Biomedical Engineering and Medical Imaging 2022/23

Contents

Biomedical Engineering and Medical Imaging

This theme focuses on the link between biomedical and physical sciences – particularly physics, engineering and computational approaches. Clinical functional and molecular imaging (MRI, PET, X-MR and PET-MR) is a major strength, along with computational modelling and biomaterials.

When choosing a project from this catalogue in the funding section of the online application form please enter: **MRCDTP2022_BE-MI**

Deadline for application: Thursday 18th November 2021, 23:59
Shortlisted candidates will be contacted in early January.

Interviews: Wednesday 26th January & Thursday 27th January 2022
The 2022/23 studentships will commence in September 2022.

Please visit the MRC DTP for information on our application process. If you require further information that is not provided on the website please contact:
mrc-dtp@kcl.ac.uk

Projects listed in this catalogue are subject to amendments, candidates invited to interview will have the opportunity to discuss projects in further detail.

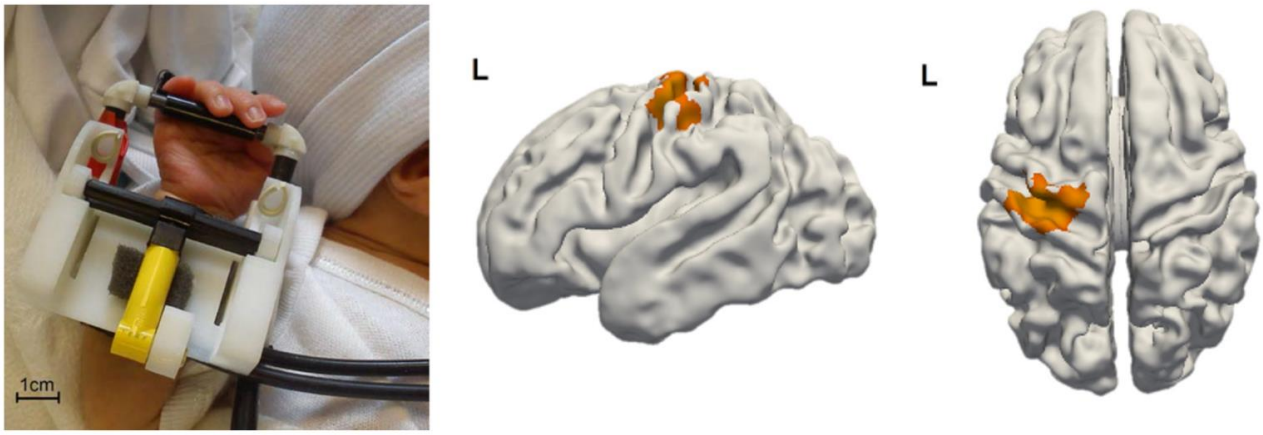
BE-MI20221 Neuroadaptive functional MRI for studying early human brain development

Co Supervisor 1A: Dr Tomoki Arichi
Research School/ Division or CAG: School of Biomedical Engineering and Imaging Sciences
Email: Tomoki.arichi@kcl.ac.uk
Website: www.perinatal-functional-imaging.co.uk and https://kclpure.kcl.ac.uk/portal/tomoki.arichi.html /

Co Supervisor 1B: Professor Robert Leech
Research School/ Division or CAG: Institute of Psychiatry, Psychology & Neuroscience
Email: Robert.leech@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/robert.leech.html

Project Description:

In early life, the human brain undergoes a dramatic sequence of maturation, during which the life-long architecture of its structural and functional connections is established. Across this period, activity has a key role in controlling regional organisation and guiding/consolidating neural connections. Recent developments in fMRI and MR-compatible robotics have enabled safe and accurate mapping of the spatial properties of this activity even in newborn infants as shown below.



fMRI experiments in newborn infants using MR-compatible robotic stimulation devices. In this example, a robot which can gently move a baby's wrist is shown on the left, with the resulting brain activity (orange areas) shown on the right (Dall'Orso et al. Cerebral Cortex 2018).

In a traditional fMRI experiment, patterns of activity induced by a specific stimulus or task are identified. Whilst powerful, this approach limits generalisability and constrains study populations to only those who can meet specific conditions. This project will apply a new methodology which specifically addresses these problems: neuroadaptive Bayesian optimisation (Lorenz et al. 2017, Trends in Cognitive Sciences) which combines real-time fMRI with machine learning to automatically search through experimental conditions and identify those that are optimal. This method is particularly attractive for studying newborn infants, who cannot be directed in a task and have a rapidly developing brain which means that generalisation across different populations and ages is not appropriate.

Objectives: Year 1/3: Training in neuroimaging methods. Development of neuroadaptive Bayesian optimisation methodology and robotic stimulation tools for neonates in collaboration with Professor Leech (KCL) and Professor Burdet (Imperial College).
Year 2/3: Data collection from newborn infants.
Year 3/3: Completion of data collection and analysis. Dissemination of results, thesis preparation.
Training: fMRI methodology and analysis, machine learning, and developmental neuroscience through the supervisory team; the School's educational program; external educational courses and conferences.

<u>One</u> representative publication from <u>each co-supervisor</u>:

Dall'Orso S, Steinweg JK, Allievi AG, Edwards AD, Burdet E, **Arichi T**. Somatotopic mapping of the developing sensorimotor cortex in the preterm human brain. Cerebral Cortex 2018; 28(7): 2507-15.

Lorenz R, Hampshire A, **Leech R**. Neuoroadaptive Bayesian optimization and hypothesis testing. Trends in cognitive sciences 2017; 21(3): 155-67.

