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Fast and robust measurement of microstructural dimensions using temporal diffusion spectroscopy

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ABSTRACT

Mapping axon sizes non-invasively is of interest for neuroscientists and may have significant clinical potential because nerve conduction velocity is directly dependent on axon size. Current approaches to measuring axon sizes using diffusion-weighted MRI, e.g. q-space imaging with pulsed gradient spin echo (PGSE) sequences usually require long scan times and high q-values to detect small axons (diameter <2 μm). The oscillating gradient spin echo (OGSE) method has been shown to be able to achieve very short diffusion times and hence may be able to detect smaller axons with high sensitivity. In the current study, OGSE experiments were performed to measure the inner diameters of hollow microcapillaries with a range of sizes (~1.5–19.3 μm) that mimic axons in the human central nervous system. The results suggest that OGSE measurements, even with only moderately high frequencies, are highly sensitive to compartment sizes, and a minimum of two ADC values with different frequencies may be sufficient to extract the microcapillary size accurately. This suggests that the OGSE method may serve as a fast and robust measurement method for mapping axon sizes non-invasively.

1. Introduction

Mapping the sizes of nerve axons may have significant clinical potential because nerve conduction velocity is directly dependent on axon size [1–3]. Diffusion MRI provides a non-invasive means to characterize the microstructure of biological tissues, and hence may be suitable for this application. Several approaches have previously been proposed to measure axon sizes using diffusion weighted MRI [3–12]. For example, in q-space imaging, data are acquired with a conventional pulsed gradient spin echo (PGSE) sequence, and the signal attenuation ($E(q)$) is plotted as a function of the wave-vector q (where $q = (2\pi)^{-1}\gamma g\delta$, γ being the nuclear magnetogyric ratio, g and δ are the pulse gradient strength and duration, respectively). Diffusion–diffraction phenomena occur in restricted systems with mono-disperse structure, and by measuring $E(q)$ the compartment size can be extracted [4]. However, such diffusion–diffraction phenomena are usually not resolved in biological systems due to the size poly-dispersity [13]. In such cases, the full-width at half-maximum (FWHM) of the Fourier transform of $E(q)$ may be used to characterize the mean compartment size [5,6]. Another approach using q-space imaging is the AxCaliber framework [3], which acquires multi-dimensional MRI data (q-values and diffusion times). The compartment size distribution is then estimated by modeling the intracellular diffusion using analytical expressions that are based either on the short gradient approximation [14] or on the constant diffusion gradient [15,16]. In addition, a method called the angular double-PGSE has been proposed to measure small compartmental dimensions with relatively low q-values [7,8]. This method usually keeps the q-value fixed but varies the orientation of the second gradient pair. The compartment dimension can be extracted from the angular dependent signal decay. However, the PGSE-based measurements usually encounter long diffusion times (>10 ms) in practice due to gradient hardware limitations, so that the root mean square displacements (RMSD) of diffusing molecules (>6 μm) are much larger than small axon sizes (e.g. diameter $d < 2$ μm). This in turn significantly reduces the sensitivity for detecting effects at small spatial scales. To enhance sensitivity to small scales, much higher q-values and/or more measurements with different degrees of diffusion

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weighting are usually necessary for PGSE measurements which in turn lead to long scan times.

The oscillating gradient spin echo (OGSE) method has been shown to be able to achieve much shorter diffusion times and hence may be able to detect smaller axons with high sensitivity [17]. Moreover, the OGSE method can probe a range of effective diffusion times by tuning the oscillating gradient frequencies, and thus an apparent diffusion spectrum can be obtained which contains more comprehensive micro-structural information on biological tissues [18]. For example, the OGSE method has previously been used to probe various length scales in biological systems, such as cultured cells [19], healthy rat brain [20], human brain in vivo [21,22], rat and mouse tumors [23–25], and brains after stroke [26]. The sensitivity of the OGSE method to intracellular structure has also been investigated [27,28], and it has been shown that unique microstructure-based contrasts can be obtained which are not available from conventional PGSE experiments [29,30]. Before studying quantitatively the micro-structural properties of biological tissues, it is important to derive and validate the analytical models of OGSE as they may be used for model fitting, parameter estimation, and to optimize experiments [31]. To this end, analytical expressions that predict OGSE signals in some typical structures have been derived and validated with computer simulations [32], which suggests the possibility of extracting small axon sizes using the OGSE method. However, these analytical expressions have not previously been validated or calibrated experimentally using well-characterized physical phantoms with known pore sizes.

In the current study, OGSE experiments were performed to measure the inner diameters of hollow microcapillaries with a range of sizes (~1.5–19.3 μm) that mimic axons in the human central nervous system [33]. The fitted sizes were compared with the known values to validate the accuracy of fitting cylinder diameters using the OGSE method. In addition, the limitation of fitting free diffusion coefficients using the OGSE method was investigated. From this, a possible fast method of mapping axon size non-invasively is proposed.

