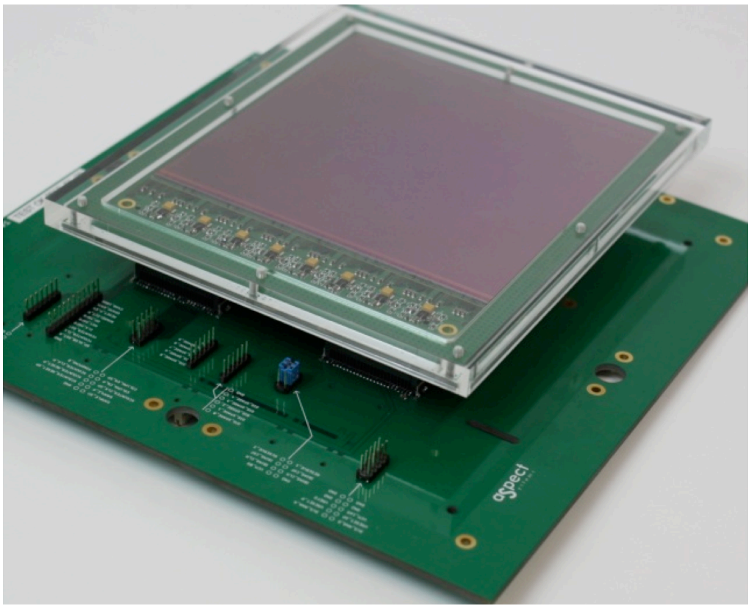
Institution: University of Lincoln

Unit of Assessment: UoA 11 – Computer Science and Informatics

Title of case study: Giving Medicine a Better Image with Wafer-scale CMOS Imagers

1. Summary of the impact



Development of the World's first radiation-tolerant, wafer-scale (13 cm square) CMOS imager (Active Pixel Sensor) which presents exciting new potential for medical, scientific and technological imaging with much improved performance and lower life-time costs. This development fully met a Grand Challenge set by EPSRC and the imager, called *Dynamite*, is being exploited in on-going trials for prostate cancer radiotherapy at the Royal Marsden Hospital/ICR and for diffraction-enhanced mammography at UCL/Ninewells Hospital, Dundee, and proton therapy imaging with Wellcome Trust support. *Dynamite* won the IET Innovation Award for Electronics (2012). A spinout company, ISDI Ltd, was formed in 2010 to further custom CMOS imager design and provision. [text removed for publication]

This case study demonstrates both major societal (healthcare) and economic impact through making commercially available new and revolutionary medical diagnostic and therapeutic imaging technology, being delivered directly a new start-up company. It also exemplifiers the entire entrepreneurial pipeline from RC-UK Basic Technology funding to successful company creation.

2. Underpinning research

Dynamite is the result of a long-term programme of research on the design and realisation of solid-state imagers by Professor Allinson and his team. Dr Thalis Anaxagoras was initially a RS and then Research Assistant within Allinson's group, and has over 10 years experience of CMOS design. The specific challenges for radiation-tolerant (necessary because most medical imaging uses high-energy x-rays) and wafer-scale (one device per 200 mm (8") wafer) is to translate design methods for radiation-hardness into a practical, commercial process and ensure very high yield of fully-functional wafers.

Our first major programme on CMOS Imagers was funded by a £4.4m Basic Technology grant, MI-3, led by Allinson, (2004 – 2009, University of Sheffield). The MI-3 consortium of 11 partners (STFC, UCL, Liverpool (x2), Glasgow, Brunel/Open University, York, Sheffield, ICR, MRC drove the development of Active Pixel sensors for scientific, medical and security applications. Six new CMOS imagers were developed including the 58 mm square Large Area Sensor (LAS). An EPSRC-funded translation grant, MI-3 Plus, was commenced in 2009 and completed in 2013. Its aim was to produce one device per wafer (wafer-scale) imagers for primarily medical applications (both diagnostic and therapeutic). MI-3 Plus was originally held at the University of Sheffield but transferred to University of Lincoln in Jan 2011 (on Prof. Allinson taking up the position of Distinguished Chair of Image Engineering). At the same time, all associated IP, including UK Patent, and commercialisation rights were transferred to Lincoln.

Initial top-level design work for *Dynamite* was commenced prior to the award of the Translation Grant; it was submitted to foundry in November 2010 and first processed wafers received during April 2011 with first-light tests performed 10 May 2011. All characterisation, demonstrator studies and commercialisation have been undertaken during the University of Lincoln's tenure. The key staff involved at Lincoln were Prof. Allinson and Dr Anaxagoras (PDRA, who now runs ISDI Ltd since Jan 2013 while retaining a 0.5 FTE research-only academic post at Lincoln). Other partners are Prof. Evans (Co-I) and Dr Osmond (PDRA) (Institute of Cancer Research, now University of Surrey); Prof Speller (Co-I) and Dr Konstantinidis (PDRA) (UCL) and Dr Wells (Co-I) and M Esposito (RA) (University of Surrey).