BE-MI20222 Real-Time Pixel-Level Semantic Interpretation of Intraoperative Optical Coherence Images for Guided Regenerative Therapy Delivery

Co Supervisor 1A: Dr Christos Bergeles
Research School/ Division or CAG: School of Biomedical Engineering and Imaging Sciences
Email: christos.bergeles@kcl.ac.uk
Website: www.rvim.online

Co Supervisor 1B: Prof Tom Vercauteren
Research School/ Division or CAG: School of Biomedical Engineering & Imaging Sciences
Email: tom.vercauteren@kcl.ac.uk
Website: www.cai4cai.ml

For translational projects:
Name of Collaborating Clinician: Prof Lyndon Da Cruz
School/Division & CAG: School of Biomedical Engineering & Imaging Sciences
Email: lyndon.dacruz1@nhs.net

Project Description:

Gene and cellular therapies are emerging transformative treatments for blinding retinal diseases. Treatment delivery into delicate retinal layers, some as thin as 10-20um, will be guided by Intraoperative Optical Coherence Tomography (iOCT) microscopes, a modality microscopically imaging not only the retinal fundus, but also the "hidden" subretinal layers where therapeutics should be delivered. This PhD project will computationally augment iOCT imaging through incorporation of real-time artificial intelligence (AI) in the acquisition and processing pathways towards the creation of a robust navigation system that guides therapy implantation.

The student will develop deep learning models for real-time pixel-level semantic understanding of iOCT images. While extensive work has been carried out on segmentation and interpretation of pre-operatively acquired OCT volumes, including retinal layer delineation and pathology identification, there is almost no work on the analysis of iOCT images. iOCT images have relatively low SNR, less spatial resolution, and must be interpreted in real time. The student will be at a unique position to develop compact powerful artificial neural networks to achieve this overarching objective given the team's expertise on pixel level semantic interpretation of video streams, as well as the extensive datasets that have been collected from a variety of vitreoretinal surgical interventions.
A tentative research plan is as follows:

Year 1 (including rotations): Onboarding onresearch on real-time quality enhancement of iOCT images.

Year 2: Pixel-level semantic segmentation and pathology identification of super-resolved iOCT images.

Year 3: Incorporation of tool segmentation using weak labels and generated iOCT images.

Year 4: Consolidation of developed networks and deployment in a clinical setting.

<u>One</u> representative publication from <u>each co-supervisor</u>:

[1] T. Pissas^, C. S. Ravasio^, L. Da Cruz*, and C. Bergeles*, “Effective semantic segmentation in cataract surgery: what matters most?” in Proceedings of Int. Conf. Medical Image Computing and Computer-Assisted Intervention, pp. 1–8, 2021.

[2] L. C. Garcia-Peraza-Herrera, L. Fidon, C. D’Ettorre, D. Stoyanov, T. Vercauteren and S. Ourselin, "Image Compositing for Segmentation of Surgical Tools Without Manual Annotations," in IEEE Transactions on Medical Imaging, vol. 40, no. 5, pp. 1450-1460, May 2021.

BE-MI20223 Uncovering pro-arrhythmia mechanisms of Arrhythmogenic Cardiomyopathy using image-based cardiac digital twin technology

Co Supervisor 1A: Dr Martin Bishop
Research School/ Division or CAG: School of Biomedical Engineering and Imaging Sciences
Email: martin.bishop@kcl.ac.uk
Website: Dr Martin Bishop (kcl.ac.uk)

Co Supervisor 1B: Dr Aldo Rinaldi
Research School/ Division or CAG: Faculty of Life Sciences & Medicine
Email: aldo.rinaldi@kcl.ac.uk
Website: Dr Aldo Rinaldi (kcl.ac.uk)

For translational projects:
Name of Collaborating Clinician: Dr Tevfik Ismail
Website: https://www.kcl.ac.uk/people/tevfik-ismail

Project Description:

Background & Motivation: Arrhythmogenic Cardiomyopathy (AC) is a prevalent form of structural heart disease which carries with a high risk of sudden cardiac death due to ventricular arrhythmias. Accurately identifying at risk patients for life-saving implanted defibrillator devices with non-invasive techniques remains an important clinical challenge. Furthermore, curative catheter ablation of incessant ventricular tachycardia in this patient groups presents challenges in accurately identifying and targeting the arrhythmogenic substrate. Biophysically-detailed computational modelling has the potential to provide detailed mechanistic insight regarding the arrhythmogenic processes associated with AC, to guide patient-specific non-invasive stratification of risk and ablation targeting using in silico digital twin technology.

Skills/Training: Substantial training on computational cardiac electrophysiology will be provided within the CEMRG (www.cemrg.co.uk) itself, along with external courses/workshops (opencarp.org), as well as access to KCL teaching resources (Bioelectricity 3rd course taught by Dr Bishop). Opportunities to engage with clinical fellows and regularly visit EP/MRI-lab will be provided throughout.

Yr1: Construct biophysically-detailed representations of structural remodelling within AC within idealised models and conduct advanced in-silico stimulation protocols to probe specific arrhythmogenic mechanisms.
Yr2: Translate the findings from idealised models into image-based, whole heart-torso digital twin models to understand how the arrhythmogenic features at the cardiac tissue level translate into changes in the patient ECGs which may be identified in patient clinical recordings.

Yr3: Use specific advanced patient MRI imaging protocols to create digital twin models of patients undergoing ablation. Perform careful validation of model predictions regarding the arrhythmogenic substrate, compared to electro-anatomical mapping data during the procedure.

