Institution: University of Sussex

Unit of Assessment: UoA 15 General Engineering

Title of case study: The use of research on imaging to predict survival rates and optimise treatment planning in cancer patients

1. Summary of the impact

Research to address the detection of weak structured signals from within highly variable cluttered imagery, originally for vehicle tracking, is being used to identify textural variations in organ tissue. The technology has been spun out into a company, TexRAD Ltd, using the methodology as a means of detecting tissue abnormalities, typically cancer, assessing response to treatment, and predicting patients' chances of survival. The detection process is being assessed through clinical research use in the UK, Europe and the USA. Regulatory approval for mainstream clinical use is being prepared.

2. Underpinning research

This impact stems from research started at Sussex by Young and Chatwin – lecturer and professor respectively – in 1996 which focused on detecting and tracking vehicles in different kinds of background scene (e.g. rural, urban) using visible and thermal infrared imaging. Hence the research addressed the detection of weak structured signals from within highly variable cluttered imagery.

The research produced a mechanism for tracking vehicles using modified Wiener type filters, optimised by including the statistics of the clutter-noise within the filter [see Section 3, R1]. The process represented a background by parametrically estimating the average of a large number of different cluttered backgrounds, within which the object could be expected to be found. The results demonstrated excellent sensitivity in detecting objects in varied backgrounds. This research produced very effective detection of weak signals in complex images [R2].

With the ability to identify objects, with low dynamic ranges, with unspecified backgrounds, medical applications identifying variations in organ-tissue texture became a possibility. In 2004, Young and Chatwin began collaborating with Professor Miles at Brighton and Sussex Medical School (BSMS) to detect degrees of tissue heterogeneity associated with cancer. The project also supported the doctoral research of Balaji Ganeshan.

The images, within which objects (heterogeneous tissue) are identified, are generated by computerised tomography (CT) or, with contrast material present, perfusion CT. Using the previously described approach, modified Wiener Filters [R3] enabled texture variation to be identified and quantified to generate quantitative heterogeneity biomarkers.

In 2007, analysis of 28 colorectal cancer patients' historical CT data [R3] demonstrated a relationship between liver texture and blood-flow, and provided a rationale for the use of liver-texture analysis as an indicator for patients with colorectal cancer. Texture analysis at different image spatial frequencies correlated with disease severity and progression. Similarly, liver blood-flow variations reflected as subtle coarse texture changes can be used to identify colorectal cancer patients with an apparently normal liver appearance [R4].

In 2009, an historical study of 48 patients with colorectal cancer [R5] assessed the utility of the texture analysis of liver CT images by comparing the abilities of texture analysis and hepatic perfusion CT to help predict the survival of these patients. This study provided evidence that the analysis of liver texture on portal phase CT images is potentially a superior predictor of survival for

patients with colorectal cancer than CT perfusion imaging. Hepatic attenuation and texture were assessed from non-contrast enhanced CT in three groups of colorectal cancer patients [R6]. It was shown that relative texture analysis of unenhanced hepatic CT can reveal changes in apparently disease-free areas of the liver that have previously required more complex perfusion measurements for detection; this reduces costs, radiation burden and risk.

The research was undertaken by Young and Chatwin, who remain at Sussex as Reader and Professor respectively; Miles, who left the University in 2011; and Ganeshan, who completed his PhD in 2008. Ganeshan was supported by the University's Enterprise Development Fund, and has been the Technical Director of the resulting spin-out, TexRAD, since its foundation in 2011. He transferred to the spin-out company, TexRAD, in 2012. Miles was the founding clinical director of TexRAD.

3. References to the research

R1 Jamal-Aldin, L.S., Young, R.C.D. and Chatwin, C.R. (1997) 'Application of nonlinearity to wavelet-transformed images to improve correlation filter performance', *Applied Optics*, 36(35): 9212–24.

R2 Tan, S., Young, R.C.D., Richardson, J.D. and Chatwin, C.R. (1999) 'A pattern recognition Wiener filter for realistic clutter backgrounds', *Optics Communications*, 172(1): 193–202.

R3 Ganeshan, B., Miles, K.A., Young, R.C.D. and Chatwin, C.R. (2007) 'In search of biologic correlates for liver texture on portal-phase CT', *Academic Radiology*, 14(9): 1058–68.

R4 Ganeshan, B., Miles, K.A., Young, R.C.D. and Chatwin, C.R. (2007) 'Hepatic enhancement in colorectal cancer: texture analysis correlates with hepatic hemodynamics and patient survival', *Academic Radiology,* 14(12): 1520–30.

R5 Ganeshan, B., Miles, K.A., Young, R.C.D. and Chatwin, C.R. (2009) 'Texture analysis in non-contrast enhanced CT: impact of malignancy on texture in apparently disease-free areas of the liver', *European Journal of Radiology*, 70(1): 101–10.

R6 Miles, K.A., Ganeshan, B., Griffiths, M.R., Young, R.C.D. and Chatwin, C.R. (2009) 'Colorectal cancer: texture analysis of portal phase hepatic CT images as a potential marker of survival', *Radiology*, 250(2): 444–52.

Outputs can be supplied by the University on request. Outputs R1, R2, R3 best indicate the quality of the underpinning research.

