity and carrier lifetime values are both provided by the foundry. The former derives from the particular process specification (doping level) used for each sensor, while the latter results from TCAD simulations of the electrical properties of the these sensors.

| Sensor ID | Epi thickness (µm) | Resistivity (epi) (Ohm cm) | Carrier lifetime (epi) (µs) | Resistivity (substrate) (Ohm cm) | Carrier lifetime (substrate) (µs) |
|-----------|-------------------|---------------------------|-----------------------------|----------------------------------|----------------------------------|
| W1        | 16.5              | 8                         | 5                           | 0.015                            | 0.048                            |
| W3        | 14                | 500                       | 8                           | 0.015                            | 0.048                            |
| W5        | 24                | 1000                      | 9                           | 0.015                            | 0.048                            |
2.1 Electro-optical performance

Standard electro-optical characterisation for the three sensors reported in table 1 was performed following the EMVA 1288 standard [27]. Mean-variance and linearity curves are shown in figure 2(a) and (b), respectively.

Noise, conversion gain and Full Well Capacity (FWC) were calculated from the mean-variance curves of figure 2(a) and are reported in table 2. Quantum Efficiency (QE) to green light (523 nm) is calculated from the linearity curves of figure 2(b), after conversion of signal value from Digital Numbers (DN) to $e^{-}$ through the previously measured conversion gain, and is reported in table 2 for the three sensors.

![Figure 2. (a) Mean-variance curve and linearity curve (b) obtained following the EMVA 1288 standard for the three sensor under investigation (W1, W3 and W5 in table 1).](image)

Electro-optical parameters reported in table 2 suggest similar performance of the three sensors in terms of noise, gain and FWC. However, the W1 sensor appears to have a significantly lower QE (24%) compared to the other two sensors (51% for W3 and 59% for W5). This difference can be explained by accounting for the lower resistivity of the epitaxial layer reported for the sensor W1 in table 1. Sensor W1 is excluded from further tests, due to its low QE.

2.2 The DynAMITe detector

A CMOS Active Pixel Sensor, named DynAMITe, whose performance for proton imaging has been extensively studied both with experimental data [23–25] and simulations [29], has been used to compare the response of the PRaVDA CMOS sensors for individual proton imaging. Details of the sensor architecture, electro-optical performance and radiation hardness are reported elsewhere [19, 22, 28]. Electro-optical performance parameters for this sensor are reported in table 2, for comparison with the PRaVDA CMOS APSs. For the purposes of this work, note that the 50 µm pixel resolution was used and detector was readout in ROI mode, to allow for faster readout. Epitaxial layer for this sensor is 12 µm.
Table 2. Electro-optical performance parameters measured for the three different sensors evaluated (W1, W3, W5) and for the DynAMiTe detector.

| Sensor ID | Gain e^-/DN | Read noise e^- | QE % | FWC e^- |
|-----------|-------------|----------------|------|---------|
| W1        | 76.9        | 138.2          | 24.0 | 8.2×10^4 |
| W3        | 72.6        | 129.6          | 51.2 | 7.5×10^4 |
| W5        | 79.8        | 141.9          | 59.3 | 8.7×10^4 |
| DynAMiTe [19, 28] | 50 | 150 | 45 | 2.8×10^5 |

3 Experiments

3.1 Proton irradiation

Sensors W3 and W5 were irradiated with 29 MeV protons at the MC40 cyclotron, University of Birmingham. A Region-Of-Interest (ROI) comprising 54 rows was chosen for both sensors and readout at 692 fps with a 14 bit readout. A beam current of 5 pA was used to avoid pile-up events.

Images acquired for this experiment were dark-corrected by subtraction of the average of a number of dark frames, and, subsequently, thresholded with respect to a reference value equal to three times the noise level. A clustering algorithm was used to account for single hit events spread over multiple pixels.

Signal spectra for sensors W3 and W5 were measured, as sum of the signal generated in each pixel of a cluster. Cluster size distribution was also evaluated.

To compare the detection performance of sensors W3 and W5 with the DynAMiTe APS, whose response to individual protons is used here as benchmark, sensors were exposed to protons over a range of energies (6–29 MeV). The pristine 29 MeV was degraded to lower energies by insertion of PMMA absorbers at the beam nozzle. Same experimental and image processing procedures as described previously were used. It is to note, however, that a small ROI (10 rows) was used for the DynAMiTe detector, given the lower readout speed. Most Probable Signal and average cluster size were assessed from this experiment.

3.2 Radiographs

Sensor W3 was used to produce proton radiography images at iThemba LABS (South-Africa) with 60 MeV protons, the average energy expected after the patient in proton CT and radiography.