One representative publication from each co-supervisor:
MJB: Balaban, G., Halliday, B. P., Bai, W., Porter, B., Malvuccio, C., Lamata, P., et al. (2019). Scar shape analysis and simulated electrical instabilities in a non-ischemic dilated cardiomyopathy patient cohort. *PLoS Computational Biology*, *15*(10), e1007421–18. http://doi.org/10.1371/journal.pcbi.1007421

AR: Mendonca Costa C, Neic A, Kerfoot E, Porter B, Sieniewicz B, Gould J, Sidhu B, Chen Z, Plank G, Rinaldi CA, Bishop MJ, Niederer SA. Pacing in proximity to scar during cardiac resynchronization therapy increases local dispersion of repolarization and susceptibility to ventricular arrhythmogenesis. Heart Rhythm. 2019 Oct;16(10):1475-1483. doi: 10.1016/j.hrthm.2019.03.027. Epub 2019 Mar 29. PMID: 30930329; PMCID: PMC6774764.

BE-MI20224 Neuroimaging in the management of brain abnormalities: optimizing deep learning methodology

Co Supervisor 1A: Dr Thomas C Booth
Research School/ Division or CAG: School of Biomedical Engineering and Imaging Sciences
Email: thomas.booth@kcl.ac.uk
Website: Dr Thomas Booth (kcl.ac.uk)

Co Supervisor 1B: Marc Modat
Research School/ Division or CAG: School of Biomedical Engineering and Imaging Sciences
Email: marc.modat@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/marc.modat.html

Project Description:

Aim:
To develop a decision-making tool that identifies abnormalities on MRI brain scans using deep learning in 'real-world' conditions.

This will be applied to patient groups where there are non-specific symptoms such as headache or memory loss.

Objectives:
1. Clean datasets for patient groups with non-specific symptoms (e.g. headache or memory loss).
2. Complete analytical validation of classification model identifying relevant abnormalities on brain MRI scans to demonstrate >0.95 accuracy/precision/recall/F1-score.
3. As 2 but out-of-sample external validation (using prospectively-acquired brain MRI datasets from multiple NHS sites).

Main tasks:

Year 1:
Develop initial classifier. Implement several approaches and contrast them, including: recurrent neural network (long short-term memory), Transformer and variational auto-encoder approaches.

Year 1-2:
(a) Ensure KHP neurodegenerative disease datasets (memory loss) are cleaned and pre-processed for training and undergo hold-out testing.
(b) Build KHP datasets for those patients presenting with other non-specific symptoms such as headache and organise (i) demographic/presenting clinical co-variates (where possible) and (ii) subsequent outcomes (headache outcome classes would include normal/mass/bleed/inflammation/vascular subgroups) using radiology reports and our NLP classifier[1].

Year 1-3:
Training and hold-out testing for patient groups from (b) using developed models through transfer learning of (a); if not successful for any particular patient group to rebuild classifier de novo.

Skills learnt: Machine learning, MRI translational design, statistics. Also broader topics including Careers & Employability, Communication & Impact, Personal Effectiveness, and Writing & Publishing. Complemented by faculty and departmental lectures and seminars along with one-to-one supervisions to develop skill in data handling and analysis.

<u>One</u> representative publication from <u>each co-supervisor</u>:

• Wood, D.A., Kafiabadi, S., Al Busaidi, A… **Booth T.C.** Deep learning to automate the labelling of head MRI datasets for computer vision applications. *Eur Radiol* (2021). https://doi.org/10.1007/s00330-021-08132-0

Fast free-form deformation using graphics processing units. **Modat M.,** Ridgway GR, Taylor ZA … Ourselin S. Comput Methods Programs Biomed. 2010 Jun;98(3):278-84. doi: 10.1016/j.cmpb.2009.09.002. Epub 2009 Oct 8.

BE-MI20225 Deep learning to explore early brain development using fetal MRI: application to high risk of preterm birth and Autism Spectrum Disorder

Co Supervisor 1A: Dr Maria Deprez
Research School/ Division or CAG: School of Biomedical Engineering and Imaging Sciences
Email: maria.deprez@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/maria.deprez.html

Co Supervisor 1B: Dr J-Donald Tournier
Research School/ Division or CAG: School of Biomedical Engineering and Imaging Sciences
Email: jacques-donald.tournier@kcl.ac.uk
Website: Dr Jacques-Donald Tournier (kcl.ac.uk)

Project Description:

Background: Investigation of fetal brain development can offer important information about biological mechanisms of vulnerability to Autism Spectrum Disorder (ASD) and neurodevelopmental consequences of preterm birth, before the brain is shaped by extra-uterine environment. Latest advances in fetal diffusion MRI allow detailed visualisation of microstructural brain development in-utero, but novel tools to analyse microstructure of the fetal brain are needed to find differences in early brain development in high risk populations.

Aim: We will develop Deep Learning techniques to quantify tissue properties of developing fetal brain to uncover biomarkers of ASD and high risk of preterm birth.

Workplan:
We will benefit from 300+ multimodal MRI scans of healthy fetuses from the Developing Human Connectome Project, plus additional scans of high risk fetuses.

Rotation project: Deep learning segmentation of transient fetal brain structures in multiparametric MRI. The training segmentations will be prepared using clustering of multimodal features of developing brain tissues. A convolutional neural network will be trained to provide fully automatic segmentation.
Year 1: Design novel microstructural measures to quantify average normal fetal brain development.
Year 2: Deep-learning techniques to obtain the novel microstructural measurements in individual babies.
Year 3: Comparison of developmental trajectories of different cohorts of fetuses (e.g. healthy, high risk of ASD or preterm birth), and assessment of brain development of individual babies.

