Project Title: Development of MRI brain tumour fingerprinting for clinical assessment of brain tumour biology

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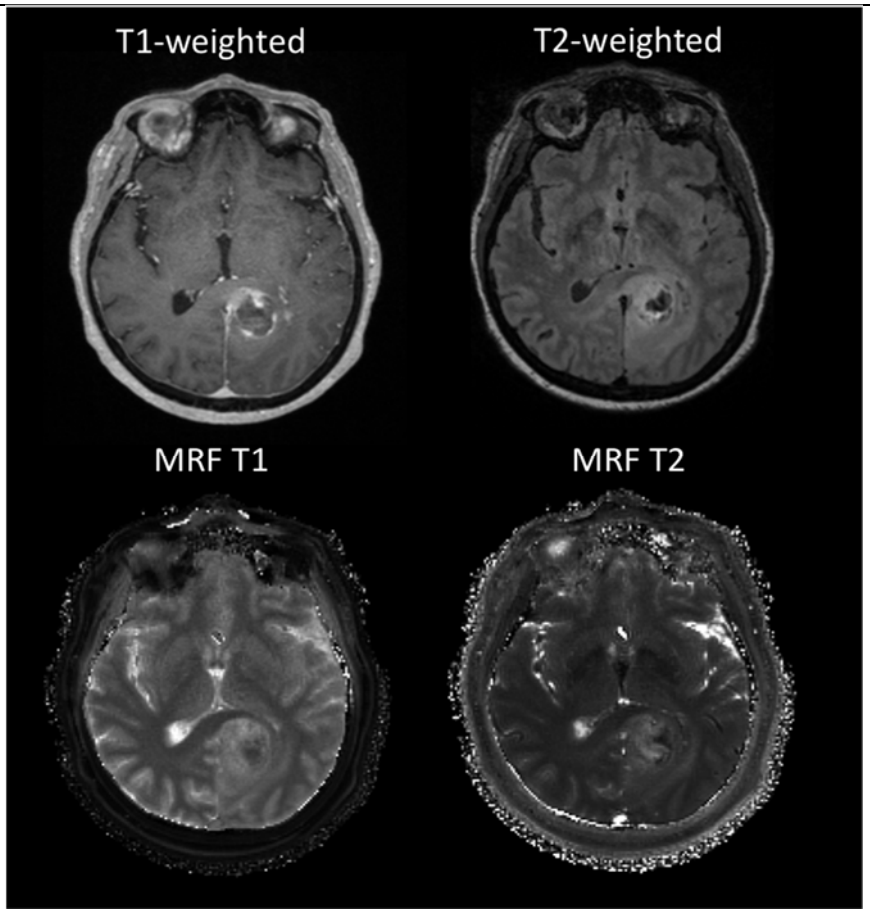
Proposal outline

Brain tumours are one of the four cancers which are hardest to treat and for which there is a strong need for further research (Cancer Research UK). In particular, clinical imaging of brain tumours is limited by a lack of quantitative imaging techniques which can study the physical properties of the underlying tissue, and hence provide in-vivo biomarkers of changes within the tumour.

Magnetic Resonance Fingerprinting (MRF) is a novel rapid imaging technique which aims to assess the physical properties of different tissues using one short MRI sequence (Ma *et al.*, 2013). It provides quantitative measures of T1 and T2 relaxivity values (Coppo *et al.*, 2016). MRF was however developed as a generic tool and limited literature exists of its application to brain tumours (Badve, Yu & Dastmalchian, 2017). There is a need to develop this tool specifically for cancer imaging, taking into consideration the clinical challenges faced by Radiologists. MRF could be tailored to produce quantitative values representing the biology specific to the tumour imaged – such as blood flow and microstructure. Within this PhD we aim to develop new MRI brain tumour fingerprinting (BTF) tools. It is critical that the development of such sequences is carried out using input from both a strong physics team, and a strong clinical radiology team.