A patient collimator (see figure 5(a)) was used to assess the capability of the sensor to image complex shapes, in a clinical scenario. The collimator was made of a 6-cm thick brass ring with a 12 cm diameter, and an inner part made of of a 3-cm thick Cerrobend alloy with an internal diameter of 7.5 cm, shaped to match anatomical features. The collimator was placed at the beam nozzle and the sensor at the iso-centre in the proton therapy vault. A full frame readout (95 fps) was used for this experiment.

An imaging phantom was also used to assess the imaging capability of the sensor W3. The imaging phantom features a stepped region, different-size holes as well as different-thickness holes. Phantom specifications are schematically shown in figure 5(b). The phantom was placed in close contact with the detector, and both positioned at the patient position in the proton therapy setting.
4 Results

4.1 Individual proton detection

Normalised signal spectra, in units of DN, measured for the W3 and W5 sensors, exposed to 29 MeV protons, are shown in figure 3(a). For both sensors spectra resemble spread-out Landau energy-loss curves [30], with the addition of low-signal noise which could be either due to external noise sources (e.g. secondary particles) or to “split events”, i.e. hits which fall partially outside the small readout ROI (54 rows). Low-energy tails have been excluded from subsequent analysis by applying a threshold at 100 DN. Mean detected signal is 364 DN for W3 and 551 DN for W5, suggesting a different QE and Charge Collection Efficiency (CCE) for the two sensors.

Cluster size distributions are shown for both sensors in figure 3(b). Mean cluster size is 3.3 pixel for sensor W3 and 9.1 pixel for sensor W5.

![Figure 3. (a) Normalised signal spectra for the sensors W3 and W5 exposed to 29 MeV protons. (b) Cluster size distributions for sensors W3 and W5 for individual events generated by 29 MeV protons.](image)

4.2 Comparison with the DynAMITe detector

The response of the PRaVDA sensors W3 and W5 and the DynAMITe detector to protons in the energy range 6–29 MeV is reported in figure 4. Figure 4(a) shows the Most Probable Signal, obtained from Landau fitting of the signal spectra and converted in unit of e⁻, was plotted as function of proton energy for the three sensors under study. While the response of sensor W3 and DynAMITe is comparable, sensor W5 shows a much increased signal for the lowest energy.

Figure 4(b) shows average cluster size as a function of beam energy. While W3 and DynAMITe exhibits a comparable cluster size (in terms of number of pixels), W5 shows larger clusters.

Differences in the response of the three sensors will be discussed in section 5.
Figure 4. Most probable signal (a) and average cluster size (b). Average cluster size for the PRaVDA sensors W3 and W5 and the DynAMITe detector as a function of proton energy.

4.3 Planar imaging

Radiography of a patient collimator is shown in figure 5(a), together with the collimator used and described in section 3. The complex shape of the collimator appears to be correctly reproduced. In figure 5(b), a radiography of the imaging phantom described in section 3 shows the main features of the phantom (stepped regions, holes) as well as the ‘halo’ effect due to Multiple Coulomb Scattering and discussed in [23].

Although both radiographs show the potential for the PRaVDA sensor W3 to be used for proton radiography, some artefacts such as a horizontal misalignment between the two sensor halves tiled together, a row at the tiling position and a different responsivity of both sensor halves are evident. This makes the need for further image correction techniques for this sensor to be used in proton radiography.

5 Discussion

Three sensors (W1, W3 and W5) were designed and manufactured by the PRaVDA collaboration with different epitaxial thickness and resistivity (see table 1), with the aim to find the optimal specifications for individual proton imaging. After optical characterisation, one sensor (W1) was excluded from further studies due to a low QE, while the other two sensors appeared to show electro-optical performance comparable with the required specifications.

Although both sensors W3 and W5 showed capabilities of individual proton imaging (see figure 3), some important differences in terms of signal spectra and cluster size were found.

Deposited charge, collected charge and Charge Collection Efficiency (CCE) and average cluster size for 29 MeV protons (W3 and W5) and 27.3 MeV protons (DynAMITe) are reported in table 3, together with other relevant design parameters such as epitaxial thickness and pixel pitch. Deposited charge was calculated using the NIST PSTAR reference database [31], collected charge corresponds
Figure 5. Radiography of a patient collimator (a) and of an imaging phantom (b) obtained with the W3 sensor. A photograph of the patient collimator is shown as well as a sketch plan of the imaging phantom, featuring a stepped region, different-size holes as well as different-thickness holes.