Skills: The student will obtain a mix of deep learning, neuroimaging, image analysis and neuroscience skills. Training will be provided through opportunities to attend modules from MSc in Healthcare Technologies (Machine Learning, Medical Image Computing).

One representative publication from each co-supervisor:

M. Deprez et al., “Higher Order Spherical Harmonics Reconstruction of Fetal Diffusion MRI with Intensity Correction,” IEEE Trans. Med. Imaging 39(4), 2020.

Pietsch M, Christiaens D, Hutter J, Cordero-Grande L, Price AN, Hughes E, Edwards AD, Hajnal JV, Counsell SJ, Tournier JD. “A framework for multi-component analysis of diffusion MRI data over the neonatal period.” Neuroimage. 2019 Feb 1;186:321-337.

BE-MI20226 Developing combined *in vitro* & *in silico* models to study the impact of fluid flow on vascular cells in health and disease

Co Supervisor 1A: Eileen Gentleman
Research School/ Division or CAG: Centre for Craniofacial & Regenerative Biology/FoDOCS
Email: eileen.gentleman@kcl.ac.uk
Website: https://www.kcl.ac.uk/people/eileen-gentleman

Co Supervisor 1B: Pablo Lamara
Research School/ Division or CAG: School of Biomedical Engineering and Imaging Science
Email: Pablo.lamata@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/pablo.lamata.html

Project Description:

Aortic aneurysms result from excessive degradation of the extracellular matrix (ECM) comprising the vessel wall. Genetic predisposition impacts aortic aneurysm risk; however, 4D MRI imaging has revealed high wall shear stresses that correlate with increased expression of degradative enzymes at susceptible sites. This suggests that aberrant fluid flow both along the endothelium and interstitially through the vessel wall may contribute to aneurysm. Indeed, pathological flow likely imparts sufficient shearing forces to elicit mechanotransductive effects on both endothelial cells and ECM-synthesising vascular smooth muscle cells (VSMCs)/fibroblasts within the aortic wall.
This project aims to build in vitro&in silico models of the vessel wall to study the mechanisms of aneurism formation. In vitro bioreactors will deliver physiologically relevant luminal and transmural shear stresses to vascular cells within matrix-mimicking 3D synthetic hydrogels. Digital twin computational models will infer the shear and physical variables not directly observed in experiments. This dual reductionist platform will allow us to relate cellular response to flow-driven mechanical stresses.
Objectives:

1. Create bioreactors to deliver luminal&transmural shear stresses to endothelial/VSMC within 3D hydrogels.
2. Develop the digital twin of the bioreactor, the computational model that describes the flow physics and is tailored to the experimental conditions, to identify shear stresses not measurable through direct methods.
3. Evaluate the impact of normal&pathophysiological flow on endothelial/VSMC encapsulated within hydrogels using a combination of molecular biology and imaging techniques.

This is an exciting opportunity to work within our dynamic interdisciplinary team and is highly adaptable to the student's skills and interests.

One representative publication from each co-supervisor:

Lust ST, Shanahan C, Shipley RJ, Lamata P, Gentleman E (2021) "Design considerations for engineering 3D models to study vascular pathologies *in vitro*." ***Acta Biomaterialia***. doi: 10.1016/j.actbio.2021.02.031

Corral-Acero J, Margara F, Marciniak M, … and Lamata P "The Digital Twin to enable the vision of precision cardiology" European Heart Journal https://doi.org/10.1093/eurheartj/ehaa159

BE-MI20227 Biophysical Modelling for Surgical Interventions

Co Supervisor 1A: Dr Alejandro Granados
Research School/ Division or CAG: Dr Alejandro Granados
Email: alejandro.granados@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/alejandro.granados.html

Co Supervisor 1B: Dr Patrick Mesquida
Research School/ Division or CAG: Department of Physics
Email: Patrick.mesquida@kcl.ac.uk
Website: Dr Patrick Mesquida (kcl.ac.uk)

For translational projects:

Name of Collaborating Clinician Consultant and Prof of Neurosurgery Ashkan Keyoumars
School/Division & CAG: King's College Hospital, Denmark Hill
Email: k.ashkan@nhs.net
Website: https://www.kch.nhs.uk/profiles/40239/keyoumars-ashkan

Project Description:

Cognitive, behavioural and sensorimotor deficits affecting the quality of life of millions of people worldwide are associated with aging, trauma and neurodegenerative diseases. Implantable neuroprostheses alleviate many of the symptoms associated with these conditions and range from cochlear implants, to deep brain and spinal cord stimulation.

Despite our understanding of biophysical models is rapidly advancing, knowledge at lower scales is rarely taken into account during neurosurgery. Little is known about how microstructural components contribute to the macroscopic mechanical behaviour of tissue. Clinical translation of biophysical models is hindered by the difficulty to generate patient-specific predictions.

To this end, holistic mechanical modelling across different scales is a central tool to improve our understanding and prediction capabilities of the dynamics of brain behaviour. Machine learning brings opportunities to revisit multiscale models and to generate patient-specific models without the need to generate them from scratch.

The goal of this PhD project is to investigate how biophysical models can add value to surgical interventions, and to provide a platform for modelling patient-specific cases that can be translated into clinical practice. The specific objectives are:

- **Year 1** investigate biophysical models applied to surgery and spatiotemporal dynamics of tissue
- **Year 2** design simulation of biophysical models in contact with implants
- **Year 3** incorporate multiscale models and inverse problems
- **Year 4** design models for the discovery of biophysical components from sparse data across scales

This project is multidisciplinary and offers a combination of skills in biophysics, machine learning, multiscale modelling, and software development all applied to neurosurgery.