Over the period of two major RC-UK grants (MI-3 and MI-3 Plus), some 60 individuals have been involved in progressing the design, characterisation and application of our CMOS imagers. Through this programme, we possess in the UK a leading capability to produce advanced imagers for diverse applications. Original work includes architectures for ultra-low noise, full 2D stitching for large area sensors, radiation-hard operation (tested up to 8 MRad radiation), minimal butting loss for imager mosaics, multiple independent camera operation in a single device, dual resolution in a single device, etc.

Dynamite is not only one of the largest integrated circuits ever fabricated, it is probably one of the most complex imaging devices – incorporating 4 separate cameras with 2 different spatial resolutions in one device with a wealth of readout modes including non-destructive (allowing virtually noiseless operation) and minimal butting loss along 2-sides to permit a seamless 26 cm x 26 cm imaging area. Very large imagers are essential in medical imaging because of not only the human scale but because the focussing of x-rays is essentially infeasible (so only 1:1 imaging is possible). Current medical imaging for x-ray CT and fluoroscopy (chief applications for all healthcare imaging) use amorphous silicon screens, which are lacking in sensitivity and speed. For these and other reasons, the development of large imaging arrays for use in medical applications and imaging of explosives and weapons was set as a challenge in EPSRC's *Grand Challenges in Silicon Technology* (2008).

Prior to the realization of *Dynamite*, wafer-scale CMOS imagers had been demonstrated by Dalsa, Inc (2009) and Canon, Inc (2010). Neither realization was radiation-hard nor exhibited the multi-resolution, partial readout and low noise capabilities of Dynamite. Yole Développement, a leading market research and technology analysis company, predicts the medical image sensor market to grow by 9% compound annual growth for 2012-17 to an expected global value of US$112m, with CMOS imagers replacing amorphous flat panels for most x-ray imaging needs.

3. References to the research

Papers 1 – 7 refer to earlier work on CMOS and CCD imagers and imaging systems; papers 8 – 11 refer to the *Dynamite* sensor and in particular its application.

1. T Anaxagoras, P Kent, N Allinson, R Turchetta, T Pickering, D Maneuski, A Blue and V O'Shea (2010), *eLeNA: A Parametric CMOS Active Pixel Sensor for the evaluation of reset noise reduction architectures*, IEEE Trans. on Electron Devices **57**, 2163 - 2175
2. H M Zin, Anastasios, C Konstantinidis, E J Harris, J P F Osmond, A Olivo, S E Bohndiek, A T Clark, R Turchetta, N Guerrini, J Crooks, N M Allinson, R Speller and P M Evans (2010), *Characterisation of regional variations in a stitched CMOS active pixel sensor*, Nuclear Instruments and Methods in Physics Research A **620**, 540-48
3. N. Allinson and 48 others, (2009), *The Multidimensional Integrated Intelligent Imaging project (MI-3)*, Nuclear Instruments and Methods, **604**, 196-198
4. B Pokric, N M Allinson, A J Ryan, P Fairclough, B R Dobson, G E Derbyshire, W Helsby, P G Long and K Moon (2002), *A double area detector system for simultaneous small and wide-angle x-ray scattering*, Nuclear Instruments and Methods in Physics Research A **477**, 329-334
5. M Pokric, N M Allinson, A R Jorden, M P Cox, A Marshall, P G Long, K Moon, P Jerram, P Pool, C Nave, G E Derbyshire and J R Helliwell (2002), *Large area high-resolution CCD-base x-ray detector for macromolecular crystallography*, Nuclear Instruments and Methods in Physics Research A **477**, 166 –171
6. M Pokric and N M.Allinson (2002), *Testing of gadolinium oxy-sulphide phosphors for use in CCD-based x-ray detectors for macromolecular crystallography*, Nuclear Instruments and Methods in Physics Research A **477**, 353 –359
7. J P F Osmond, H M Zin, E J Harris, G Lupica, N M Allinson, and P M Evans (2011*), Imaging of moving fiducial markers during radiotherapy using a fast, efficient active pixel sensor based*

EPID, Med. Phys. **38**, 6152 – 60

8. M Esposito, T Anaxagoras, A Fant, K Wells, A Konstantinidis, J P F Osmond, P M Evans, R D Speller, and N M Allinson (2011), *DynAMITe: a wafer scale sensor for biomedical applications*, J Instrumentation, **6**,

9. M Esposito, J Newcombe;, T Anaxagoras, N M Allinson, and K Wells (2012), *Using a large area CMOS APS for direct chemiluminescence detection in Western blotting electrophoresis*, Proc. SPIE (Medical Imaging 2012: Biomedical Applications in Molecular, Structural, and Functional Imaging) **8317**,

