Quantitative Tissue Structure Characterization with Temporal Diffusion Spectroscopy

J. Xu[1], M. D. Does[1], K. Li[1], D. F. Gochberg[1], and J. C. Gore[1]
[1]Institute of Imaging Science, Vanderbilt University, Nashville, TN, United States

Introduction: Diffusion-weighted magnetic resonance imaging (DWI) is dependent on the micro-structural properties of biological tissues, so it is possible to obtain quantitative structural information non-invasively from DWI measurements (1). However, due to hardware limitations, the diffusion times achieved in practice using conventional pulsed gradient spin echo (PGSE) methods are relatively long and insensitive to sub-cellular structure variations. In contrast, the oscillating gradient spin echo (OGSE) method has been reported to have the ability to probe short diffusion time behavior and is sensitive to intracellular structure variations, such as nuclear sizes (2). In the present work, we provide analytical expressions for MR signals with OGSE methods for restricted diffusion in some typical structures, such as spheres, based on the theory of temporal diffusion spectroscopy (3). A novel model is introduced to interpret DWI data obtained from OGSE measurements to quantitatively characterize tissue structures, such as obtaining averaged cell nuclear sizes.

Methods and Results:

Analytical Equations: Based on the theory of temporal diffusion spectroscopy, we derived analytical expressions for the DWI signal attenuation for restricted diffusion with the cosine-modulated OGSE sequence, namely $\exp(-\beta(2\tau))$ where

$$\beta(2\tau) = 2(\gamma g)^2 \sum_k \frac{B_k a_k^2 D^2}{(a_k^2 D^2 + \omega^2)^2} \left\{ \frac{(a_k^2 D^2 + \omega^2)\sigma}{2 a_k D} - 1 + \exp(-a_k D\sigma) + \exp(-a_k D\tau)(1 - \cosh(a_k D\sigma)) \right\} \quad [1]$$

D is the intrinsic diffusion coefficient, ω is the angular frequency of diffusion gradients, σ the duration of each diffusion gradient waveform, τ half of echo time and B_k and a_k are structure dependent coefficients (3).

Simulations: An improved finite difference method (4) was used to simulate a 3D multi-compartment tissue model shown in Fig.1, which is a close-packed system of spherical cells (size 10μm, spacing 10.6μm) and each cell contains a central spherical nucleus (size 7.5μm). As a result, there are three distinct diffusion compartments: intra-nuclear, cytoplasmic and extra-cellular spaces. All simulation parameters were chosen from published experimental results (5, 6): the intrinsic diffusion coefficients for nucleus = 1.31μm^2/ms, cytoplasm = 0.48μm^2/ms and the extra-cellular space = 1.82μm^2/ms. Water exchange was assumed intermediate/slow according to Ref. (2). All pulse sequence parameters are experimentally practical values (7), such as diffusion gradient amplitudes (11 values, ranging evenly from 0 to 100 G/cm) and four gradient frequencies (50, 100, 200 and 500 Hz) with TE = 40ms. The simulated data are shown in Fig.2.

Modeling & Fitting: The diffusion inside the intra-nuclear and cytoplasmic spaces is restricted and can be modeled using the analytical equation derived above and diffusion in the extra-cellular space can be modeled as hindered diffusion ascribed a constant diffusion coefficient. The total signals can be modeled as $signal = f_1\exp(-\beta_{nuclear}) + f_2\exp(-\beta_{cyto}) + (1-f_1-f_2)\exp(-bD_{extra})$, which contains 7 fitting parameters. A simulated annealing algorithm was used to fit simulated data and the fitted curves are shown as solid lines in Fig.2. In the absence of noise, all fitted parameters have <3% deviation compared to real values.

Background Noise: To study the sensitivity of our model to background noise inherent in diffusion measurements, the statistical properties of fitted parameters obtained from our model, such as nuclear size, were analyzed with different levels of background noise, which was implemented in the simulated data using the method proposed in Ref. (8). Fig.3 shows *Rnuclear* and *Rcell*, ratios of mean fitted nuclear/cell size to corresponding standard deviation, derived from N=5000 trials, as a function of the signal-to-noise ratio (SNR).

Conclusion: A novel model has been developed using the temporal diffusion spectroscopy theory to interpret data obtained from OGSE measurements. Compared with other models with conventional PGSE methods, this model has the ability to quantitatively extract tissue structural information including cell nuclear sizes which are usually not obtainable using conventional methods. This approach provides new structural parameters which may be helpful to follow intracellular changes in tissues and potentially can be used for applications such as monitoring tumor response to treatment *in vivo*.

References: (1) Assaf et al. MRM 2004 (2) Xu et al. MRM (in press) (3) Stepisnik. Physica B 1993 (4) Xu et al. Phys Med Biol 2007 (5) Anderson et al. MRI 2000 (6) Grant et al. MRM 2001 (7) Does et al. MRM 2003 (8) Pierpaoli and Basser. MRM 1996

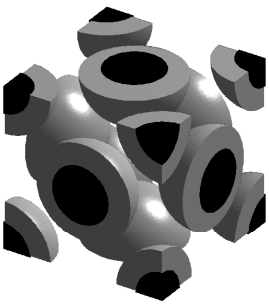

Fig.1 A 3D multiple-compartment tissue model.

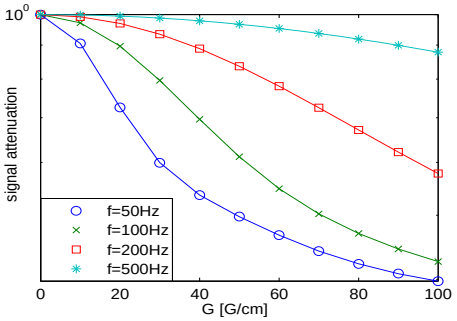

Fig.2 Simulated (circles) and fitted (lines) signal attenuation as a function of diffusion gradient amplitudes and frequencies.

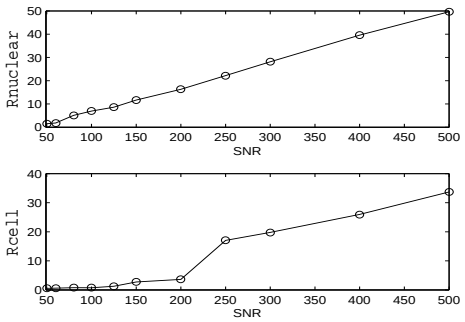

Fig.3 *Rnuclear* and *Rcell*, ratios of mean fitted nuclear/cell sizes to corresponding standard deviation as a function of the signal-to-noise ratio (SNR).