One representative publication from each co-supervisor:

A Granados, F Perez-Garcia, M Schweiger, V Vakharia, SB Vos, A Miserocchi, AW McEvoy, JS Duncan, R Sparks, S Ourselin. *A generative model of hyperelastic strain energy density functions for multiple tissue brain deformation*. **Int J of Computer Assisted Radiology and Surgery**; 16: 141–150 (2021). https://link.springer.com/article/10.1007/s11548-020-02284-y

E Gachon, P Mesquida. *Mechanical Strain Alters the Surface Charge of Collagen Fibrils*. **ACS Nano**; 15(6): 9820–9826 (2021).
https://pubs.acs.org/doi/10.1021/acsnano.1c00682

BE-MI20228 CARdiac and Placental imaging in pregnancy (CARP)

Co Supervisor 1A: Jana Hutter
Research School/ Division or CAG: School of Biomedical Engineering and Imaging Sciences
Email: jana.hutter@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/jana.hutter.html

Co Supervisor 1B: Kuberan Pushparajah
Research School/ Division or CAG: School of Biomedical Engineering and Imaging Sciences
Email: kuberan.pushparajah@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/kuberan.pushparajah.html

For translational projects:

Name of Collaborating Clinician: Mary Rutherford
School/Division & CAG: School of Medical Engineering
Email: mary.rutherford@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/mary.rutherford.html

Project Description:

Gestational hypertensive disorders, with preeclampsia (PE, incidence 4-7%) at their extreme end, are a leading cause of maternal death and a major cause of perinatal mortality and morbidity. They also come with a lifelong increased risk for cardiovascular disease. The aetiology of PE remains largely unknown, hampering early diagnosis and prediction of long-term risks. The poor understanding and subsequent inferior diagnostic and therapeutic capacities might be a consequence of single organ studies and reliance on system-level biomarkers.

The aim of this PhD proposal is to non-invasively characterise unifying elements between the observed organ changes and the order of events resulting in PE and later cardio vascular disease risk. Advanced Magnetic Resonance Imaging, building upon previous efforts shown to reveal early signs of both placental and cardiac pathophysiology, will provide the novel comprehensive multi-organ characterization required to translate the imaging into a risk prediction for each woman -a core step towards more effective diagnosis and therapy.

Training skills: Assessment cardiac and placental MRI data, experience with fetal and maternal MRI, knowledge about how to correlate and how to assess causality between observations based on physiology.

Year 1: Assessment of acquired cardiac data; calculations of essential flow and cardiac quantities (eg stroke volume, cardiac work, cardiac index, strain); assessment of placental data (eg density of the villous tree)
Year 2: Observe and describe disease phenotypes; assess vascularity changes in both placenta and heart.
Year 3/Year 4: Correlate findings as per before with post-partum cardiac outcome; work towards identification of common risk factors.

One representative publication from each co-supervisor:

Steinweg JK, Hui GTY, Pietsch M, Ho A, van Poppel MP, Lloyd D, Colford K, Simpson JM, Razavi R, Pushparajah K, Rutherford M and Hutter J. T2* placental MRI in pregnancies complicated with fetal congenital heart disease. Placenta. 2021;108:23-3

BE-MI20229 Coherent Multi-Transducer Ultrasound Elastography

Co Supervisor 1A: Laura Maria Peralta Pereira
Research School/ Division or CAG: School of Biomedical Engineering and Imaging Sciences
Email: laura.peralta_pereira@kcl.ac.uk
Website: https://www.kcl.ac.uk/people/laura-peralta

Co Supervisor 1B: Jo Hajnal
Research School/ Division or CAG: School of Biomedical Engineering and Imaging Sciences
Email: jo.hajnal@kcl.ac.uk
Website: https://www.kcl.ac.uk/people/jo-hajnal

Project Description:

Ultrasound elastography is an emerging noninvasive imaging technique for detecting alterations in mechanical properties of tissue. As such, it can improve early diagnosis and the prognosis of treatments. Some applications include breast lesion characterization, assessment of liver fibrosis, and ablation guidance and monitoring. However, all these applications suffer from low sensitivity and specificity and may fail for individuals with high body mass index because elastography requires accurately estimate tissue displacements in all directions, which remains challenging with current hand-held ultrasound transducer technology.

The coherent use of multiple ultrasound transducers can lead to multi-view images with significant improvements in resolution and sensitivity that potentially would allow a much more accurate estimation of displacements from ultrasound data. This could be transformative for ultrasound elastography, improving the specificity in differentiating benign and malignant lesions and avoid unnecessary biopsies. The main goal of this project is to explore this potential through a new framework and devise the basis for the next generation elastography methods.

Objectives:
1) Design and implement 3D tracking estimate algorithms for multi-transducer ultrasound data.
2) Define and calculate the full strain field.
3) Investigate efficient inverse problem strategies to extract the relevant mechanical parameters.

The student will gain knowledge about medical ultrasound and its place in healthcare. They will obtain skills in ultrasound physics, elastic wave modelling, and signal processing techniques, including both numerical and experimental methods. They will work in a vibrant environment with state-of-the-art laboratory facilities, with training needs regularly reviewed.

