Institution: University College London

Unit of Assessment: 11 – Computer Science and Informatics

Title of case study: Camino diffusion MRI toolkit: microstructure imaging and connectivity mapping to avoid cognitive deficits after neurosurgery

1. Summary of the impact

Professor Alexander's work on diffusion magnetic resonance imaging (MRI) modelling and processing has had significant and lasting impact on medical practice. In particular, neurosurgical support systems rely on his work to map the major connection pathways in the brain, helping the surgeons avoid damaging them during intervention. Specific examples are in epilepsy, where, since 2010, surgeons perform about one operation per week using these systems, and brain tumour resection, where surgeons in Milan have since early 2013 been using a similar system based on UCL's latest microstructure imaging techniques. The key impact is on patients, whose likelihood of permanent post-operative deficits in, for example, visual, verbal or motor skills, is significantly reduced.

2. Underpinning research

In the early 1990s, a new magnetic resonance imaging technique was developed, called diffusion tensor imaging (DTI), which enables reconstruction of the connectivity of the brain through a subsequent computational image analysis process called tractography. While revolutionary for neuroscience, the technique has several fundamental limitations that cause problems for widespread adoption in clinical practice. The body of research that underpins the impact documented here aimed to ameliorate those limitations by developing alternative computational imaging, modelling, and data analysis techniques that provide more complete information to support brain connectivity mapping.

Substantial additional effort went into making all the advances freely available to the research community and beyond. This was achieved through the Camino diffusion MRI software toolkit www.camino.org.uk, which was first released in 2004. Daniel Alexander (Professor of Imaging Science) led this research effort and the development of the Camino toolkit during his employment at UCL, which started in January 2000. The one-page abstract [4] gathers general citations for the toolkit, although many go to the original papers on the techniques implemented in Camino. However, the website gives a better feel for the latest contents and utility.

Alexander's work on diffusion tensor image warping algorithms [1], enabling the construction of statistical atlases over groups [2], began in 1999 while he was at the University of Pennsylvania and continued after his arrival at UCL in 2000 until final publication in 2001. Exploitation of the work within the academic community began through collaborations, for example with Derek Jones, then at King's College London and now Professor at Cardiff University, and Lewis Griffin, then researcher at King's College London and now Senior Lecturer in Computer Science at UCL. That collaboration led to [2], which constructed the first group-averaged atlas of diffusion tensor images.

From 2001-2005 Alexander worked on a range of tractography algorithms for reconstructing brain connectivity from magnetic resonance images [3]. These particular tractography algorithms were the first to exploit the new generation of computational models and data processing algorithms coming out of Alexander's work that recover multiple fibre orientations in each image voxel (DTI can recover only one so fails at fibre crossings). He worked closely with Geoff Parker, now at Manchester University, to incorporate these algorithms into tractography; see for example [3].

From 2005 onwards, Alexander has had a significant research effort on experiment design optimisation algorithms for diffusion MRI; output [5] is one example. Specifically, he developed a range of optimisation algorithms to improve the experiment design in various diffusion MRI techniques and thus improve the precision and accuracy of the information it provides. In output [5] below, for example, he used simulated annealing to determine an optimal ordering for measurement acquisition that makes data usable even if only part of the full data set is acquired. This is particularly useful in clinical applications where patients sometimes demand to get out of the scanner before the acquisition is complete; without the optimisation, the data is then unusable.

The development of microstructure imaging techniques is a major on-going research effort for Alexander, which started in 2007. It has produced various new imaging techniques that add a variety of important new kinds of information beyond DTI. The research effort involves the construction of mathematical and computational models for the diffusion MRI signal, implementation of a variety of model fitting and model selection techniques, as well as the development of sophisticated simulation systems for testing and validation. One particular technique, called NODDI [6], is designed for clinical application, which has led to clinical impact, as described later. The research started in 2011 and was led by Alexander in collaboration with Gary Zhang, then a post-doc at UCL, who became lecturer in 2012, as well as Claudia Wheeler-Kingshott (Reader) and Torben Schneider (post-doc) at the Institute of Neurology at UCL. NODDI improves on DTI by providing biologically specific parameters, such as the density, direction and dispersion of neural fibres at each location in the brain.

3. References to the research

UCL researchers (at the time of publication) in bold. Publications [1,3,6] in particular highlight the research quality, although all are of high quality and highly cited.