10. A Konstantinidis, T Anaxagoras, M Esposito, N Allinson, and R Speller (2012), *DynAMITe: a prototype large area CMOS APS for breast cancer diagnosis using x-ray diffraction measurements*, Proc. SPIE (Medical Imaging 2012: Physics of Medical Imaging), **8313**,

11. M Esposito, T Anaxagoras, J Larner, N M Allinson, and K Wells (2013), *^{14}C autoradiography with a novel wafer scale CMOS Active Pixel Sensor*, J Instrumentation, **8**,

All papers are obtainable from eprints.lincoln.ac.uk

Grant support for this programme of work included:

EPSRC – ***Basic Technology: M-I3 - Multidimensional Integrated Intelligent Imaging*** **(**GR/S85733/01) – Sept 2004 – Feb 2009 – £4,412k (University of Sheffield)

EPSRC – ***Ultimate Microscopy: Wavelength-Limited Resolution Without High Quality Lenses*** **(**EP/E034055/1) – Sept 2007 – March 2012 – £4,310k (Partner with responsibility to develop new CMOS imagers for electron microscopy) (University of Sheffield)

EPSRC – ***MI-3 Plus*** **(**EP/G037671/1 and /2) – Aug 2009 - Jan 2013 – £1,194k (University of Sheffield, transferred to University of Lincoln).

4. Details of the impact

The workhorse for x-ray medical imaging is the amorphous (am-Si) flat panel which are available in sizes up to 40 cm square – they are relatively slow, possess high readout noise and image smearing. Imaging using superior CMOS devices has long been an aspiration by the medical community. Three factors have held back their employment – relatively small size of CMOS devices (above 2 cm x 3 cm requires the 2D stitching in the photolithographic masking process), ease of damage by ionising radiation (diagnostic x-rays are 30 keV – 160 keV, while therapeutic applications require 1 MeV and higher), and higher cost. Through developing *Dynamite*, based on our extensive experience with CMOS imager design, we were able to translate the radiation-hard design concepts developed for relatively small CMOS devices by the space and high energy physics communities into a full wafer-scale and commercially attractive device. Working closely with our chosen silicon foundry, we were able to optimise the 2D stitching process as well as our unique pixel structure. Though *Dynamite* is a complex chip, with four independent cameras at two different spatial resolutions and very flexible readout capabilities, we designed for high yield and flexible operation. The noise floor is approximately two orders of magnitude less than for am-Si panels, frame rate is at least 10x faster, no image lag and a "best in class" radiation-hardness. Yield is [text removed for publication].

To further the exploitation of wafer-scale and other custom CMOS Imagers, the spinout company, ISDI Ltd was formed in 2010. Using a network of top-flight CMOS designers across Europe and solid relationship with several foundries, it is possible to build a company without selling equity Extensive discussions [text removed for publication].

In conclusion, through the generous support of the UK Research Councils, the Universities and other bodies associated with the development of specialised CMOS imaging devices and systems, the UK (through ISDI Ltd and its partners across Europe) is a world-leader in this expanding field.

Dynamite itself, and our ability to manufacture very large CMOS imagers, has attracted much publicity and recognition – for example, short-listed for British Engineering Excellence Awards (2011), awarded IET Innovation Prize for Electronics (2012), and invited presence at SPIE

Photonics Europe Conference and Tradeshow, Brussels (2012).

Currently *Dynamite* is being used within the £1.6m Wellcome Grant, PRaVDA, to provide proof-of-principle for Proton CT – the Holy Grail of radiotherapy. Experiments are conducted at the Birmingham Cyclotron and at the iThemba Proton Therapy Centre (Cape Town). Partners are University of Lincoln (Lead), University of Surrey, University of Birmingham, University of Liverpool, University of Cape Town, University Hospital Coventry and Warwickshire NHS Trust, University Hospital Birmingham NHS Foundation Trust, Christie NHS Foundation Trust, United Lincolnshire NHS Trust, and iThemba Laboratories. ISDI Ltd is a named suppler for PRaVDA.

5. Sources to corroborate the impact

- ISDI Ltd – Spinout company (UK Company No. 07314677) – incorporated 14/7/2010. See http://www.isdicmos.com
- For details of marketing and sales of CMOS medical imagers [text removed for publication].
- For details of ISDI contract [text removed for publication].
- Short-listed for British Engineering Excellence Awards, 2011
  – see http://www.beeas.co.uk/beeas-shortlist-2011.html
- SPIE Photonics Europe – Innovation Village, see http://spie.org/x85380.xml
- IET Innovation Prize for Electronics, 2012
  – see http://conferences.theiet.org/innovation/categories/electronics/index.cfm
- Relevant patents are GB2011/051300 (Radiation Detector and Method) PCT filed 12th July 2011, and |P300185GB| (Increasing the Dynamic range of imagers).