4-Year PhD Programme
Cardiovascular & Diabetes
Project proposal

Title: Development of novel diffusion MRI methods for characterising cardiac microstructure

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Abstract:

The function of the heart is governed by its structure. Diffusion magnetic resonance imaging (DMRI) is a unique method for assessing the 3D architecture and microstructure in the intact heart. Here, water diffusion serves as a sensitive marker of tissue integrity and orientations of cellular and laminar structures. We have previously optimised high-resolution diffusion MRI ex vivo [1], and now seek to implement robust DMRI techniques in vivo.

Diffusion metrics, such as the apparent diffusion coefficient and fractional anisotropy are potentially important biomarkers in cardiac disease, including myocardial infarction, ischaemia and hypertrophy. However, DMRI in vivo remains highly challenging in the face of sensitivity to motion, strain and perfusion. Intra-voxel incoherent motion (IVIM) is a promising diffusion MRI technique for separating the effects of perfusion and microscopic motion of water [2]. The aim of this project is to further develop IVIM techniques, in conjunction with appropriate strategies for mitigating motion and strain and accelerating data acquisition, for accurate, reproducible and tractable diffusion MRI in the heart in vivo. The project will primarily be conducted at the new Preclinical Imaging Facility, with the goal of translating key developments to the clinic, via our strong link with the clinical cardiac MR group.

References


Background

**Biology**: The heart is a remarkably efficient and effective electro-mechanical pump for supplying the continuous flow of blood that is obligatory for life. The critical importance of its function is represented by the very high incidence of mortality and morbidity associated with cardiac pathology both in the U.K. and western world. A key determinant to the pump function of the heart is the complex architecture of the myocardium, comprised of muscle and connective tissue. In particular, this micro-structural architecture fundamentally defines both the electrical conductivity and mechanical stiffness of the heart wall. Its dysregulation in heart failure is correspondingly a strong independent predictor of mortality (1).

This central role of cardiac micro-structure in both health and disease has motivated the development of techniques to image cardiac structure. In particular, diffusion magnetic resonance imaging (DMRI) is a rapidly developing field within both the pre-clinical and clinical communities due its non-invasiveness. Cardiac DMRI measures the diffusion of water molecules in the myocardium due to Brownian motion. Water diffusion serves as a sensitive marker of tissue integrity and orientations of cellular and laminar structures. More specifically, the main directions of diffusion provide a surrogate measure of cardiac cell orientations, which in turn define indices of electrical conductivity and mechanical stiffness that fundamentally determine electro-mechanical cardiac function. The key role of structure means that cardiac DMRI data are also increasingly being used to validate computational models of electrical conductivity and mechanical function of the heart in both clinical applications and basic science research. The accurate interpretation of DMRI data is therefore vital.

**DMRI**: Diffusion is measured quantitatively using a pair of magnetic field gradients (2). The first gradient induces phase dispersion across the sample. This phase dispersion is rewound by the second magnetic field gradient. However, in the presence of diffusing spins, residual phase dispersion remains, resulting in a quantifiable signal loss representing diffusivity of water. Hence, DMRI extracts the parameters from processes that cause a signal reduction, impacting on the signal-to-noise-ratio (SNR). The most commonly applied DMRI technique is **Diffusion Tensor Imaging (DT-MRI)**, which models diffusion as a Diffusion Tensor (DT). The DT is a symmetric 3×3 matrix, which requires at least 6 measurements with different diffusion gradients plus one reference scan for full characterization. This large number of measurements combined with SNR requirements, means that even with long scan times spatial resolution remains limited.

In the heart, water molecules diffuse preferentially along the long axes of cardiomyocyte chains (‘myofibres’). The primary eigenvector of the DT (with the largest eigenvalue) indicates this preferred direction. The secondary eigenvector points transverse to the fibre direction in the plane of myocardial sheets formed by close association of 4-5 cardiomyocyte layers. The tertiary eigenvector identifies the sheet-normal (3,4). Furthermore, diffusion metrics, such as the apparent diffusion coefficient and fractional anisotropy are potentially important biomarkers in cardiac disease, including myocardial infarction, ischaemia and hypertrophy.

DMRI has been applied ex vivo on fixed hearts of several species, from sheep to mice (5-7). We have previously optimised high-resolution DT-MRI ex vivo (8), allowing us to identify fine anatomical cardiac features not previously described with DT-MRI, and novel segmentation of cardiomyocyte populations. However, movement of the heart...
(the motion scale of which is at least 3 orders of magnitude larger than the one of diffusing water molecules), sensitivity to strain and perfusion place significant technical challenges on the in vivo application of DMRI. We now seek to implement robust DMRI techniques in vivo to characterize the micro-architecture of the beating heart. While several studies have reported on the application of DMRI on the human heart (9-11), very little has been published on small animal models (e.g. (12,13)).

In particular, in vivo DMRI is affected by perfusion, and the measured diffusion coefficients are determined by both the microscopic motion of water (i.e. molecular diffusion) and by the microcirculation of blood in the capillary network. The intravoxel incoherent motion (IVIM) model, which was introduced in the late 80’s, links diffusion and perfusion to the measured MR signal (14). While the fundamental principles are the same as for DT-MRI, IVIM requires a larger number of scans with different diffusion weightings in order to accurately estimate the respective parameters. Although IVIM-derived parameters such as pseudo-diffusivity have been shown to reflect changes in myocardial perfusion, its measurements vary by more than 4-fold in the literature, underscoring the need for more robust measurements (15-17).

