Frontiers in Advanced MRI 1

SY03-1

Magnetic Resonance Susceptometry: Principles and Applications in Biomedicine

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Introduction. Accurate measurement of magnetic susceptibility of nominally non-magnetic medium requires strong applied magnetic field combined with sensitive detection. Such measurements traditionally utilized superconducting sensors in a dedicated cryogenic setup. Modern high-field MRI provides an ideal combination of strong magnetizing field and sensitive measurement readily applicable to biological tissue. Furthermore, the inherent localization capability of MRI allows detailed magnetic imaging of an object both in-vivo and ex-vivo, with or without magnetic contrast agents. This talk will overview the principles and practices of MR susceptometry with emphasis on applications in biomedicine.

Principles. In the limit of rapid molecular motion, the free induction decay (FID) time of liquid-state hydrogen nuclear spin is governed by the spin-lattice relaxation time (T_1). Since T_1 increases with the Larmor frequency, the relative precision of the NMR frequency measurement grows with the main magnetic field. With the help of carefully designed hardware, an NMR field probe with frequency resolution approaching $1{:}10^{12}$ was demonstrated recently[1]. In our lab, we observed nuclear polarization-dependent MR frequency shift, on the order of $1{:}10^{9}$, in a regular water phantom in a clinical 3T scanner[2]. These experiments highlight the potential of MRI for high-precision magnetic susceptometry.

QSM. During imaging, most of the FID time is used for spatial encoding, and a few discrete phase samplings at different echo times are used to extract the NMR frequency offset *df* in the rotating frame, through voxel-wise solution of *Delta_phi* (measured) = 2pi*df**Delta_TE* (control variable). Such limited phase sampling can still allow local frequency shift determination with precision on the order of $1{:}10^{8}$. Quantitative susceptibility mapping (QSM) has successfully achieved numerical inversion of the dipole-to-magnetic field equation to produce 3D tissue susceptibility maps with similar precision, sufficient to distinguish sub-mm brain structures[3] based on their normal susceptibility variation.

Other applications. Sensitive magnetometers have traditionally been used to measure weak magnetic susceptibility of prepared samples (MPMS, Quantum Design, CA, USA) and biological organs (Liver susceptometer, Tristan technologies, CA, USA). Scanning SQUID microscopes also produce 2D magnetic maps of a flat specimen (Magma SSM, Neocera, MD, USA). Such low-dimensional measurements could readily be carried out in conventional MR scanners, with applications in material screening as well as combined optical-magnetic measurement of biological tissue. For example, 2D susceptibility mapping could be useful to determine metallic ion distribution in brain slices routinely prepared for histology. 2D dipolar field inversion is theoretically free from magic-angle “streaking” artifacts found in 3D, which benefits reconstruction fidelity.

Conclusion. The high sensitivity in relative frequency measurement and high spatial resolution of MRI make it a powerful tool for magnetic susceptibility measurement and mapping in biomedical research, with promising paths to clinical translation. With further improvements in the stability and robustness of phase imaging and processing, new applications are expected to emerge in the areas such as dynamic/functional susceptibility mapping and bio-metal transport and metabolism.

[1] Gross S et al., Nat Comm doi:10.1038/ncomms13702 (2016) [2] Park Jinil et al., MRM doi: 10.1002/mrm.26570 (2016) [3] Lee S-K et al., 25th Annual Meeting of ISMRM (2017)

Keywords : Magnetic susceptibility, Susceptometry, QSM

Frontiers in Advanced MRI 1

SY03-2

Diffusion-weighted Spectroscopy

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Introduction

Diffusion-weighted spectroscopy (DWS), which acquires diffusion of metabolite, is expected to provide more specific biological information about tissue microstructure and functions compared to diffusion-weighted imaging (DWI) which acquires diffusion of water. Intracellular specific information: cell size and intracellular transport, can be investigated by using endogenous intracellular metabolites as probes. For example, neuronal information can be efficiently investigated by using N-acetylaspartate (NAA) which mostly exists in neurons. However, DWS has not been widely used because highly accurate measurement techniques have not been developed. In this presentation, I will talk about technical developments to improve its accuracy by reducing motion artifacts, and its application to medical studies on ischemia and Alzheimer's disease (AD) using animal models.

Technical Developments for Improved Accuracy

Recent improvements of MRI system, ex. increased static magnetic field, have enabled increasing SNR of DWS, and thus, current most challenging issue is to reduce motion artifacts caused by respiration or cardiac pulsation. Signal phase dispersion due to imbalance of motion probing gradients (MPG) leads to signal loss in accumulation and ghosting artifact in DW spectroscopic imaging (DWSI). We have developed two techniques for DWSI: DW line-scan echo-planar SI (DW-LSEPSI) and DW echo-planar SI using a pair of bipolar gradients as MPG (DW-EPSI with BPGs). DW-LSEPSI uses line-scan and echo-planar techniques instead of phase encoding technique to avoid ghosting artifacts, and uses water signal for phase correction to avoid signal loss in accumulation. DW-EPSI with BPGs removes phase errors caused by uniform motion during MPG. Both techniques were developed on a 7-T MRI for small-animal study. Effectiveness of the both techniques in reducing motion artifacts were demonstrated by using moving phantom and normal rat brains.