Funding:

- EPSRC-ROPA (GR/L/71230), 1998–2000, £155,240
- EPSRC (GR/L90774), 1998–2000, £278,959

4. Details of the impact

Algorithms originally developed for recognising vehicles in security situations [see Section 3, R1, R2] are being used commercially to produce quantitative CT-based biomarkers in oncology; the tumour imaging biomarkers that have been created are: Heterogeneity, Perfusion, Attenuation, Size. These are being used in clinical studies of historical medical imaging data for risk stratification, prognosis characterisation and treatment response. The research impact is very wide-reaching in that it is applicable to colorectal, breast, lung, prostate, oesophagus, renal, gliomas and pancreatic cancers, as well as to other areas of medical imaging. The method and technology were created by the underpinning research. An initial patent was filed in 2007, patent 0705223.6 [see Section 5, C1], and the algorithms and software functionality developed over the following four years.

The potential applications in patient prognosis, treatment and monitoring led to funding from medical sources. The charity Prostate Cancer UK funded the inclusion of patient prognostic reports (2009–10), the then-Regional Development Agency, SEEDA, via CommercialiSE-PoC, funded the development of the software package, and the University's Enterprise Development Fund supported commercial development. This was followed in February 2011 by the incorporation of a spin-out company, TexRAD Ltd, as a joint venture between the University of Sussex, Imaging Equipment Ltd, Cambridge Computed Imaging Ltd, and Miles Medical [C2].

The resultant software has been licensed to a number of hospitals in the UK, Europe and the USA, to be used to undertake medical studies and clinical trials These include:

- the University of Mississippi Medical Centre, USA, which undertook texture analysis on computerised tomography (CT) images to validate the overall survival in patients treated with induction chemotherapy for cell carcinoma of the head and neck. Andrew D. Smith M.D. Ph.D., Director of Radiology Research, has commented:

  > TexRAD software has allowed us to predict survival outcomes in several different tumors and treatment situations in a research setting. The data acquisition process and analysis have been streamlined for large studies, and the applications and support by TexRAD software engineers and leaders have led to some amazing results [C3].

- University College London Hospitals, UK [C4] undertook analysis of the CT component of a combined positron emission tomography/computerised tomography (PET/CT) to analyse patient survival predictions for those with non-small-cell lung cancer.

- Kings College, London, UK [C5] has undertaken several sets of work looking at the texture analysis of CT scans to determine patients' prognoses. These include the response to tyrosine kinase inhibitors to metastatic renal cell cancer, 5-year survival predictions of primary colorectal cancer patients using whole-tumour texture analysis, and survival predictions for primary oesophageal cancer sufferers treated with definitive chemotherapy and radiation therapy.

- Brighton and Sussex University Hospital NHS Trust, UK [C6] looked at non-small-cell lung carcinoma and texture variations as a survival predictor.

- The Department of Clinical Engineering, Aarhus University Hospital, Skejby, Aarhus, Denmark, are conducting a 100-patient study into non-small-cell lung carcinoma and texture variations as a survival predictor [C7].

As a result of the trials detailed above and fourteen others, over 50 refereed journal and conference papers have been disseminated, including papers in *Radiology* and *Clinical Cancer Research* [C8]. The effect of these findings is to validate the use of the algorithms in the prediction of the survival and treatment response of patients with squamous cell carcinoma of the head and neck, non-small-cell lung cancer, renal cancer, oesophageal cancer and colorectal cancer.

On a commercial front, Pfizer are conducting a 400-patient renal-carcinoma drug-response study at The University of Mississippi Medical Centre, USA; the results are due around May 2014.

The TexRAD software has workstation, server and cloud-based versions, with research licence sales to 31 July 2013 of £172k [C2]. The clinical evidence generated was sufficient for the first stage of the FDA (USA) and CE (Europe) approvals process for clinical use to start in December 2012 and the TexRAD software is expected to gain ISO-13485 quality and FDA/CE approval in 2014.

TexRAD's texture analysis is a relatively inexpensive and simple process by which tissue

abnormalities, and hence prognosis, treatment plans and response to treatment, can be monitored and acted upon without invasive procedures or further images being required. The significance has been recognised by clinicians and, in turn, by those with commercial interests. Consequentially, TexRAD Ltd is currently in discussions in relation to substantial investment.

5. Sources to corroborate the impact

C1 UK patent application No.0705223.6 19 March 2007; international patent application under the PCT system PCT/GB2008/000977 19 March 2008; Canadian patent number 2682267 granted 22/01/2013; US, Europe, Japan patent pending.

C2 For confirmation of company formation details and global software sales, Managing Director, TexRAD Ltd.

C3 For confirmation of patient studies on squamous cell carcinoma of the head and neck, Director of Research Services, Body Imaging, Nuclear Medicine.

C4 For confirmation of patient survival predictions for those with non-small cell lung cancer, Professor of Nuclear Medicine, Metabolism and Experimental Therapeutics.

C5 For confirmation of patient survival predictions for renal cell cancer, colorectal cancer, oesophageal cancer treated with definitive chemotherapy and radiation therapy, Chair of Clinical Cancer Imaging, Division of Imaging Sciences and Biomedical Engineering, King's College London.

C6 For confirmation of study on patient survival of non-small-cell lung carcinoma, lead consultant in nuclear medicine, Brighton and Sussex University Hospital NHS Trust, Royal Sussex County Hospital.

C7 For confirmation of study on patient survival of non-small-cell lung carcinoma, Diagnostic Radiology Consultant, Department of Clinical Engineering.

C8 Departmental records of clinical trial articles are available for audit.