Quantitative Preclinical Imaging: Strategies, Pitfalls, and Alternatives

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Over the past 3 decades, Magnetic Resonance Imaging (MRI) has become an established medical imaging modality due to its superior soft tissue contrast and lack of ionizing radiation. Conventional diagnostic MRI scans are non-quantitative by nature, but have provided clinicians and radiologists with the ability to detect multiple disease pathologies including cancer [1-3], stroke [4-6], musculoskeletal defects [7, 8], and cardiovascular disease [9-11], among many others. Recently, efforts have been made to establish quantitative MRI assessments as biomarkers for disease detection and progression. These quantitative MRI assessments have included T_1 and T_2 relaxation times [12-15], proton density [14, 15], multiple diffusion and perfusion parameters [16-22], as well as chemical exchange and magnetization transfer [23-28]. Despite these efforts, the majority of routine clinical MRI scanning remains qualitative.

High field ($\geq$ 4.7 T) preclinical MRI scanners have been developed to provide MRI measures of disease in rodent models. In contrast to clinical MRI scanning, preclinical MRI research studies are almost entirely quantitative by nature and may require assessment of multiple imaging parameters during a single scanning session. These quantitative preclinical MRI studies provide the opportunity to assess pathophysiologic changes associated with disease progression and therapeutic efficacy. In addition, rigorous validation of these preclinical MRI assessments has the potential to inform future clinical quantitative imaging studies. Therefore, a significant effort is ongoing to develop robust and effective acquisition and reconstruction techniques that can be used routinely in clinical practice.

Conventional quantification methods in MRI are mostly based on linear or nonlinear curve fitting to various MRI models [12, 29, 30]. The implementation of these established model-based methods, such as T_1 and T_2 relaxation time estimation, are straightforward. However, these conventional quantification methods are susceptible to multiple sources of errors including cardiac and respiratory motion artifacts [31-33], as well as heterogeneity in the main magnetic field (B_0) and radiofrequency (RF) excitation profile (B_1) [34-36]. Importantly, the potential for these errors are significantly increased on high field preclinical MRI scanners where B_1 and B_0 heterogeneities are increased; rodent heart rates can be as high as 500-600 beats / minute; and breathholds are not possible (**Figure 1**). In addition, temporal errors can be observed in preclinical studies that require multiple imaging parameter estimates (ex. diffusion and perfusion) as extended periods of anesthesia can cause physiologic changes during sequential scans. Therefore, new MRI acquisition and reconstruction methods for preclinical imaging applications that are immune to these error sources and can simultaneously obtain estimates of multiple imaging parameters are needed.

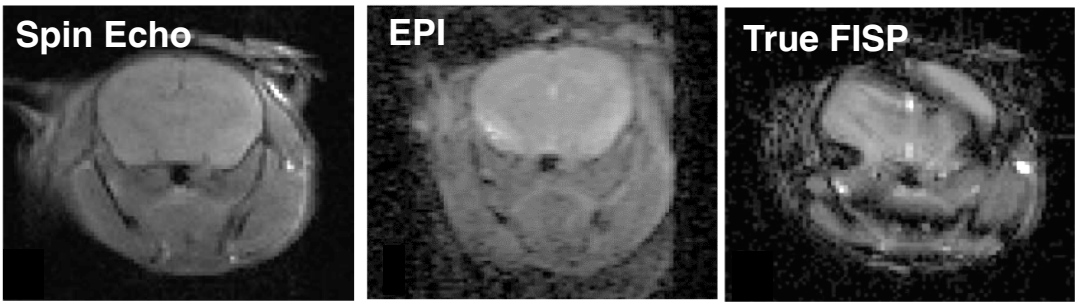

Figure 1: Axial images of a mouse brain obtained with conventional spin echo, echo-planar imaging (EPI), and True FISP imaging techniques. While the long spin echo acquisitions provide good quality images, the more rapid imaging techniques exhibit enhanced distortion / ghosting (EPI) and banding (True FISP) artifacts on high field MRI scanners.

Over the last few years, a new category of quantification in MRI has emerged which uses dictionary-based methods to "match" acquired data rather than conventional parameter estimation techniques using error-minimization methods. One of these methods, compressed sensing, has been developed for both clinical and preclinical applications and has been shown to limit quantification errors and/or reduce the overall time to acquire quantitative data sets [37-41]. More recently, a new Magnetic Resonance Fingerprinting (MRF) methodology has been proposed [42, 43]. MRF uses an entirely unique acquisition and quantification strategy that combines *a priori* acquisition parameter variation with a dictionary-

based matching algorithm to obtain quantitative assessments of multiple imaging parameters simultaneously. The MRF technique was initially developed for low-field (1.5T–3T), clinical MRI scanners and was used to simultaneously generate T_1, T_2, and M_0 maps in both humans and rodent models. Further, these initial reports have shown that the MRF technique is inherently resistant to errors from motion artifacts as motion is not "encoded" into the MRF dictionary. Therefore, MRF may provide an ideal basis to generate multi-parametric assessments for preclinical imaging applications with limited impact of motion artifacts.

In this study educational session, we are going to review the current state-of-the-art in quantitative, high field preclinical MR imaging. This educational session will primarily be a "how-to" session providing information on the challenges, solutions, and future opportunities for many investigators to obtain reliable quantitative assessments of diffusion, perfusion, chemical exchange, etc in animal models. We will begin by describing the technical challenges associated with obtaining high quality images on high field, preclinical MRI scanners including B0/B1 inhomogeneities and increased artifacts including susceptibility, banding eddy currents, motion artifacts, chemical shift artifacts, etc. We will describe the advantages / disadvantages of conventional spin echo and gradient echo imaging readouts and then describe how other imaging readouts including GRASE and FISP as well as non-Cartesian trajectories can be used to provide improved imaging quality and/or reduced acquisition time as a basis for improved image quantification. Finally, we will describe some examples of compressed sensing and MR fingerprinting strategies that offer the opportunity to diminish the impact of respiratory and/or cardiac motion artifacts that are extremely problematic for preclinical MRI studies.

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