Institution: Imperial College London

Unit of Assessment: 11 Computer Science and Informatics

Title of case study: Case Study 4: Quantitative Image Analysis – Novel Biomarkers for Clinical Trials and Diagnostics (IXICO)

1. Summary of the impact (indicative maximum 100 words)

A biomarker is a measurement or physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions, or survives. Biomarkers can be used to assess changes induced by a therapy or intervention on a clinically meaningful endpoint.

New quantitative image analysis techniques developed at Imperial College have enabled the computation of ***imaging biomarkers*** that are now widely used in clinical trials as well as for healthcare diagnostics. This case study illustrates the resulting key impacts including:

1. The development of a spin-off company, IXICO, which has licenced the developed image analysis techniques and imaging biomarkers.
2. The use of the image analysis techniques and imaging biomarkers in more than 40 clinical trials involving more than 10000 subject visits.
3. The approval of imaging biomarkers by European regulators as a tool to enrich recruitment into regulated clinical trials in Alzheimer's disease (AD).

2. Underpinning research (indicative maximum 500 words)

The underpinning research has been carried out in the Biomedical Image Analysis (BioMedIA) Group between 1999 and now. Professor Daniel Rueckert founded the group in 1999 when he moved to Imperial College and has been leading the research described below.

Much of the early work of the group has focused addressing one of the fundamental problems in computer vision and medical image computing, namely the problem of ***image registration***. The goal of image registration is to find automatically a transformation between points in two or more images. For the transformation to be meaningful, the transformation must map corresponding points across the coordinate systems. If the transformation sought is ***rigid***, the problem is relatively straightforward to solve, as the number of unknowns is small (typically 3 in 2D and 6 in 3D). However, when the transformation sought is ***non-rigid*** the problem is much harder to solve since the degree of freedom is much higher (typically in the order of hundreds of thousands or even millions). Yet in practice non-rigid registration is often required to compensate for intra-subject variation (for example tissue deformation, respiratory or cardiac motion) as well as for inter-subject variation.

In 2001, Professor Rueckert and his team developed a solution to this problem that is based on a flexible and versatile deformation model using B-spline free-form deformations [1]. Moreover, this approach is capable of registering mono-modal and multi-modal images. Furthermore, the solution developed by us was the first one to adopt the use of adaptive, hierarchical B-spline free-form deformations that offer the ability to deal with complex deformations. This proposed solution has been widely adopted; in a recent comparison study it also has been shown to be amongst the most accurate solutions for this problem [2]. In 2006, they proposed an improved solution to the registration problem that uses a diffeomorphic deformation to allow the modelling of very large deformations that may occur when registering the images of different subjects [3].

The ability of the developed image registration techniques to deal with very large deformations has led us to develop novel solutions to the classical problem of image segmentation that are based on image registration. As part of the EPSRC-funded IXI [i] and IBIM [ii] projects, we have pioneered the use of non-rigid registration of multiple atlases followed by vote or label fusion for the automatic segmentation of images [4]. Standard atlas-based segmentation uses image registration to transfer anatomical information from an atlas to new, unseen images. In contrast to this, our multi-atlas segmentation [4] uses multiple atlases and registrations followed by machine learning approaches such as decision fusion to provide a consensus estimate of the segmentation. This provides a

much more robust and accurate segmentation of medical images. This approach has become the de-facto standard solution for medical image segmentation in many applications, in particular for neurological, abdominal, and cardiac images. The name of the research project in [i] ("IXI") has also inspired the name of the resulting spin-off company ("IXICO" – see section 4 for more details).

More recently, as part of the *PredictAD* FP7 project [iii] we have further developed the methodology described above to enable the robust and accurate extraction of several imaging biomarkers, in particular in the context of neurodegenerative diseases such as dementia. For example, our methodology allows the accurate measurement of hippocampal volume [5] and hippocampal volume loss [6].

3. References to the research (indicative maximum of six references)
Publications that directly describe the underpinning research
* References that best indicate quality of underpinning research.

[1] J. A. Schnabel, D. Rueckert, M. Quist, J. M. Blackall, A. D. Castellano Smith, T. Hartkens, G. P. Penney, W. A. Hall, H. Liu, C. L. Truwit, F. A. Gerritsen, D. L. G. Hill, and D. J. Hawkes. A generic framework for non-rigid registration based on non-uniform multi-level free-form deformations. In Fourth Int. Conf. on Medical Image Computing and Computer-Assisted Intervention (MICCAI), 2208 pages 573–581, 2001.
http://dx.doi.org/10.1007/3-540-45468-3_69

[2] A. Klein, J. Andersson, B. A. Ardekani, J. Ashburner, B. Avants, M.-C. Chiang, G. E. Christensen, D. L. Collins, J. Gee, P. Hellier, J. H. Song, M. Jenkinson, C. Lepage, D. Rueckert, P. Thompson, T. Vercauteren, R. P. Woods, J. J. Mann, R. V. Parsey. Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. Neuroimage, 46(3):786-802, 2009.
http://dx.doi.org/10.1016/j.neuroimage.2008.12.037

