Institution: University of Oxford

Unit of Assessment: 15, General Engineering

Title of case study: UOA15-05: Imaging software for cancer diagnosis

1. Summary of the impact

Key advances in the earlier diagnosis of cancer, leading to better treatment and higher survival rates, have resulted from the commercialisation of unique imaging software that exploits research from the Department of Engineering Science. The software products that came from this research, Volpara™, XD and XRT are now used at major cancer centres worldwide (with approximately 1100 software installations), aiding treatment of tens of thousands of patients every year. Between 2009 and July 2013, Volpara™ scanned over 1.2 million mammograms, enabling the early detection of around 1800 cancers. The products' success has catalysed significant improvements in cancer care, and generated an estimated £9M in sales over the past two years for the spinout companies established to develop them (Matakina, based in New Zealand, and Mirada Medical, based in the UK).

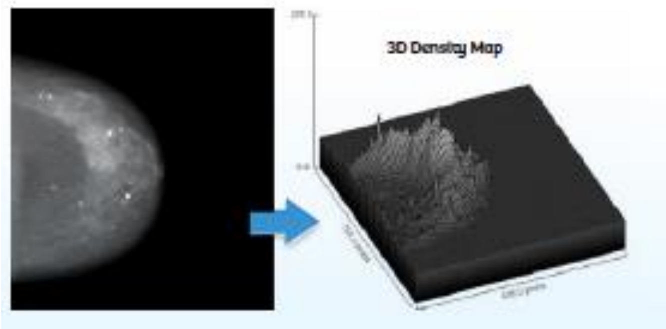
2. Underpinning research

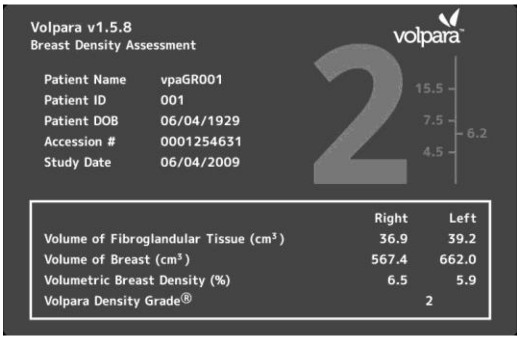
Whilst the key concepts behind these life-saving products were at first controversial, they are now firmly established as underpinning quantitative mammographic techniques. The beginnings of the work go back to 1989, and a key phase was Ralph Highnam's postdoctoral work 1992-1999 [1, 2, 3], with further developments continuing since then. The research was led by Prof. Mike Brady, (Professor of Information Engineering, 1985-2010 and Professor of Oncological Imaging 2012-present). The research underpinning the advances achieved is summarised below:

- *Mammography imaging and analysis*. A key problem, prior to Brady's work, was that mammography systems relied on human perception and judgement. The image in a mammogram is affected by X-ray machine parameters as well as the breast tissue through which the X-rays pass. But conventionally, information about parameters such as exposure time, tube voltage (set by the user) and anode type (which varies from machine to machine) was recorded inaccurately, for digital mammograms, or even not at all, for film-screen mammograms. The result was that tissue from the same breast might appear to have changed in images taken a short time apart – making accurate analysis of the tissue much more difficult. This subjectivity led to inconsistent clinical assessments of patients.

  Working with Dr Ralph Highnam (PDRA 1992-1999 and later co-founder and CEO of Matakina), Brady incorporated explicit mathematical models of the physics of image acquisition into medical image analysis, as well as taking account of the 3D nature of this problem. This approach underpins Matakina's Volpara™ product, which estimates breast tissue density from conventional mammography scans and produces a simple-to-read 'score' giving an accurate indication of this key breast cancer risk factor [1, 2, 3, 4]. As a mammogram is a 2D image of the 3D breast, so information in the third dimension (*i.e.* perpendicular to the compression plates) is inevitably lost. Brady and Highnam discovered that, starting from estimates of various, often unknown parameters, their model's predictions could be matched against the mammogram and adjusted until a best fit was achieved. This provided a way of estimating, at the pixel level, the amount of dense tissue in the apparently lost third dimension and measuring the amount of non-fat tissue in the breast – enabling images of tumours to be enhanced.

  This model-based approach, which makes it much easier to analyse the amount of dense tissue as it varies from pixel to pixel, has transformed mammogram analysis, enabling those at greatest risk of developing breast cancer to be identified much more easily and, in many cases, much earlier than previously possible (see Section 4). While Matakina and other companies such as GE Healthcare and Hologic have developed software systems based on this research, Brady and Highnam have continued to refine their mathematical model to extend its capabilities and further refine its clinical value [5, 6].