One representative publication from each co-supervisor:

Peralta, L., Gomez, A., Luan, Y., Kim, B. H., **Hajnal, J. V.**, & Eckersley, R. J. (2019). Coherent Multi-Transducer Ultrasound Imaging. IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control, 66(8), 1316-1330. https://doi.org/10.1109/TUFFC.2019.2921103

Peralta, L., Ramalli, A., Reinwald, M., Eckersley, R. J., and **Hajnal, J. V.** (2020). "Impact of aperture, depth and acoustic clutter on performance of coherent multi-transducer ultrasound imaging," Applied Sciences, 10(21), 7655. https://doi.org/10.3390/app10217655

BE-MI202210 Advanced quantitative susceptibility mapping (QSM) of the heart using novel acquisition strategies and artificial intelligence.

Co Supervisor 1A: Dr. Sebastien Roujol
Research School/ Division or CAG: School of Biomedical Engineering and Imaging Sciences
Email: sebastien.roujol@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/sebastien.roujol.html

Co Supervisor 1B: Pier Giorgio Masci
Research School/ Division or CAG: School of Biomedical Engineering and Imaging Sciences
Email: pier_giorgio.masci@kcl.ac.uk
Website: https://www.kcl.ac.uk/people/pier-giorgio-masci

Project Description:

Acute myocardial infarction (MI) is responsible for ~100,000 hospital admissions/year in the UK. Acute MI results in myocardial tissue injury which often lead to inflammation and other frequent complications such as myocardial haemorrhage, associated with adverse outcomes. Cardiac magnetic resonance imaging (CMR) is an attractive imaging modality for the monitoring of these patients. Myocardial haemorrhage is associated with high iron concentration. In the presence of a strong magnetic field (such as an MRI scanner), iron deposits act like little magnets which affect the local magnetic susceptibility. Magnetic susceptibility is an MR-parameter which can be quantified using advanced MRI acquisition and post-processing techniques. The initial feasibility of cardiac quantitative susceptibility mapping (QSM) has been recently demonstrated and shows great promise for iron deposition assessment in the heart. However, these methods remain sensitive to motion artefacts and have long scan/reconstruction time, which prevents their feasibility in a clinical scenario. The aim of this PhD is to develop the next generation CMR QSM framework which is feasible in patients. The specific aims are:

Aim 1: To develop a novel 3D free breathing cardiac QSM approach with high spatial resolution and improved motion robustness. As data will be acquired at different breathing positions, the estimation of a 4D model (3D + respiratory motion) of the data will be evaluated using undersampled data from each respiratory phase.

Aim 2: To further accelerate cardiac QSM using high underdamping strategies. Deep learning techniques will be explored for accelerated QSM acquisition/reconstruction.

Aim 3: To evaluate the developed prototype QSM techniques in 30 acute MI patients.

One representative publication from each co-supervisor:

S. Roujol, S. Weingartner, M. Foppa, K. Chow, K. Kawaji, L. Ngo, P. Kellman, W.J. Manning, R.B. Thompson, and R. Nezafat. Accuracy and reproducibility of four T1 mapping sequences: A head-to-head comparison of MOLLI, ShMOLLI, SASHA, and SAPPHIRE. Radiology, 272(3):683-9, 2014.

Right ventricular ischemic injury in patients with acute ST-segment elevation myocardial infarction: characterization with cardiovascular magnetic resonance.
Masci PG, Francone M, Desmet W, Ganame J, Todiere G, Donato R, Siciliano V, Carbone I, Mangia M, Strata E, Catalano C, Lombardi M, Agati L, Janssens S, Bogaert J. Circulation. 2010 Oct 5;122(14):1405-12. doi: 10.1161/CIRCULATIONAHA.110.940254. Epub 2010 Sep 20. PMID: 20855663

BE-MI202211 Utilising and exploring biosynthetic pathways in cancer cells to biosynthesise near infrared quantum dots for tools in image guided surgery

Co Supervisor 1A: Dr Graeme Stasiuk
Research School/ Division or CAG: School of Biomedical Engineering and Imaging Sciences
Email: Graeme.stasiuk@kcl.ac.uk
Website: Dr Graeme Stasiuk PhD, MChem, FHEA, MRSC (kcl.ac.uk)

Co Supervisor 1B: Professor Mark Green
Research School/ Division or CAG: School of Biomedical Engineering and Imaging Sciences
Email: mark.a.green@kcl.ac.uk
Website: **https://www.kcl.ac.uk/people/mark-green**

For translational projects:
Name of Collaborating Clinician: Professor Arnie Purushotham
School/Division & CAG: Comprehensive Cancer Centre
Email: arnie.purushotham@kcl.ac.uk
Website: https://www.kcl.ac.uk/lsm/research/divisions/cancer/icc/profiles/purushothama

Project Description:

The primary treatment for cancer is surgery, which often does not remove all the tumour is then followed by a significant chemotherapy regime. The aim of this project is to utilise the cancer cells to biosynthesise a fluorescent tool for image guided surgery (IGS) and understand how this biological process works. Tools will specifically delignate the tumour margins and allow for greater resection of the tumour and lessen the need for chemotherapeutics. In this study breast cancer cells will be used to biosynthesise Ag_2S quantum dots. The near-infrared emitting QDs will grow directly in the tumour and upon external light excitation, will be visible as a fluorescent tag for the cancer. The project will validate and bring understanding to the biosynthesis of the Ag_2S QDs in breast cancer cells, developing biocompatible tools to be used in IGS.

Year 1 – Developing cell culture techniques and validating toxicological of the precursors with cancer and health cell lines (MDA-MB-231, MCF7 and HEK 293). MTS/MTT Toxicology assays, confocal microscopy and flow cytometry.

Year 2 – Preparation and understanding the biosynthesis of Ag_2S in tumour cells. Using salts to biosynthesis the QDs in cancer cells. Use FACs, and western blotting to quantify/localise metal transporter proteins to understand mechanism of entrance into the cancer cell, using antibodies and antagonists to block these transporter proteins.