CCE is comparable for DynAMiTe and W5 ($\approx 90\%$), while sensor W3 shows a CCE $> 1$ suggesting than more charge than that deposited in the epitaxial layer is collected, likely due to charge collection from the substrate. Charge collection from the substrate depends on substrate resistivity and thus minority charge carrier lifetime, which is comparable for W3 and Dynamite ($\approx 0.048 \, \mu s$). Charge collection from the substrate also depends on the doping profile across the wafer, i.e. how sharp is the transition from the high doping region of the substrate to the low doping
Table 3. Deposited and collected charge, CCE and mean cluster size for sensors W3 and W5 (29 MeV protons) and DynAMiTe (27.3 MeV protons). Design parameters such as epitaxial layer thickness and pixel pitch are also reported for comparison.

| Sensor     | Epi thickness (µm) | Pixel pitch (µm) | Deposited charge (e⁻) | Collected charge (e⁻) | CCE (%) | Mean cluster size (pixel) |
|------------|--------------------|------------------|------------------------|-----------------------|---------|--------------------------|
| W3         | 14                 | 198              | 1.3×10⁴                | 1.4×10⁴               | 107     | 3.3                      |
| W5         | 24                 | 198              | 2.3×10⁴                | 2.1×10⁴               | 92      | 9.1                      |
| DynAMiTe   | 12                 | 50               | 1.1×10⁴                | 1.0×10⁴               | 90      | 2.9                      |

region of the epitaxial. However, it is worth nothing that a moderate degree of charge collection from the substrate does not represent an issue for proton imaging, while it would be for other applications (e.g. X-ray imaging) due to the different nature of the interaction.

Cluster size provides information on charge sharing. Mean cluster size for DynAMiTe and W3 (≈ 3 pixel) is comparable, although DynAMiTe has a smaller pitch (50 µm) than W3 (198 µm) effectively resulting in larger clusters. However, given the similar pixel design for the two sensors (i.e. diodes placed at the pixel corners), the similar number of pixels suggests that energy deposited in a single pixel is then shared by nearby diodes of adjacent pixels. For W5, on the other hand, the cluster size is larger (9.1 pixel) and this can be related to a higher degree of charge diffusion in the thicker epitaxial (24 µm) resulting in a larger charge spread before collection, and a longer charge carrier lifetime due to the higher resistivity (1000 Ohm cm) allowing for charge spread at larger distance from the diodes to be collected.

The large cluster size measured for W5 can limit detection performance for individual proton imaging. In fact, such large clusters, expected to become even larger at lower energies, entail pile-up issues. For this reason, only sensor W3 has been included in further testing related to planar integrated imaging.

Planar imaging showed the capability for the PRaVDA APS to be used for proton radiography, although image correction algorithms need to be employed to reduce variation in response between the two sensor halves as well as correcting for artefacts showing at the interfaces between the two halves.

6 Conclusions

A novel high-speed large-area CMOS APS for imaging in proton therapy has been presented together with initial results. The PRaVDA CMOS sensor is the first prototype offering a large imaging area (5×10 cm²) with a fast readout (kHz) The optimisation of such sensors, in terms of modifying epitaxial thickness and resistivity, has been discussed and comparative results provided. Though the radiation hardness of conventional CMOS sensors will always be lower than SSDs, they can through careful design and fabrication still provide a long and economical viable operating life [22]. Though operating speeds are several magnitudes lower than for SSDs, their pixel-based architectures permit much higher number of detected protons per readout cycle. Coupled with the ease of recovering accurate event locations, APS are a practicable sensor for future instrument designs.
Acknowledgments

The authors wish to thank aSpect Systems GmbH and ISDI Limited for their support and development of the PRaVDA system. The authors further acknowledge the support and insight of the whole PRaVDA team. This work was supported by the Wellcome Trust Translation Award Scheme, grant number 098285.

References

[1] G. Poludniowski, N.M. Allinson and P.M. Evans, Proton computed tomography reconstruction using a backprojection-then-filtering approach, *Phys. Med. Biol.* **59** (2014) 7905.

[2] R.P. Johnson, Review of medical radiography and tomography with proton beams, *Rep. Prog. Phys.* **81** (2018) 016701.

[3] R.P. Johnson et al., A fast experimental scanner for proton ct: Technical performance and first experience with phantom scans, *IEEE Trans. Nucl. Sci.* **63** (2016) 52.

[4] M. Scaringella et al., The prima (proton imaging) collaboration: Development of a proton computed tomography apparatus, *Nucl. Instrum. Meth. A* **730** (2013) 178.