Standard structural MRI (top row) and quantitative MR Fingerprinting (bottom row) in a patient with glioblastoma (GBM). MRF is able to produce reproducible quantitative features of the brain tumour. Images produced and analysed through an international collaboration between Imperial College London (Matthew Grech-Sollars) and Essen University Hospital (Lale Umutlu).

The student joining our team through this PhD will develop the physics for Brain Tumour Fingerprinting to answer challenging clinical questions faced by Neuroradiologists, in particular, the early determination of tumour transformation in patients with lower grade tumours and tumour response to treatment. Current imaging methods have limited accuracy in differentiating between pseudo-progression and true progression or pseudo-response and true-response (Hygino Da Cruz *et al.*, 2011) and we aim for these clinical questions to be addressed using machine learning and BTF. The student developing BTF will also integrate novel machine learning tools to be used as part of the image reconstruction and post-processing pipeline. The PhD student will therefore require training in MRI pulse sequence design, machine learning and neuro-oncology. We will incorporate MR perfusion for studying blood flow and MR diffusion for studying microstructure, into BTF. As BTF inherently measures a number of varying physical properties of the underlying tissue, it is hypothesized that it will provide additional information on the growth and development of brain tumours.

The first part of the project will involve the use of currently available implementations of MR Fingerprinting sequences on our scanners at Imperial and ICR. The sequences will be set up for Siemens scanners across both sites. The student will then develop BTF in conjunction with clinical radiologists and physicists/engineers. Sequence development will take into account the needs and current limitations for cancer imaging as determined across the clinical, biological and physical sciences. Initially a cohort of healthy volunteers will be used for developing the sequence.

Furthermore, machine learning techniques are an important element in MR Fingerprinting techniques, both in sequence design, and in image reconstruction, so the student will integrate machine learning tools to ensure the outcome of the project is a sequence, or set of sequences, that are optimised for use within a clinical environment for imaging brain tumours.

Following satisfactory setup and tests in healthy volunteers BTF will be applied to patients with primary brain tumours. The feasibility of BTF to assess the variety of different tissue presentations in brain tumours will be explored. Given the expected short scan times for BTF, clinical data will be obtained by including the sequence in current clinical imaging protocols, following appropriate ethical approval and consent.

In future projects, techniques developed during this PhD will be built upon and combined with an existing technique for taking targeted biopsies from multiple regions within brain tumours, developed by the lead supervisor (Grech-Sollars *et al.*, 2017). This will combine radiological diagnostic criteria with regional histopathological and genetic criteria to test out the biological significance of the imaging technique. We also envisage that BTF will provide a basis for the creation of a more generic cancer imaging sequence.

The main direction of this PhD is to develop and optimise novel clinical sequences that will differentiate between the different types of tissue regions within brain tumours. It will be used to assess tumour changes in patients under a watch and wait protocol, and tumour response to treatment. This physics-based project will be directly applicable to a clinical environment and initial studies on patients will be carried out with the aim of having a technique useful for routine use in the clinic to improve patient outcomes.

Feasibility

The project will involve development of Brain Tumour Fingerprinting (BTF) associated physics for a clinical environment. The PhD student will provide cutting edge research with publications on the development of the BTF physics, on machine learning algorithms for use within the technique, and on the applicability of BTF in the clinic.

In the first year they will use current MRF sequences while learning sequence development and gain background knowledge of neuro-oncology. They will develop BTF in the second and third years of the study. Clinical application will be conducted in the fourth year.

Resources and facilities will be made available including scan time on the clinical MR scanners, which is likely to be out of office hours for healthy volunteer scanning. The student will be given the MR physics training needed to operate in a clinical environment through close collaboration with supervisors from both academic and clinical backgrounds.

As BTF acquisition time is short, obtaining clinical data will be done by integrating the sequence into existing routine clinical imaging protocols after obtaining the necessary ethical approvals.

The PhD will consist of chapters on the Physics of BTF, the development and integration of BTF in a clinical environment, the use of machine learning for BTF and an analysis of its utility in assessing brain tumour patients. It will lead to advancing the field on an international level and will ensure that the collaborative effort between Imperial College and ICR will set us apart in sequence development to address clinical needs.

