Analysis of High b-Value Diffusion Images Using Fractional Order Calculus

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INTRODUCTION

In biological tissues, it is well known that diffusion-induced MR signal loss deviates from mono-exponential decay, exp [-(*bD*)], especially at high b-values (e.g., ≥1500 s/mm^2). This discrepancy has been attributed to tissue heterogeneity manifested by cellular structures, cell membrane, and/or differences between the intra- and extra-cellular spaces [1]. A bi-exponential model has thus been used to better describe the diffusion signal characteristics. The measured slow diffusion compartmental fraction, however, correlates poorly with known cell volume fractions [2]. To improve signal characterization, several recent studies have investigated the so-called stretched exponential model, exp[-(*bD*)$^\alpha$], where α ($0<\alpha\leq1$) is a measure of tissue complexity that can be derived from fractal models [3-5]. This approach suggests an underlying fractional order dynamics in the observed diffusion-induced magnetization changes, as dictated by the Bloch-Torrey equation.

Fractional order calculus is a mathematical tool that has already been employed to generalize the Gaussian probability function of Brownian motion to what is termed anomalous diffusion (i.e., sub and super diffusion) [6]. In this paper we demonstrate that the stretched exponential model follows from a fundamental extension of the Bloch-Torrey equation through application of the operators of fractional calculus. Additionally, we show that fractional order generalization of the integer order time and space derivatives in the Bloch-Torrey equation yields solutions that can be used to describe complex diffusion behaviors observed in MR experiments on human brain tissues as well as porous media.

THEORY

If *C(x,t)* represents the concentration of the diffusing species in one dimension, then a fractional order partial differential equation (Eq. [1]) emerges from Fick's first law, where D' is the generalized diffusion coefficient. With this formalism, a fractional order generalization of the Bloch-Torrey equation can be written as Eq. [2], where $\lambda = -i\gamma(\mathbf{r}\cdot\mathbf{G})$, ${}_0^C D_t^\alpha$ is the Caputo form of the Riemann-Liouville fractional order derivative in time [6], $\nabla^{2\beta} = \left(D_x^{2\beta} + D_y^{2\beta} + D_z^{2\beta}\right)$ is a Riesz fractional order Laplacian operator in space [6], and $\tau^{\alpha-1}$ and $\mu^{2(\beta-1)}$ are fractional order time and space constants needed to preserve units ($0<\alpha\leq1$, and $0<\beta\leq1$). For the fractional order dynamics in space (i.e., α=1, $0<\beta<1$), the transverse magnetization was derived for constant, bipolar, and Stejskal-Tanner gradients, respectively. The result for the Stejskal-Tanner gradient is given in Eq. [3]. For the fractional order dynamics in time (i.e., $0<\alpha<1$, β=1), only the transverse magnetization for the case of constant gradient was obtained (Eq. [4]).

$$\frac{\partial^\alpha C(x,t)}{\partial t^\alpha} = D'\frac{\partial^{2\beta} C(x,t)}{\partial |x|^{2\beta}} \quad [1];\quad \tau^{\alpha-1}\,{}_0^C D_t^\alpha M_{xy}(\mathbf{r},t) = \lambda M_{xy}(\mathbf{r},t) + D\mu^{2(\beta-1)}\nabla^{2\beta} M_{xy}(\mathbf{r},t) \quad [2]$$

$$M_{xy} = M_0 \exp[-D\mu^{2(\beta-1)}(\gamma G_z \delta)^{2\beta}(\Delta - \frac{2\beta-1}{2\beta+1}\delta)] \quad [3]$$

$$M_{xy} = M_0 E_\alpha[-i\gamma G_z z\tau(t/\tau)^\alpha]\exp[-B(t/\tau)^{3\alpha}] \quad [4],\quad where\ B = \frac{2\Gamma(2-\alpha)D\gamma^2 G_z{}^2\tau^3}{3\alpha^2\Gamma(2\alpha+1)} \quad [5]$$