[3] *D. Rueckert, P. Aljabar, R. Heckemann, J. Hajnal and A. Hammers. Diffeomorphic Registration using B-Splines. In Ninth Int. Conf. on Medical Image Computing and Computer-Assisted Intervention (MICCAI), 4191pages 702-709, 2006.
http://dx.doi.org/10.1007/11866763_86

[4] *R. A. Heckemann, J. V. Hajnal, P. Aljabar, D. Rueckert and A. Hammers. Automatic anatomical brain MRI segmentation combining label propagation and decision fusion. NeuroImage, 33(1):115-126, 2006
http://dx.doi.org/10.1016/j.neuroimage.2006.05.061

[5] *R. Wolz, P. Aljabar, J. V. Hajnal, A. Hammers, D. Rueckert. The Alzheimer's Disease Neuroimaging Initiative 2. LEAP: Learning embeddings for atlas propagation. NeuroImage, 49(2): 1316-1325, 2010 (***Patent filed US2012/281900 A1 and exclusively licensed to IXICO***)
http://dx.doi.org/10.1016/j.neuroimage.2009.09.069

[6] R. Wolz, R. A. Heckemann, P. Aljabar, J. V. Hajnal, A. Hammers, J. Lötjönen, D. Rueckert. The Alzheimer's Disease Neuroimaging Initiative 1. Measurement of hippocampal atrophy using 4D graph-cut segmentation: Application to ADNI. NeuroImage, 52(1): 109-118, 2010 (***Patent filed US2012/281900 A1 and exclusively licensed to IXICO***)
http://dx.doi.org/10.1016/j.neuroimage.2010.04.006

Grants that directly funded the underpinning research

[i] Information eXtraction from Images (IXI). EPSRC GR/S21526/01. D. Rueckert (Co-I). £544,143, October 2003 – December 2006.

[ii] IBIM – Integrated Brain Image Modelling, EPSRC GR/S82503/01, D. Rueckert (Co-I). £786,327, October 2004 – December 2007.

[iii] PredictAD – From patient data to personalized healthcare in Alzheimer's disease, EU FP7 STREP FP7-224328, D. Rueckert (PI). €531,786, June 2008 – June 2011.

4. Details of the impact (indicative maximum 750 words)

The underpinning research has led to the development of novel imaging biomarkers that are now routinely used in clinical trials to assess the efficacy of new drugs and treatments. The biomarkers are also starting to be used in healthcare diagnostics, e.g. for dementias such as Alzheimer's disease (AD).

Economic impacts

To maximize the economic impact of the research, a team of Imperial researchers (Rueckert, Hajnal) started IXICO with colleagues from UCL (Hawkes, Hill) in late 2004. It became IXICO plc and is now listed on the Alternative Investment Market (AIM) of the London Stock Exchange in a deal agreed in April 2013. Between 2008 and 2013, IXICO has grown from 5 employees to more than 40 employees. Its revenues have more than trebled during the last three years to £3.6M (year ending 31 May 2013). IXICO is a profitable business and has won more than £17m in business from the global pharmaceutical industry (GSK, Pfizer, Bristol-Myers Squibb, Novartis, EliLily). IXICO's image analysis technology is based on the underpinning research described in section 2 and has been transferred from Imperial during IXICO's formation and later as part of an IP pipeline agreement with Imperial. It has been, and/or is currently being used to analyse tens of thousands of medical images collected from a total of more than 400 imaging centres across North America, Latin America, Europe, Asia and Australasia, including 25 hospitals in 10 cities across China. Since 2008 IXICO has been involved in over 40 clinical trials and analysed images from more than 10000 subject visits using its image analysis technology [A].

The research also had a significant impact on the pharmaceutical industry where medical imaging is rapidly becoming an important tool in clinical trials to assess the safety and efficacy of new drugs using imaging biomarkers. In clinical trials phase 1 is typically used to screen for safety, phase 2 establishes the testing protocol, phase 3 is used for final testing while post-approval studies are referred to as phase 4 trials. Clinical trials (especially phase III) are typically very expensive. The average cost of developing new drugs can reach billions of dollars for each one approved. According to a Deutsche Bank Market Report (August 2012), the average cost of a new, approved drug has increased from $100M in 1979 to $1.9B in 2011 [B]. Imaging can significantly reduce these costs by enriching the enrolled population, providing early evidence of target engagement, or evidence of disease modification by being more precise than clinical measures. However, the detection and quantification of these subtle changes requires highly accurate and sensitive imaging biomarkers that are determined via automatic and quantitative image analysis. Such imaging biomarkers have been developed in the underpinning research, in particular for the assessment of neurodegenerative diseases and their progression.