Multidisciplinary approach

The PhD will be supervised by members of staff with an Engineering, Physics and a Clinical Radiology background. Through this project we are offering a scientist with a physics/engineering/computing background the opportunity to train in cancer research and to improve and develop their scientific skills in a clinical environment. The student will be supervised by members of staff from Imperial College London, Imperial College Healthcare NHS Trust, the Institute of Cancer Research and the Royal Marsden Hospital.

Matthew Grech-Sollars is an MR Physicist and Imperial College Research Fellow. He has a background in Engineering and Clinical Science and expertise in Neuro-oncology Neuro-Imaging. He leads on the development of MRF at Imperial in collaboration with Siemens and Essen University Hospital. He also led two multi-centre studies including one previous collaborations with the Institute of Cancer Research (Grech-Sollars *et al.*, 2015). He lectures in Advance Medical Imaging and has experience supervising Masters students and is co-supervising a Clinical Research Fellow PhD. He will provide oversight of the project at Imperial and day-to-day supervision.

Dow-Mu Koh is a Consultant Radiologist and Professor in Functional Cancer Imaging at Institute of Cancer Research and the Royal Marsden. His current clinical and research interest is in the development and application of functional imaging techniques for tumour assessment. His group have established an ongoing collaboration with the group that developed the original MRF sequence at Case Western Reserve University in Cleveland, Ohio, USA. He will provide clinical input to the PhD student and act as main supervisor at ICR.

Neal Bangerter is a Reader in Magnetic Resonance Physics within the Department of Bioengineering at Imperial College London. He has expertise in developing novel MRI sequences (e.g. (Quist *et al.*, 2012)) and has experience in supervising PhD students in MRI sequence development. He will provide MR sequence development support at Imperial and the student will share knowledge with his team of sequence developers.

Rebecca Quest is Head of MR Physics at Imperial College Healthcare NHS Trust and Senior Lecturer at Imperial College London. She has a background in Physics and extensive experience in clinical and academic MRI. She lectures in Advanced Medical Imaging and has supervised many Master students. Research interests are functional MRI, neuroimaging and novel MRI methodologies. She will provide physics support within the Trust.

Kyriakos Lobotesis is a consultant neuroradiologist and is currently Neurointerventional Lead. Beyond his clinical responsibilities, he is an honorary clinical senior lecturer at Imperial College London. His primary interests lie in new medical devices and technologies and is currently involved in a number of research trials, with collaborative links nationally and abroad. He will provide clinical neuroradiology input to the project.

Matthew Orton is a Staff Scientist in the Division of Radiotherapy and Imaging at the Institute of Cancer Research. He has a background in signal processing and data modelling with particular expertise in their application to the processing of functional MRI such as diffusion-weighted and perfusion imaging. He has assisted in the supervision of three PhD students and provided expert support to many more. He will provide physics support at ICR and act as day-to-day supervisor at ICR.

The project will be supported by the Imaging Research Team within Imperial College Healthcare NHS Trust, who will train and support the student in the processes of good clinical practice and the ethical implication of conducting clinical research.

The PhD student will have a hands on experience of working in a clinical environment with both scientists and clinicians. The project will require development of MR Physics knowledge, pulse sequence programming and machine learning and as such will require integration of concepts from physics, engineering and computing as applied to address

tumour biology and clinical needs. The PhD student will therefore attend courses on MRI Physics (through a Masters module on Advanced Medical Imaging at Imperial College), pulse sequence programming (course run by Siemens in the USA) and machine learning (lectures within the Computing Department at Imperial College). They will also attend courses to gain knowledge of brain tumour biology and clinical needs (Queen Square Multidisciplinary Neuro-oncology Teaching Course). They will gain further training through participation in conferences and interactions within the physics and clinical teams at ICR and at Imperial College. Ongoing support will be provided by the supervisory team. This will lead to a scientist able to work across the clinical and scientific disciplines to produce clinically relevant and important scientific imaging tools for assessing cancer.

Literature references

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