Application to Medical Studies

DW-EPSI with BPGs was applied to investigate the change in apparent diffusion coefficient (ADC) of NAA, Choline-containing compounds (Cho) and Creatine (Cr) after a middle cerebral artery occlusion (MCAO) in rat brains at 7T. Apparent diffusion coefficients (ADCs) of metabolites were reduced after MCAO; however, the reduction rates were smaller than ADC of water. The difference in the reduction rates may mean that ADC of metabolites is influenced by only some of the causes that reduces ADC of water, because these metabolites exist mostly in intracellular space.

Single-voxel DWS was applied to investigate the diffusion of metabolites in mouse brains of AD model. The ADCs of NAA, Cho, Cr and water were compared between wildtype and transgenic mice at 14T. Although the ADCs of water, Cr and Cho did not show significant differences; however, the ADC of NAA showed marginally significant difference. The difference in ADC of NAA may mean that neuronal changes at AD: axonal beading and reduced axonal transport, can be efficiently detected only by NAA.

Conclusion

We have developed measurement techniques to reduce motion artifacts of DWSI, and have shown the effectiveness of DWS for ischemia and AD studies. Although further investigation in both technical developments and understanding mechanism of metabolite diffusion, DWS will be a powerful tool to develop non-invasive biomarkers for neurological diseases *in vivo*.

Keywords : Diffusion, Spectroscopy, Motion artifact, Ischemia, Alzheimer's disease

Frontiers in Advanced MRI 1

SY03-3

Feature-preserved Fast MR Imaging

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Accelerating MR scan is of great significance for clinic, research and applications. Many advanced techniques have been exploited and exhibited promising performance with large acceleration factor. One main effort to achieve this is the utilization of compressed sensing (CS) theory. Nevertheless, the existing CS-MRI approaches still have limitations such as fine detail/structure (called features) loss which may reduce the image quality. To improve the reconstruction accuracy, many efforts have been made. These endeavours can be roughly categorized into two directions, namely, avoid losing details from the very beginning and recover the useful information during iterative reconstruction. In this work, we will first present our work on this topic from two directions. And then, we will give a brief introduction on our new framework on fast imaging by using deep learning.

Keywords : Feature-preseving, Compressed sensing, Fast MR imaging, Deep learning

Frontiers in Advanced MRI 1

SY03-4

Probing Tumor Heterogeneity Using Advanced Diffusion MRI

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Intra-tumor heterogeneity has been identified as one of the most important factors in making accurate diagnoses and tailoring therapy to individual patients, as demonstrated in a number of recent papers in high-impact journals. Tumor heterogeneity arises from a variety of origins such as genetics, epigenetics, physiology, and pathology, all of which lead to structural heterogeneity at a specific spatial scale. Characterization of tumor structural heterogeneity can thus provide a unique avenue to probe the underlying biological processes and contribute to improved cancer patient care. Unfortunately, the current spatial resolution (e.g., hundreds of micrometer to a few millimeter) for human MRI is far from adequate to identify tissue structural heterogeneity at a microscopic level (e.g., ~5-50 micrometer). Efforts to further improve the resolution face formidable technical challenges. An alternative strategy is to use the present spatial resolution, but focus on extracting sub-voxel information by linking a macroscopic voxel-level measurement to a microscopic intra-voxel physical process that reflects tissue structural heterogeneity.

Using a novel diffusion model based on fractional order calculus (FROC), our group has observed an increasing number of evidences suggesting a strong link between macroscopic anomalous diffusion parameters and microscopic intra-voxel tissue heterogeneity. This presentation will review the FROC diffusion model, describe the associated diffusion imaging techniques, and demonstrate a number of clinical applications. In these applications, anomalous diffusion parameters have been found useful to probe tumor heterogeneity at a sub-voxel level to improve diagnostic accuracy or predict cancer response to targeted therapy.

In a study on 67 children with histopathology-confirmed brain tumors (28 low-grade and 39 high-grade tumors), an anomalous diffusion parameter known as beta, showed a significantly lower value in the high-grade tumors as compared to that in the low-grade tumors. Based on this parameter, an area under the curve of 0.962 was achieved in an ROC analysis for differentiating high- and low-grade pediatric brain tumors. According to the FROC model, a lower beta value corresponds to a higher degree of diffusion heterogeneity, which is consistent with the increased structural heterogeneity in high-grade brain tumors. Very recently, similar results were also confirmed in a study involving 54 adult glioma patients. These studies provide strong evidence showing the correlation between diffusion heterogeneity from the FROC model and intra-tumor structural heterogeneity. In another study using the FROC model with high b-value diffusion imaging, we analyzed a total of 74 lesions in patients with gastrointestinal stromal tumor (GIST), who underwent sunitinib treatment after imatinib resistance. The beta value from the FROC model showed a significant difference between the responding (n=42) and non-responding (n=32) groups at a time point as early as two weeks after the initiation of sunitinib treatment. Since tissue heterogeneity can change drastically during targeted therapy, this study provides another promising evidence showing that the tissue heterogeneity can be captured by advanced diffusion imaging.

Keywords : Tumor heterogeneity; anomalous diffusion; diffusion imaging; cancer imaging