Probing Intracellular Structure by Diffusion-weighted Imaging with Oscillating Gradients

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Introduction: Diffusion-weighted magnetic resonance imaging (DWI) has proven useful for detecting cancer but more importantly, measurements of apparent diffusion coefficient (ADC) are being used for characterizing tumors and their response to treatment (1). However, due to hardware limitations, conventional in vivo ADC measurements have been limited by gradient strengths, making the measured diffusion time relatively long. The MR signal obtained with a long diffusion time is usually dominated by diffusion-barrier-induced effects which conceal any intracellular information. For example, conventional pulse gradient spin echo (PGSE) methods measure no variation in ADC in human brain at diffusion times from 16-79ms (2). The oscillating gradient spin echo (OGSE) sequence has been shown to be able to probe very short diffusion times (3) and may be useful for probing the intracellular structure in tissues and to increase DWI imaging contrast. Numerical studies have been performed on some model systems to investigate weather OGSE measurements are sensitive to variations in tissue intracellular structure. Results show that conventional PGSE measurements cannot reveal much difference between model tissues for conventional long echo times, whereas OGSE can differentiate systems that differ over very short length scales. This feature can be used to improve our ability to monitor the state of tumors.

Methods and results: For better efficiency and accuracy, an improved finite difference method is used in this work (4). This method rewrites the Bloch-Torrey equation for transverse magnetization in a matrix form and includes a revised periodic boundary condition for removing the computational edge effect artifact. The simulation results by this method have computational errors less than 1%.

Since the purpose of this work is to investigate the feasibility of probing intracellular structure, two types of tissue models (shown in Fig.1) are assumed to have almost the same structure except the nuclear size inside the intracellular space. Hence, both tissue models have the same cell size, cell density, membrane permeability, and intrinsic diffusion rates, whereas they have quite different nucleus volume fractions. Tissue_1 corresponds to a tissue with 4% nucleus volume fraction and tissue_2 has 25%. Pulse sequences which can probe diffusion length scales less than the cell size will detect ADC differences for these two tissue models.

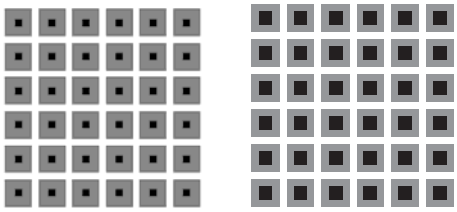

Fig.1 Two types of tissue models. The extracellular space is white, cytoplasm is grey and nucleus black. Both tissue models only have intracellular structure difference. Tissue_1 has 4% nucleus volume fraction and tissue_2 has 25%.

Simulations were performed with the following parameters: the membrane permeability 0.024μm/ms (5), b=1ms/μm^2, echo time TE=20ms and cell size 2μm (similar to a typical cellular dimension in gray matter). A cosine-modulated gradient waveform was used for OGSE. Simulation I was first performed with the intrinsic diffusion coefficients chosen from the experimental values of single neurons (6): diffusion coefficients for nucleus 1.31μm^2/ms, cytoplasm 0.48μm^2/ms and extracellular space = 1.82μm^2/ms. Fig.2 shows the results. The conventional PGSE gives little difference (0.3%) between the ADCs of the two tissue models which implies that PGSE cannot be used to differentiate these two types of tissues. In contrast, the OGSE shows a much larger difference (10.0%) for both applied gradient frequencies 500Hz and 1kHz. This feature can be used to enhance diffusion weighted image contrast. Due to the relatively long diffusion times used in the PGSE diffusion measurements (10-18ms), the measured diffusion coefficients are determined by boundary effects and are not the real intrinsic values. Simulation II was performed assuming a uniform distribution of the intrinsic diffusion coefficients over the whole tissues. The normalized simulated ADCs are shown in Fig.3. The PGSE still shows only a modest difference (1.6%) of both ADCs, whereas the OGSE gives 8% and 15.8% difference for gradient frequencies 500Hz and 1kHz, respectively.

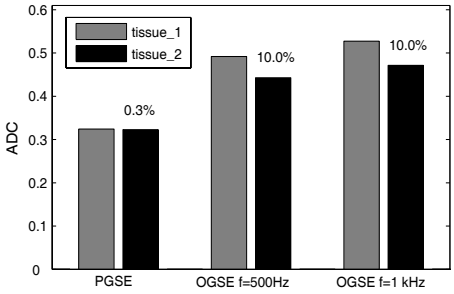

Fig.2 Simulation I. The intrinsic diffusion coefficients are chosen from published experimental values.

Discussion: For conventional PGSE, the MR signal is dominated by diffusion barrier effects and does not reveal much information about intracellular structural variations. In contrast, OGSE method at moderate frequencies is sensitive to intracellular changes. Fig.2 and 3 show all ADCs with the high frequency (1kHz) are larger than those with the low frequency (500Hz), which means barrier-induced effects are reduced and the results reveal more information about the intrinsic diffusion. However, the maximum frequency is usually limited by hardware restrictions. Nevertheless, the frequencies used in this work (500Hz, 1kHz) are available in practical measurements and show the feasibility of OGSE probing intracellular structure.

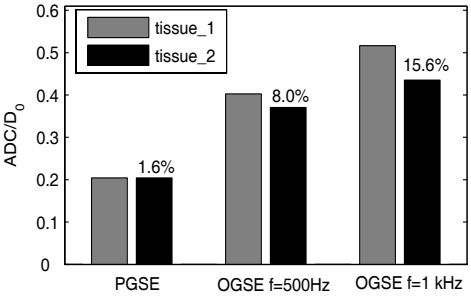

Fig.3 Simulation II. The intrinsic diffusion coefficient is assumed uniform everywhere. The simulated ADCs are normalized by the intrinsic diffusion coefficient.

References: (1)Sugahara, JMRI, 1999 (2)Le Bihan, Neuroreport,1993 (3)Parsons, MRM, 2006 (4)Xu, submitted, 2006 (5)Anderson, MRI,2000 (6)Grant, MRM, 2001