Volpara™ calculates a patient's breast tissue density automatically and objectively from digital mammography data (left), and then presents it the results in an easy-to-read format (right)

- *Mirada Solutions' technology:* XD and XRT are firmly rooted in the scientific insights and implementation methods developed by Brady and his colleagues. The focus is on the concept of 'image registration' which concerns the alignment of images, typically of different types acquired at different times and different spatial resolutions.

  The challenge of image registration was made significantly more complex by the emergence, around the year 2000, of combined PET-CT machines – and specifically by the drive to fuse separate 3D PET (positron emission tomography) and CT (computed tomography) images into a single, better quality image. Aligning a PET image of a patient's entire body with a CT image of a chest cavity or other body part required a painstaking computing process typically taking 1-2 hours to complete. Building on work Brady conducted in the 1990s on deformable registration of images of different types, Mirada Solutions successfully developed an image alignment method taking just 5 minutes, and seldom requiring the user's intervention. Since this breakthrough, the company has continued to harness and apply a stream of scientific advances achieved by Brady and his team (*e.g.* in dosimetry for X-radiation therapy).

3. References to the research (best indicators of research quality are marked ***'Q'***)

1. Brady, J.M. and Highnam, R.P. 'Mammographic Image Analysis' (1999). Kluwer Series on Medical Image Understanding. ISBN 0-7923-5620-9. ***'Q'***

   Monograph outlining the mammography methods pioneered by Brady and Highnam, as well as their work on MRI and PET analysis of breast images.

2. Highnam, R.P., Brady, J.M. and Shepstone, B.J. 'Computing the Scatter Component of Mammographic Images' (1994). *IEEE Transactions on Medical Imaging*, 13, pp 301-313. http://ieeexplore.ieee.org/stamp/stamp.jsp?arnumber=00293922

3. Highnam, R.P., Brady, J.M. and Shepstone, B.J. 'A Representation for Mammographic Image Processing' (1996). *Medical Image Analysis,* 1(1), pp 1-18, Oxford University Press. http://ieeexplore.ieee.org/stamp/stamp.jsp?arnumber=00543472 ***'Q'***

   The two above papers set out Brady and Highnam's model of mammographic image formation.

4. Behrenbruch, C.P., Marias, K., Armitage, P.A., Yam, M., Moore, N., English, R.E., Clarke, P.J. and Brady, J.M. 'Fusion of Contrast-Enhanced Breast MR and Mammographic Imaging Data' (2003). *Medical Image Analysis*, 7(3), pp 311-340, Elsevier. http://dx.doi.org/10.1016/S1361-8415(03)00015-X

   Although much of Mirada Solutions' work on image registration was confidential, this paper summarised the methods and showed a number of fusion results in the case of breast imaging.

5. Highnam, R.P., Pan, X., Warren, R., Jeffreys, M., Davey Smith, G. and Brady, J.M., 'Breast Composition Measurements Using Retrospective Standard Mammogram Form (SMF)' (2006). *Physics in Medicine and Biology*, 51, pp 2695-2713 http://dx.doi.org/10.1088/0031-9155/51/11/001 ***'Q'***

Extend Brady and Highnam's method and makes it applicable to all mammograms.

6. Highnam, R.P, Brady, J.M, Yaffe, M.J., Karssemeijer, N. and Harvey, J. 'Robust Breast Composition Measurement – Volpara™' (2010). Digital Mammography, *Springer Lecture Notes in Computer Science*, 6136, pp 342-349. http://link.springer.com/chapter/10.1007%2F978-3-642-13666-5_46

The methods outlined in Refs. 1-5 address the general physics of mammography; Ref. 6 focusses on issues more specific to the Volpara™ product.

Grants in support of this research:

- Cancer Research UK: Quantitative Assessment of Mammograms, 2001-2004, £113,980. Principal Investigator: Mike Brady.
- EPSRC: From Medical Images and Signals to Clinical Information, 2001-2007, £1,986,920 (Oxford component) (ref: GR/N14248/01). Principal Investigator: Mike Brady.
- EPSRC: eDiamond Grid Project, 2002-2005, £1,290,367 (award to investigate breast cancer) (ref: GR/S20956/01). Principal Investigator: Mike Brady.
- EPSRC: Investigating a Model-based Approach to Breast Imaging, 2008-2010, £389,273 (ref: EP/E031978/1). Principal Investigator: Mike Brady.
- EU FP7: ASSURE (Adapting Breast Cancer Screening Strategy Using Personalised Risk Estimation), 2012-2015, €5.6M. Principal Investigator: Nico Karssemeijer (University of Nijmegen).