1. **Alexander, D. C.,** Pierpaoli, C., Basser, P. J., Gee, J. C. (2001). Spatial transformations of diffusion tensor magnetic resonance images. *IEEE Transactions on Medical Imaging* 20(11), 1131-1139. http://dx.doi.org/10.1109/42.963816
2. Jones, D. K., **Griffin, L. D.**, **Alexander, D. C.**, Catani, M., Horsfield, M. A., Howard, R., Williams, S. C. R. (2002). Spatial normalization and averaging of diffusion tensor MRI data sets. *NEUROIMAGE* 17(2), 592-617. http://dx.doi.org/10.1006/nimg.2002.1148.
3. Parker, G. J. M., **Alexander, D. C.** (2003). Probabilistic Monte Carlo based mapping of cerebral connections utilising whole-brain crossing fibre information. *Lecture Notes in Computer Science*. (Proc. Information Processing in Medical Imaging) Vol. 2732 pp.684-695. http://dx.doi.org/10.1007/978-3-540-45087-0_57
4. **Cook, P. A.**, **Bai, Y.**, **Nedjati-Gilani, S.**, **Seunarine, K. K.**, **Hall, M. G.**, Parker, G. J., **Alexander, D. C.** (2006). Camino: open source diffusion MRI reconstruction and processing. *International Society for Magnetic Resonance in Medicine 14th Annual Scientific Meeting and Exhibition: 2006 Proceedings*. Page 2759. Berkeley, US. http://www0.cs.ucl.ac.uk/research/medic/camino/files/camino_2006_abstract.pdf
5. **Cook, P. A., Boulby, P. A., Symms, M. R., Alexander, D. C.** (2007). Optimal acquisition orders of diffusion-weighted MRI measurements. *Journal of Magnetic Resonance Imaging* 25(5), 1051-1058. http://dx.doi.org/10.1002/jmri.20905.
6. **Zhang, H., Schneider, T., Wheeler-Kingshott, C. A., Alexander, D. C.** (2012). NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. *Neuroimage* 61(5), 1000-1016. http://dx.doi.org/10.1016/j.neuroimage.2012.03.072.

The research was supported by a series of EPSRC grants (GR/R13715/01, GR/T22858/01, EP/E056938/1, EP/E007748) awarded between 2001 and 2008 and totalling around £2 million, as well as EU funding via the €2 million CONNECT project www.brain-connect.eu from 2010-2012.

4. Details of the impact

The key area for impact of the Camino toolkit and the research it implements is on patients undergoing neurosurgery. The research has enabled neurosurgeons to visualise white matter fibre pathways, which form the communication network of the brain, prior to their intervention. This helps them avoid cutting these fibres during the operation, **helping patients avoid severe cognitive deficits** unrelated to the original problem that led to the surgery.

Source [a] provides general corroboration for this claim stating that the more complete knowledge of brain connectivity that arose from Alexander's atlasing work documented in output [2] generally supports neurosurgeons to ensure better post-operative outcomes for their patients. The atlas in output [2] underpinned the discovery of new connections in the brain documented in Catani et al (see [a]). The report by Benzagmout et al in [a] is from 2007, but the impact on patients continues to the present, as the knowledge that arose from Alexander's atlasing work, via Catani et al, is now common among surgeons performing such operations and used to avoid brain damage during intervention.

The following describes two more specific examples of supporting evidence for the impact of Camino on brain surgeons and their patients:

Improved outcomes for epilepsy patients: Surgeons use tractography algorithms, specifically that published in output [3], and refined and implemented in the Camino toolkit, to recover pathways of white matter fibres in the brain from pre-operative MRI scans. An image acquisition and analysis system is in place in the National Hospital for Neurology and Neurosurgery (NHNN) in London specifically to support neurosurgeons making anterior temporal lobe resections (they cut away brain tissue to remove the seizure focus) to cure refractory epilepsy (cases in which standard medicines do not control seizures). They use the system on roughly one patient a week and it has been fully operational since mid-2012 [b], although a preliminary version was in clinical use for about a year prior to that. The system helps surgeons **avoid damaging fibre pathways**, which can otherwise lead to visual deficits that would, for example, prevent driving.