Hypothesis

We hypothesize that IVIM will further our understanding of the myocardial microstructure in small animal models of cardiac disease, by accounting for both myocardial diffusion and perfusion. IVIM parameters are anticipated to serve as sensitive markers of disease.

Aim

The aim of this project is to develop optimized IVIM techniques to provide novel micro-structural characterization of the healthy and of the diseased myocardium, with the ultimate vision to translate the developments to the clinical setting and to apply the techniques to humans (volunteers and patients with heart disease).

Objectives

- To develop in vivo DMRI techniques in mouse hearts.
- To implement IVIM in mouse hearts.
- To apply cardiac DMRI and IVIM to a mouse model of hypertrophy.

Workplan

The student will be introduced to the topic of DMRI by completing two mini projects (see details below) aimed to provide basic skills / knowledge and to facilitate the research of the main project. While the work will take place in the preclinical setting, the project will enjoy close interactions with clinical scientists. This will ultimately help to translate the technical developments into the clinic.

During year 1 of the main project, the student will complete the Home Office training course to obtain a personal licence authorizing the animal work. He / she will also be
trained in preclinical cardiac MR and MR sequence programming.
In year 1, work will also begin to address a key requirement, i.e. to establish dedicated measurement techniques. Most of the post-processing tools are already available. Our pilot work previously used a stimulated echo imaging sequence, which inherently provides 50% less signal compared to spin-echo sequences. Thus, the applicability of spin-echo and faster imaging sequences (for example based on echo-planar or non-cartesian imaging), which are inherently challenging at high magnetic fields, will be explored. The sequence of choice will need to be combined with dedicated motion compensation schemes in order to minimize motional influence of the fast heartbeat and respiration on the data acquisition. Optimizing sequence type and timing are imperative for maximizing the achievable spatial resolution and signal-to-noise ratio. In the next phase, scan time reduction schemes (i.e. based on Compressed Sensing) will be explored. This will allow for optimizing the number of different diffusion directions / weightings required for DMRI and IVIM within physiologically acceptable scan times. Work on the scanner will be complemented by simulations, which are aimed to determine optimal acquisition strategies for quantifying the IVIM parameters. Technical developments and optimization work will take up most of year 1 and 2 of the project. Year 3 will see the validation of the developed techniques on healthy mouse hearts first, with the aim to establish baseline values for the contributions of diffusion and microcirculation. This will be followed by an application to a mouse model of cardiac hypertrophy.

References
MINI PROJECT 1 – PRECLINICAL DMRI

The aim of the first mini project is to get insights into the preclinical MR environment and first exposure to DMRI.

Plans of Investigation

Mentor: Dr Irvin Teh

Training plan:

1. Acquisition of preclinical ex vivo cardiac DMRI data
   Hands-on training will be provided in the preparation of samples and the conduct of cardiac DMRI experiments ex vivo. The student will learn about the differences in imaging in the preclinical and clinical environment, including the technical differences of imaging at different field strengths. These will form a basis for designing strategies for optimisation of DMRI acquisitions.

2. Introduction to pulse sequence programming
   Pulse sequences are the highly orchestrated combination of radiofrequency pulses, gradients and readouts that create signal, encode spatial information and enable data acquisition. The student will have the opportunity to apply his/her theoretical MRI physics knowledge to modify and simple program pulse sequences.

3. Assessing the influence of MR parameters on DTI metrics
   The accuracy of the measured diffusion parameters, such as diffusivity and fractional anisotropy, depend on various experimental determinants, including spatial resolution, available signal-to-noise ratio (SNR), number of diffusion directions etc. Here we will use high-resolution, high-quality MRI data acquired ex vivo in a fixed mouse heart as ground truth. Parameters such as SNR or spatial resolution will be retrospectively altered in post-processing, and the impact on the diffusion analysis will be quantified.

4. To build in-silico models of myocardial microstructure
   Computer models are vital to informing study design and interpretation of data. They enable simulation of results in a controlled manner that can be used to validate experimental data, or probe parameter space that is unfeasible with physical experiments. The aim here is to develop models of microstructure that simulate the highly organised structure of the myocardium. These models will be used for validation of advanced DMRI techniques.
MINI PROJECT 2 – CLINICAL DMRI

The aim is to assess diffusion parameters in the healthy and diseased human heart. The student will understand the translational value of the preclinical work by getting familiar with acquisition and post processing of cardiac MRI images, and, more specifically, DMRI. The student will have the opportunity to understand the challenges of CMR clinical applications.

Plans of Investigation

Mentor: Dr Erica Dall’Armellina

Training plan:

1. Introduction to clinical MRI and its applications in heart disease, specifically ischemic heart disease and hypertrophic cardiomyopathy.
2. Exposure to clinical MRI acquisitions: the student will learn about MR safety, and will be introduced to the challenges of clinical scanning including breath-holding and ECG gated acquisitions. Such limitations (amongst others) challenge the effective and rapid translation of techniques into the clinical setting.
3. The student will be exposed to image post processing, acquiring knowledge of the human cardiac anatomy in volunteers and aspects of pathological heart / myocardium
4. The student will be given the possibility to analyse in vivo DMRI data obtained in volunteers and in patients. This will contrast and complement the work from mini project 1, which utilises high quality ex vivo data.