Year 3 – Optimisation of biosynthesis and use in biological imaging.
Fully characterised biosynthesised QDs (UV, PL, XRD, TEM). Preclinical imaging studies of the biosynthesis in murine model of breast cancer.

One representative publication from each co-supervisor:

"Synthesis of super bright InP based quantum dots through thermal diffusion", M. T. Clarke, F. N. Viscomi, T. W. Chamberlain, N. Hondow, A. M. Adawi, J. Sturge, S. C. Erwin, J.-S. G. Bouillard, S. Tamang and G. J. Stasiuk*, Communication Chemistry, 2, Article number: 36 (2019). (NPG)

'Biosynthesis of Luminescent Quantum Dots in an Earthworm.' S. R. Stürzenbaum, M. Hoeckner, A. Panneerselvam, J. Levitt, J.-S. Bouillard, S. Taniguchi, L.-A. Dailey, R. Ahmad Khanbeigi, E. V. Rosca, M. Thanou, K. Suhling, A. V. Zayats, M. Green.* Nature Nanotechnology, 2013, 8, 57.

BE-MI202212 Virtual Heart Assay

Co Supervisor 1A: Steven Niederer
Research School/ Division or CAG: School of Biomedical Engineering and Imaging Sciences
Email: steven.niederer@kcl.ac.uk
Website: Professor Steven Niederer (kcl.ac.uk) and www.**cemrg.com**

Co Supervisor 1B: Dr Tevfik F Ismail
Research School/ Division or CAG: School of Biomedical Engineering and Imaging Sciences
Email: tevfik.ismail@kcl.ac.uk
Website: **https://www.kcl.ac.uk/people/tevfik-ismail and https://www.guysandstthomas.nhs.uk/our-services/consultant-profiles/cardiovascular/cardiology/tevfik-ismail.aspx**

Project Description:

Heart Failure (HF) is a progressive and prevalent disease, where the heart is unable to pump enough blood to meet the demands of the body. HF has many causes, however, decreased pump function remains a key factor. Cardiac function is regulated across multiple scales and physics. This can make the identification of specific mechanisms underpinning HF challenging. This project will use biophysical cardiac models, that describe cardiac biomechanics of the sarcomere, cell, tissue, organ, and pre/after load, to create a virtual heart assay, that will be calibrated to individual patients using machine learning techniques. This will estimate the mechanisms underpinning a patients HF.

Year 1
- Data curation and Model Sensitivity: Automatic workflows for segmenting and tracking motion from CMR heart failure images will be created, verified, and validated. A sensitive analysis will identify the key parameters in the model that can be calibrated by clinical data.

Year 2:
-Model Calibration: Machine learning emulators will be trained to provide surrogates for the full model to allow Bayesian model calibration.

Year 3-4:
-Application of Virtual Heart Assay: We will apply the workflow to patient to identify the underlying mechanisms causing HF and compare these with patient outcomes.

The project will require working with clinical data, image segmentation and feature tracking, creating, and running finite element models and machine learning based model calibration. The project will rely heavily on Python, TensorFlow / PyTorch, Linux and simulations on high performance computing and would suite a student with a technical background.

One representative publication from each co-supervisor:

Longobardi S, Lewalle A, Coveney S, Sjaastad I, Espe EKS, Louch WE, Musante CJ, Sher A and ***Niederer SA***. Predicting left ventricular contractile function via Gaussian process emulation in aortic-banded rats. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences*. 2020;378:20190334.

Georgiopoulos G, Figliozzi S, Sanguineti F, Aquaro GD, di Bella G, Stamatelopouls K, Chiribiri A, Garot J, Masci PG, ***Ismail TF***. Prognostic Impact of Late Gadolinium Enhancement by CMR in Myocarditis: A Systematic Review and Meta-analysis. *Circulation Cardiovasc Imag* 2021;14:e011492.

BE-MI202214 Silent Motion-Insensitive Multi-Contrast MR Neuroimaging

Co Supervisor 1A: Prof Steve C.R. Williams
Research School/ Division or CAG: Dept Neuroimaging, School of Neuroscience, IoPPN
Email: Steve.Williams@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/steve.williams.html

Co Supervisor 1B: Prof Gareth J. Barker
Research School/ Division or CAG: Dept Neuroimaging, School of Neuroscience, IoPPN
Email: Gareth.Barker@kcl.ac.uk
Website: https://www.kcl.ac.uk/people/gareth-barker-1

For translational projects:
Name of Collaborating Clinician: Prof Dag Aarsland
School/Division & CAG: IoPPN/Psychiatry & Old Age Psychiatry
Email: dag.aarsland@kcl.ac.uk
Website: https://www.kcl.ac.uk/ioppn/depts/oldage/people/dag-arsland

Project Description:

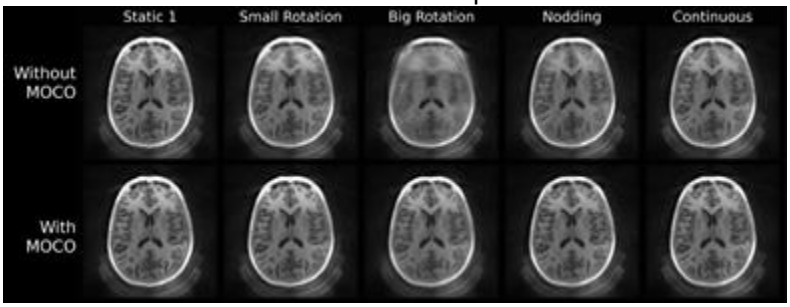
Objective: To develop silent, motion-insensitive, multi-contrast MR imaging for neurology and psychiatry.