The system itself is documented in [c]. It relies on the experiment design optimisation in output [5] for image data acquisition as well as the tractography algorithm in output [3] implemented in Camino. Early evaluation of the system (see [b]) demonstrates its impact by using the system in 21 patients undergoing anterior temporal lobe resection. The outcomes are compared to a control group who underwent the same surgery without the system. None of those who had their visual pathway displayed to the surgeon via the Camino-based system had a visual field deficit that would prevent driving, compared to 13% in the control group. The experiment shows a **significantly better retention of visual skills in the patients operated on using the system**.

The impact came about through Alexander establishing a collaboration in 2004 with the epilepsy group at NHNN, which began to use Camino in their research into ways of ameliorating neurological deficit after neurosurgery. The surgical-support system they now use was engineered at UCL in collaboration with the epilepsy group at NHNN using the Camino toolkit largely as an off-the-shelf software library. As of mid-2013, around 140 patients have benefited from surgery at NHNN performed by Camino tractography, which the head of NHNN confirms is of "enormous importance for improving the precision and safety of neurosurgical treatment." [b]

Improved outcomes for brain tumour patients: Since 2012, neurosurgeons in Milan have been using tractography based on the NODDI technique in place of existing connectivity mapping for planning interventions to remove brain tumours. As in the epilepsy surgery described above, this helps surgeons avoid damaging white matter pathways so the impact on patients is that they are **less likely to have unrelated post-surgical cognitive deficits**. Common cognitive deficits resulting from brain tumour resection are verbal, sensory, or motor problems; surgical planning informed by tractography reduces the likelihood and severity of these deficits. The surgeons have been experimenting with off-the-shelf tractography for some time for presurgical planning. They switched to using NODDI tractography in 2012, because it reveals **"white matter fibres in the vicinity of tumours much more clearly than conventional tractography**, because it is less vulnerable to pathological effects, such as oedema, which arise commonly in and around brain tumours. This is a **significant benefit to surgeons** planning brain tumour resections, because they get a much clearer picture of white matter pathways near the tumour." (from source [d]). They have now imaged around 130 brain-tumour patients using NODDI, about 80 of whom went on to surgical intervention planned via NODDI tractography (see [d]).

Within the CONNECT consortium Alexander established a range of collaborations around Europe to develop microstructure imaging techniques and translate them to clinical practice. A neuroradiologist who was involved in the same consortium, and works closely with brain surgeons in Milan, picked up on the NODDI technique and began using it, under the guidance of the Camino team, in particular Gary Zhang, for tractography in brain tumour patients. He discovered the benefits in connectivity mapping in the vicinity of tumours, which led to its direct application for planning interventions on brain tumour patients.

5. Sources to corroborate the impact

[a] The clinical study by Benzagmout et al discusses how neurosurgeons routinely use newly found brain connections, discovered by Catani et al using the atlas constructed in output [2] above, during surgical planning and intervention to avoid severing vital brain connections and thus improve patient outcome compared to before any of the work was done. Benzagmout et al, Resection of World Health Organization grade II gliomas involving Broca's area: methodological and functional considerations, Neurosurgery, 61(4), October 2007, 741-753, DOI: http://dx.doi.org/10.1227/01.NEU.0000298902.69473.77. Catani et al, Perisylvian language networks of the human brain, Annals of Neurology, 57(1), January 2005, 8–16), DOI: http://dx.doi.org/10.1002/ana.20319.

[b] For corroboration of neurosurgeons' use of Camino tractography outputs [3,4] and experiment design output [5] in anterior temporal lobe resection, see the statement from the head of NHNN and epilepsy group leader. Available on request.

[c] Further corroboration on neurosurgeons' use of Camino in anterior temporal lobe resection appears in Winston et al, which documents the neurosurgery support system that exploits the Camino tractography output [3] and imaging experiment design output [5]. See specifically, page 335 of Winston et al, section "Tractography" (their refs 18 and 21 are output [4] and output [3]) and section "DTI Acquisition" (their ref 16 is output [5]). Optic radiation tractography and vision in anterior temporal lobe resection, Winston et al, Annals of Neurology, 71(3), pp. 334–341, March 2012, DOI: http://dx.doi.org/10.1002/ana.22619.

[d] For corroboration of neurosurgeons' use of tractography based on the NODDI technique output [6], see the statement from the chief of the Neuroradiology Unit at Milan's Istituto Clinico Humanitas IRCCS. Available on request.