4. Details of the impact

Brady's research has triggered the development of products that are having a direct impact on cancer prevention, detection and treatment regimes. By saving lives and simplifying clinical practice, the benefits accrue to millions of patients and thousands of healthcare professionals worldwide. Working with colleagues in academia and industry, Brady set up the two spin-out companies to exploit the potential of the research, and he continues to work closely with them:

- **Mirada Solutions:** formed in 2000 from a merger of two previous spinouts established by Brady (OMIA and OXIVA), this firm focused on image fusion and underwent a series of acquisitions and name-changes before Brady and three former colleagues bought it back. This led to the formation of Mirada Medical (www.mirada-medical.com) in 2009, which is based in Oxford and specialises in cancer diagnosis and radiation planning software.

- **Matakina** (www.matakina.com): set up in 2009 to exploit Brady and Highnam's breakthroughs in mammography software, this company also harnesses the outstanding research skills of Professor Nico Karssemeijer (University of Nijmegen, the Netherlands) and Professor Martin Yaffe (University of Toronto, Canada).

Health Impact – earlier diagnosis of cancer

Women with very dense breast tissue have a 4-6 times higher risk of developing breast cancer than those with tissue consisting predominantly of low-density fat. Uniquely, Volpara™ converts any digital breast mammogram into a 'normalised' image, presented to a clinician as a summary screen (see photo on p. 2). Thanks to these capabilities, the software is used as a time-saving device in cancer screening worldwide. In summary, Volpara™ has substantially changed clinical practice in the hospitals using it. Endorsements from clinical practitioners include:

- “Volpara was implemented here since October 2010, and we have found it to be accurate and reliable” [7].
- “Volpara is easy to use with minimal training” [8].
- “Volpara has made the whole [mammogram] process much more streamlined and convenient for women” [9].
- “Volpara has been used in a large, screening trial because of its robust clinical record” [10].

Mirada Medical’s software is delivering quicker, easier, more effective diagnosis and monitoring for a range of additional cancers, including lung cancer, melanoma, liver cancer and head and neck cancer.

Economic Impact – wealth creation and job generation

As of July 2013, Matakina’s Volpara™ software is being used in Australia, Belgium, Canada, Chile, Denmark, Finland, Ireland, Italy, Japan, Malaysia, the Netherlands, New Zealand, Norway, Saudi Arabia, South Africa, South Korea, Sweden, Switzerland, Thailand and the US, as well as the UK. In 2012 alone, over 500,000 women had their breast density assessed using the software – including 72,000 at Eastern Radiology in Greenville, North Carolina, 50,000 at Radboud Hospital in Nijmegen and 48,000 at the Samsung Medical Center in Seoul, South Korea [11].

Mirada Medical’s software is used at all major cancer centres in the US (e.g. the Johns Hopkins University Hospital in Baltimore, Maryland, and the MD Anderson Cancer Center in Houston, Texas), in the UK (e.g. the Oxford University Hospitals NHS Trust and the Western General Hospital in Edinburgh) and in Denmark, India and the Netherlands. In addition, the firm sells its products to companies such as Toshiba, Siemens, Vital, Carestream, McKesson and Sectra who incorporate them into their own products. Major equipment suppliers Varian and GE Healthcare have also placed contracts with the company to develop innovative software.

This extensive worldwide take-up of the spinouts’ range of software products has translated directly into impressive commercial performance. Matakina has 116 installations in 20 countries and Mirada has around 1000 installations in 10 countries, with a combined annual turnover now around £5 million. Such figures highlight the fact that Brady’s pioneering research has ultimately had a significant global impact not only in healthcare but also in economic terms.

5. Sources to corroborate the impact

7. M.D., Eastern Radiology, North Carolina. Corroborates VolparaTM being accurate and reliable. Testimonial at www.volparasolutions.com
8. M.D., Jules Bordet Institute, Belgium. Corroborates Volpara™ is easy to use with minimal training. Testimonial at www.volparasolutions.com
9. Radiologist, Sutter Health, US. Corroborates the impact of Volpara™ being more convenient. Testimonial at www.volparasolutions.com
10. Associate Professor of Clinical Epidemiology, University Medical Centre, Utrecht, the Netherlands. Corroborates the utility of Volpara™. Testimonial at www.volparasolutions.com
11. CEO, Matakina. Corroborates widespread uptake Volpara™ internationally.