[5] Y. Saraya, T. Izumikawa, J. Goto, T. Kawasaki and T. Kimura, Study of spatial resolution of proton computed tomography using a silicon strip detector, *Nucl. Instrum. Meth. A* **735** (2014) 485.

[6] M. Naimuddin et al., Development of a proton computed tomography detector system, *2016 JINST 11 C02012*.

[7] P. Pemler et al., A detector system for proton radiography on the gantry of the paul-scherrer-institute, *Nucl. Instrum. Meth. A* **432** (1999) 483.

[8] D. Lo Presti et al., Design and characterisation of a real time proton and carbon ion radiography system based on scintillating optical fibres, *Phys. Med.* **32** (2017) 1124.

[9] S. Uwe, P. Peter, B. Jürgen, P. Eros, L. Antony and K. Barbara, Patient specific optimization of the relation between ct-hounsfield units and proton stopping power with proton radiography, *Med. Phys.* **32** 195.

[10] P. Giubilato et al., impact: Innovative pct scanner, *IEEE Nucl. Sci. Symp. Med. Imag. Conf. (NS'15/MIC)* **2015** (2015) 1.

[11] P.J. Doolan, G. Royle, A. Gibson, H.-M. Lu, D. Prieels and E.H. Bentefour, Dose ratio proton radiography using the proximal side of the bragg peak, *Med. Phys.* **42** (2015) 1871.

[12] H. Pettersen et al., Proton tracking in a high-granularity digital tracking calorimeter for proton ct purposes, *Nucl. Instrum. Meth. A* **860** (2017) 51.

[13] S. Mattiazzo et al., impact: An innovative tracker and calorimeter for proton computed tomography, *IEEE Trans. Radiat. Plasma Med. Sci.* (2018) 1.

[14] M. Esposito et al., Pravda: The first solid-state system for proton computed tomography, *Phys. Med.* submitted.

[15] J. Taylor et al., Proton tracking for medical imaging and dosimetry, *2015 JINST 10 C02015*.

[16] J. Taylor et al., A new silicon tracker for proton imaging and dosimetry, *Nucl. Instrum. Meth. A* **831** (2016) 362.

[17] Y. Lo, Solid state image sensor: technologies and applications, *Proc. SPIE* **3422** (1998) 70.
[18] R. Turchetta, N. Guerrini and I. Sedgwick, Large area CMOS image sensors, 2011 JINST 6 C01099.
[19] M. Esposito et al., Performance of a novel wafer scale cmos active pixel sensor for bio-medical imaging, Phys. Med. Biol. 59 (2014) 3533.
[20] R. Lacoe, J. Osborn, R. Koga, S. Brown and D.C. Mayer, Application of hardness-by-design methodology to radiation-tolerant ASIC technologies, IEEE Trans. Nucl. Sci. 47 (2000) 2334.
[21] B. Pain et al., Hardening CMOS imagers: radhard-by-design or radhard-by-foundry, Proc. SPIE 5167 (2004) 101.
[22] M. Esposito, T. Anaxagoras, O. Diaz, K. Wells and N.M. Allinson, Radiation hardness of a large area cmos active pixel sensor for bio-medical applications, IEEE Nucl. Sci. Symp. Med. Imag. Conf. (NSS/MIC) 2012 (2012) 1300.
[23] G. Poludniowski et al., Proton-counting radiography for protontherapy: a proof of principle using CMOS APS technology, Phys. Med. Biol. 59 (2014) 2569.
[24] T. Price et al., Expected proton signal sizes in the pravda range telescope for proton computed tomography, 2015 JINST 10 P05013.
[25] M. Esposito et al., Cmos active pixel sensors as energy-range detectors for proton computed tomography, 2015 JINST 10 C06001.
[26] D. Scheffer, A Wafer scale active pixel CMOS image sensor for generic X-ray radiology, Proc. SPIE 6510 (2007) 65100O.
[27] EMVA, European machine vision association standard 1288 standard for characterization and presentation of specification data for image sensors and cameras, (2005).
[28] M. Esposito et al., Dynamite: a wafer scale sensor for biomedical applications, 2011 JINST 6 C12064.
[29] M. Esposito, T. Price, T. Anaxagoras and N. Allinson, Geant4-based simulations of charge collection in cmos active pixel sensors, 2017 JINST 12 P03028.
[30] C. Leroy and P. Rancoita, Principles of Radiation Interaction in Matter and Detection, World Scientific, New York U.S.A. (2004).
[31] M. Berger, J. Coursey, M. Zucker and J. Chang, Stopping-Power and Range Tables for Electrons, Protons, and Helium Ions, National Institute of Standards and Technology, Gaithersburg U.S.A.