Background: MRI is a cornerstone of radiology, but continuing concerns are the extremely loud acoustic noise during scans and that patient movement degrades image quality. Overcoming these would allow clinical assessment of the most challenging and unwell patient populations including sleeping babies, migraineurs, tinnitus patients, and those suffering from dementia or Parkinson's Disease.

Project proposal: In this project we will build on promising preliminary evidence from our team to develop a suite of high-resolution, full-brain, motion-insensitive, silent MR protocols for neuroimaging. These methods work without additional hardware or increased scan time and so can be on deployed on existing MRI systems.

The work will be divided into technical development - consisting of modification and improvement of our existing MR pulse sequences and development of new reconstruction methods incorporating retrospective motion correction and fingerprinting type approaches - followed by clinical evaluation in neurology and psychiatry patients across the lifespan.

Timeline:
Year 1 – evaluation of current motion-correction technique and extension to new contrasts
Year 2 – implementation and testing of enhanced motion correction approaches in healthy volunteers
Year 3 – extension to patient cohorts which include dementia patients and autistic individuals.



An example of early work with the current silent motion correction (MOCO)approach, for a single contrast. This project will further enhance the motion robustness and ensure it works with a range of MRI contrasts, enabling a clinically useful fully silent protocol.

One representative publication from each co-supervisor:

Silent zero TE MR neuroimaging: Current state-of-the-art and future directions
Emil Ljungberg, Nikou L Damestani, Tobias C Wood, David J Lythgoe, Fernando Zelaya, Steven C R Williams, Ana Beatriz Solana, Gareth J Barker, Florian Wiesinger
Progress in Nuclear Magnetic Resonance Spectroscopy. 2021 Apr; 123:73-93.
doi: 10.1016/j.pnmrs.2021.03.002.

Silent T1 mapping using the variable flip angle method with B1 correction
Emil Ljungberg, Tobias Wood, Ana Beatriz Solana, Shannon Kolind, Steven C. R. Williams, Florian Wiesinger, Gareth J. Barker
Magnetic Resonance in Medicine.2021 Aug; 84(2):813-824
https://doi.org/10.1002/mrm.28178

BE-MI202215 Development of Novel ^{18}F-labelled Molecular Probes for CAR T-cell Tracking with Positron Emission Tomography

Co Supervisor 1A: Ran Yan
Research School/ Division or CAG: School of Biomedical Engineering & Imaging Sciences
Email: ran.yan@kcl.ac.uk
Website: Dr Ran Yan (kcl.ac.uk)

Co Supervisor 1B**:** John Maher
Research School/ Division or CAG: School of Cancer and Pharmaceutical Sciences
Email: john.maher@kc.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/john.maher.html

Project Description:

Immunotherapy with CAR T-cells can produce potent and sustained responses in various cancers. Maher (co-supervisor) engineered an ErbB2 CAR that re-targets T-cells against human epidermal growth factor receptor 2 (HER2) expressing cancers including the childhood bone cancer, osteosarcoma. A chimeric IL-2/ IL-4 cytokine receptor (4ab) was engineered for selective CAR T-cell expansion *in vitro* with interleukin (IL)-4 (ref 2 below). An IL-4 mutein, IL-4DE has picomolar binding affinity for 4ab but does not bind to non-haematopoietic IL-4 receptors. As 4ab could be incorporated with any CAR, we envisage that a generic PET imaging method to track the persistence and proliferation of 4ab containing CAR T-cells can be developed from ^{18}F-labelled IL-4DE. Thus, the new cell tracking probe would personalise the CAR T-cell therapies by providing early insight into their safety, mechanism of action, and therapeutic efficacy.

Year one: ^{18}F-labelling of IL-4DE with bioconjugation reagents, either ^{18}F-FSB or ^{18}F-FBEM and characterisation of the resulting ^{18}F-IL-4DE variants
Milestone: identify optimal conditions to prepare ^{18}F-IL-4DE variants

Year two: systematically evaluating ^{18}F-IL-4DE variants *in vitro*
Milestone: identify the ^{18}F-IL-4DE variants that demonstrate specific binding with preservation of CAR T-cell function.

Year three: *in vivo* tracking of 4ab containing CAR T-cells using ^{18}F-IL-4DE with PET imaging in HER2 positive U2OS osteosarcoma xenograft in NSG mice
Milestone: PET imaging with ^{18}F-IL-4DE will be deemed successful if it enables clear visualisation and quantification of 4ab containing CAR T-cells in osteosarcoma xenograft NSG mice.

Year four: thesis/manuscript writing

Key techniques and skills:
^{18}F-chemistry, cell culture, CAR T-cell transduction, animal handling, PET imaging

<u>One</u> representative publication from <u>each co-supervisor</u>:

T. T. Pham, Z. Lu, C. Davis, F. Sun, J. Maher, R. Yan *Iodine-124 Based Dual Positron Emission Tomography and Fluorescent Labeling Reagents for In vivo Cell Tracking.* Bioconjugate Chemistry, 2020. 31, 4, 1107-1116.

van Schalkwyk MCI, van der Stegen SJC, Bosshard-Carter L, Graves H, Papa S, Parente-Pereira AC, Farzaneh F, Fisher CD, Hope A, Adami A, Maher J (2021) Development and validation of a good manufacturing process for IL-4-driven expansion of chimeric cytokine receptor-expressing CAR T-cells. **Cells** 10(7) 1797.