2. Methods

2.1. Theory

The cosine-modulated OGSE waveform was chosen in the current study due to its specific diffusion spectral selectivity [34]. Hence, the effective diffusion gradient is:

$$g(t)=\begin{cases} G\cos[2\pi ft] & 0<t<\sigma \\ -G\cos[2\pi f(t-\Delta)] & \Delta<t<(\Delta+\sigma) \\ 0 & \text{else} \end{cases} \quad (1)$$

Here G is the gradient amplitude, f the diffusion gradient frequency, σ the gradient duration, Δ the separation of two diffusion gradients. The corresponding b-value is [26]:

$$b=\frac{\gamma^2G^2\sigma}{4\pi^2f^2} \quad (2)$$

Under the Gaussian phase approximation [35–38], the restricted diffusion signal attenuation can be described as [39]

$$E=\exp\left(-\frac{\gamma^2}{2}\sum_k B_k\int_0^{2\tau}dt_1\int_0^{2\tau}dt_2e^{-D\lambda_k|t_2-t_1|}g(t_1)g(t_2)\right) \quad (3)$$

where 2τ is the echo time, and B_k and λ_k are structure dependent coefficients. The analytical expressions of B_k and λ_k for some typical geometries such as parallel planes, cylinders, spheres, and spherical shells can be found in the literature [32,39]. In the case of diffusion inside an impermeable cylinder with a diameter d,

$$B_k=\frac{(d/\mu_k)^2}{2(\mu_k^2-1)} \quad \text{and} \quad \lambda_k=4\left(\frac{\mu_k}{d}\right)^2 \quad (4)$$

where μ_k is the kth root of $J_1'(\mu)=0$ and J_1 is a Bessel function of the first kind. By substituting Eqs. (1) and (2) into Eq. (3) and assuming the diffusion gradient is perpendicular to the main axis of the cylinder, the measured ADC can be expressed as

$$\begin{aligned}\mathrm{ADC}(f,D,d)=8\pi^2\sum_k\frac{B_k\lambda_k^2D^2f^2}{\sigma(\lambda_k^2D^2+4\pi^2f^2)^2} \\ \times\left\{\frac{(\lambda_k^2D^2+4\pi^2f^2)\sigma}{2\lambda_kD}-1+\exp(-\lambda_kD\sigma)\right. \\ \left.+exp(-\lambda_kD\tau)(1-\cosh(\lambda_kD\sigma))\right\}\end{aligned} \quad (5)$$

where D is the free diffusion coefficient. Eq. (5) shows that ADC has a strong dependence on the gradient oscillating frequency f. If ADC measurements are performed at multiple gradient frequencies, the free diffusion coefficient D and the cylinder diameter d may be extracted simultaneously. This is a much different approach compared with previously reported PGSE-based models.

2.2. Experiment

All NMR diffusion experiments were performed on a Varian 7T scanner with a 12 mm Doty micro-gradient coil. The maximum gradient strength used in this study was 1.88 T/m. Five different types of hollow microcapillaries (Polymicro Technologies, USA) with different inner diameters (1.5–1.6, 4.3–4.5, 9.5–9.7, 14.9–15, 19.0–19.3 μm (lower bound–upper bound provided by the manufacturer)) and the same outer diameter around 150 μm were used as the phantoms. The microcapillaries were cut to ~3.5 cm in length and then immersed in distilled water for approximately two weeks. The microcapillaries were then air-dried to remove any residual water outside but retain the water inside the microcapillaries. By this means, a well-characterized one-compartment diffusion system was formed. Each type of microcapillary was packed into 5 mm NMR tubes and aligned parallel to the z-direction of the magnet. The diffusion gradients were applied perpendicular to the microcapillary main axis with a duration of 20 ms on either side of a refocusing pulse. An apodised cosine-modulated waveform which replaced the first and last quarters with half-sine lobes at double frequency was used to avoid very rapid rise times [26]. Temporal diffusion spectra [18] were acquired at 12 oscillating frequencies ranging evenly from 50 Hz to 600 Hz. At each frequency, the ADC was calculated from two acquisitions with b = 0 and b = 700 s/mm^2. The only exception was for the smallest (1.5–1.6 μm) microcapillaries, in which much higher b-values were used ranging from 700 to 50,000 s/mm^2 in order to cause higher diffusion weighting. Other parameters were: TR = 8 s, TE = 60 ms, receiver bandwidth 10 kHz, spectral resolution 78.125 Hz. NEX (number of excitations) varied from 4 to 80 for different microcapillary sizes depending on the signal-to-noise ratio (SNR). The diffusion coefficient of free water was measured with distilled water in a 5 mm NMR tube at the same temperature. The same measurement was also performed with the diffusion gradient along the z-axis in the microcapillary experiments.

2.3. Data analysis

The measured ADC spectra were fit to Eq. (5) with two unknown variables D and d using the *lsqcurvefit* function in Matlab