The developed imaging biomarkers provide several benefits to pharmaceutical companies: In concept trials of AD therapies the developed biomarkers allow pharmaceutical companies to power their studies with fewer subjects. The developed imaging biomarkers do provide evidence of efficacy with around 100 subjects per arm (an "arm" in a clinical trial refers to any of the treatment groups in a randomized trial. Most randomized trials have two "arms", e.g. untreated vs. treated groups) over 12 months rather than 400 or so per arm needed for cognitive testing. Based on a conservative cost estimate of $30k per subject enrolled, this provides a significant cost saving for the companies. Similarly, pharmaceutical companies use the developed imaging biomarkers to enrich their clinical trials. In the context of clinical trials, such enrichment allows the identification of a population of patients in whom a drug effect, if present, is more likely to be demonstrable. In AD trials that use the developed biomarkers, an increase in the conversion rate in a prodromal Alzheimer's trial from 40% to 60% saves 30% off the cost of a pair of pivotal trials that used progression free survival as an endpoint, and which might otherwise cost $800m - $1bn [B].

Impacts on public policy and services

The imaging biomarkers developed in the underpinning research have had a significant impact on informing the development of new guidelines for the use of Magnetic Resonance Imaging (MRI) and low hippocampal volume in regulatory clinical trials: It now seems likely that to modify the

course of Alzheimer's Disease, it is necessary to start the treatment in the pre-dementia (or prodromal) phase. As has been recently reported [C], the identification of patients at this stage can only be done confidently with the help of biomarkers: imaging provides a non-invasive alternative to cerebrospinal fluid (CSF) biomarkers for this purpose. The critical importance of imaging biomarkers in AD trials has been recognised by the CAMD consortium by submitting to regulators an application to qualify low hippocampal volume as a biomarker [D]. This submission – approved by EMA and currently under review by the FDA – incorporates key data obtained using the underpinning research described here: the availability of this technology, with the regulatory qualification, is having global impact on the design of future trials of AD medicines in the pre-dementia population. In particular, the EMA Committee for Medicinal Products for Human Use [E] has issued a positive opinion on the use of MRI to measure hippocampal volume as a tool to enrich recruitment into regulated clinical trials in the pre-dementia stages of Alzheimer's disease [E], in which the EMA directly refers to reference [5] of the underpinning research. This was the first imaging-based biomarker to be qualified by a regulatory agency.

Impacts on healthcare

The imaging biomarkers developed in the underpinning research have been so effective in clinical trials that IXICO has recently decided also to develop products for diagnostic use (*Brain Health Centre [F]*). IXICO's product for diagnostics directly uses the methods described in reference [5,6] of the underpinning research and has also been CE marked [G]. It is currently undergoing trials involving 200 patients as part of new NHS brain health centres [F, H].

5. Sources to corroborate the impact (indicative maximum of 10 references.)

[A] CEO, IXICO to confirm details regarding IXICO.

[B] Deutsche Bank Markets Research Report on the European Pharmaceutical Industry (August 2012) pg 11 and 29-30. Available at http://www.fullermoney.com/content/2012-08-30/PharmaforBeginners82912.pdf Archived here on 22/10/2013. Corroborates that the average cost of a new, approved drug has increased from $100M in 1979 to $1.9B in 2011 .

[C] M. S. Albert, S. T. Dekosky, D. Dickson, B. Dubois, H. H. Feldman, N. C. Fox, A. Gamst, D. M. Holtzman, W. J. Jagust, R. C. Petersen et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging – Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia, 7: 270–279, 2011. http://dx.doi.org/10.1016/j.jalz.2011.03.008

[D] Coalition Against Major Diseases (CAMD) - Critical Path Institute: European Medicines Agency Deems Imaging Biomarker a Qualified Measure to Select Patients with Early Stages of Cognitive Impairment for Alzheimer's Disease Clinical Trials available at http://c-path.org/wp-content/uploads/2013/08/MRI.pdf . Archived here on 22/10/2013

[E] Qualification opinion of low hippocampal volume (atrophy) by MRI for use in regulatory clinical trials - in pre-dementia stage of Alzheimer's disease by the European Medicine Agency (EMA) available at http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2011/10/WC500116264.pdf Archived here on 22/10/2013

[F] Description of IXICO's *Brain Health Centre* available at http://www.thebrainhealthcentre.com/ . Archived on 22/10/2013 https://www.imperial.ac.uk/ref/webarchive/qyf

[G] Description of IXICO's diagnostic tools available at http://www.ixico.com/products/assessa. Archived on 21/10/2013 https://www.imperial.ac.uk/ref/webarchive/xyf

[H] The fast-track dementia test: PM to announce creation of new NHS hi-tech brain clinics, Daily Mail, November 2012. http://www.dailymail.co.uk/health/article-2227855/The-fast-track-dementia-test-PM-announce-creation-new-NHS-hi-tech-brain-clinics-help-cut-diagnosis-time-18-months-just-three.html. Archived on 22/10/2013 https://www.imperial.ac.uk/ref/webarchive/vyf