EXPERIMENTAL

Experiments were carried out on phantoms and on human volunteers to validate the results in Eq. [3]. The phantom was constructed using glass capillary tubes filled with Sephadex (Sigma-Aldrich, St. Louis, MO) gels to simulate a porous medium with a varying degree of restriction to diffusion (Fig. 1, inset). Diffusion-weighted images were acquired at 11.7 T (Bruker Instruments, Billerica, MA) using a spin-echo diffusion sequence with the following parameters: TR = 1000 ms, TE = 60 ms, slice thickness = 1.5 mm, Δ = 45 ms, δ = 1 ms, FOV = (0.6 cm)^2, and matrix size = 64^2. The diffusion gradient was applied along the phase-encoding direction in sixteen steps with *b*-value ranging from 0-1600 s/mm^2. The human volunteer experiment was performed on a clinical 3T GE Signa HDx scanner (GE Health Care, Milwaukee, WI) using a customized diffusion-weighted single-shot EPI pulse sequence. The key acquisition parameters were: TR = 4000 ms, TE = 96.6 ms, slice thickness =4 mm, Δ = 42.6 ms, δ = 32.2 ms, FOV = (22 cm)^2, and matrix size =128 x 72. Fourteen diffusion-weighted images were acquired with increased b-values up to 4,600 s/mm^2. Image intensities from the selected ROIs were fitted to Eq. [3] using a Levenberg-Marquardt fitting algorithm to estimate the parameters *D*, β and μ.

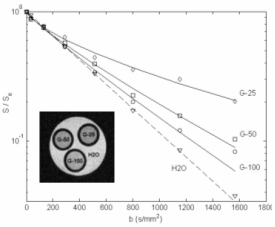

Fig. 1 Normalized signal intensity vs. b-value for the ROIs selected from the phantom (inset).

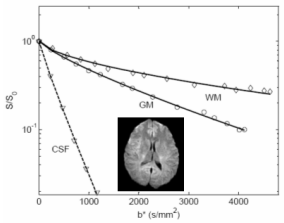

Fig. 2 Normalized signal intensity vs. b-value for three ROIs selected from the WM, GM, and CSF of the human brain (inset).

RESULTS

The phantom results are shown in Fig 1. For distilled water in the phantom, we found β = 1.0±0.003 and D = (2.1±0.02) x 10^{-3} mm^2/s, which agreed with the conventional models. For G-25, a non-linear fitting to Eq. [3] yielded β = 0.71±0.06, μ = 6.4±0.1 microns, and *D* = (1.12±0.04) x 10^{-3} mm^2/s, with the corresponding values for G-50 and G-100 falling in between. These results showed that an increase in diffusion restriction (i.e., smaller G-value of the Sephadex) was reflected by a reduction in β. Figure 2 shows the results from three ROIs selected in the white matter (WM; internal capsule), gray matter (GM; caudate nucleus), and CSF (ventricle) from the human brain images. The β values followed the expected trend of decreasing in magnitude as the diffusion became more restricted; the β values for the CSF, GM, and WM were 0.91±0.005, 0.78±0.03, and 0.60±0.008, respectively. The μ values were very similar for GM (4.9μm) and WM (4.3μm), but significantly smaller for CSF (μ = 3.0 μm). The diffusion coefficients D (in unites of x 10^{-3} mm^2/s) were found to be 2.8±0.18 (CSF), 0.75±0.08 (GM), and 0.41±0.006 (GM), respectively.

DISCUSSION AND CONCLUSIONS

Our results demonstrate that fractional order differential operators in space and time yield solutions similar in form to those developed by others [3-5]. The specific form of the fractional order solutions for the transverse magnetization depends on the applied gradient pulse waveform. Generalization of the spatial Laplacian gives stretched exponential behavior that is different from the classical and stretched exponential results [3], and includes in addition to the operational order parameter β, the unit preserving space constant μ (in units of meter). A decreased β value correlated well with increasingly restricted diffusion. We have also observed that μ values increased as the diffusion attenuation curves departed from the straight line of the exponential semi-log plot. Although no experimental data were presented for the case of fractional order time derivative, the theoretical magnetization decay curve conformed to both the classical result and to the result derived by Widom et al. [7] using a fractal model. In summary, our results suggest that a model for anomalous diffusion can be established directly from the Bloch-Torrey equation through the application of fractional calculus. Using this mathematical tool, we may extend the applications of diffusion imaging beyond simply evaluating apparent diffusion coefficients and stretched exponential constant α, and eventually reveal new parameters related to tissue micro-environment.

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