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Sensitivities of statistical distribution model and diffusion kurtosis model in varying microstructural environments: A Monte Carlo study

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ABSTRACT

The aim of this study was to investigate the microstructural sensitivity of the statistical distribution and diffusion kurtosis (DKI) models of non-monoexponential signal attenuation in the brain using diffusion-weighted MRI (DWI). We first developed a simulation of 2-D water diffusion inside simulated tissue consisting of semi-permeable cells and a variable cell size. We simulated a DWI acquisition of the signal in a volume using a pulsed gradient spin echo (PGSE) pulse sequence, and fitted the models to the simulated DWI signals using *b*-values up to 2500 s/mm^2. For comparison, we calculated the apparent diffusion coefficient (ADC) of the monoexponential model (*b*-value = 1000 s/mm^2). In separate experiments, we varied the cell size (5–10–15 μm), cell volume fraction (0.50–0.65–0.80), and membrane permeability (0.001–0.01–0.1 mm/s) to study how the fitted parameters tracked simulated microstructural changes. The ADC was sensitive to all the simulated microstructural changes except the decrease in membrane permeability. The ADC increased with larger cell size, smaller cell volume fraction, and larger membrane permeability. The σ_{stat} of the statistical distribution model increased exclusively with a decrease in cell volume fraction. The K_{app} of the DKI model was exclusively increased with decreased cell size and decreased with increasing membrane permeability. These results suggest that the non-monoexponential models of water diffusion have different, specific microstructural sensitivity, and a combination of the models may give insights into the microstructural underpinning of tissue pathology.

1. Introduction

Diffusion-weighted imaging (DWI) sensitizes the magnetic resonance (MR) signal to water molecular movement through the use of applied magnetic field gradients. In the standard Stejskal–Tanner pulsed gradient spin echo (PGSE) pulse sequence [1], two magnetic field gradients are applied before and after the 180° refocusing RF pulse. At the end of the pulse sequence, the phases of stationary spins are refocused, whereas the phase dispersion resulting from randomly moving spins decreases the MR signal intensity. For free, Gaussian diffusion, the signal decay is monoexponential [1]:

$$S(b) = S(0)e^{-bD} \tag{1}$$

where D is the diffusion coefficient, and b is the diffusion weighting factor ($b = \gamma^2 g^2 \delta^2 (\Delta - \delta/3)$) with the gyromagnetic ratio γ, gradient amplitude g, pulse duration δ, and gradient pulse spacing δ. In a typical human MRI system (g = 40 mT/m) with b = 1000 s/mm^2, the root-mean-square (RMS) molecular displacement of free diffusion is ~19 μm at the diffusion time 20 ms ($\Delta - \delta/3$). Given that intracellular compartments and inter-cellular spaces are on the order of tens to hundreds of microns in human brain, the majority of water molecules interact with microstructure during a typical MRI experiment. Restricted diffusion and water exchange between different compartments thus enables DWI to non-invasively probe tissue microstructure at a cellular level. The apparent diffusion coefficient (ADC) is measured using the monoexponential relation in Eq. (1). The ADC has been used clinically to detect ischemic stroke [2,3].

When b is larger than 2000 s/mm^2, the signal attenuation in the brain deviates from a monoexponential relation [4,5]. A focus of recent studies has been to understand the relation between the non-monoexponential decay and tissue microstructure. For high field gradient systems, q-space model [6,7] provides a theoretical framework, where the probability density function (PDF) of water molecular displacement can be directly measured through the Fourier transform of the signal decay with the short gradient pulse (SGP) condition ($\delta \to 0$). However, because of limited field gradient strengths, it is difficult to achieve the SGP condition in current human imaging systems. Therefore, the relationship between the

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measured displacement PDF and tissue structures is not well established [8,9].

Phenomenological modeling is a practical approach to extracting useful information from DWI data, because it only requires a few fitted parameters for the non-monoexponential decay. The bi-exponential model was proposed to fit non-monoexponential DWI decay [5,10,11]. The bi-exponential model was originally motivated by the hypothesized association of slow and fast apparent water diffusion rates with intra- and extracellular compartments. While this association is likely incorrect [12–14], the bi-exponential model is nonetheless useful to describe the decay. Some studies have attributed the two apparent water diffusion rates to water exchange between intra- and extracellular compartments [15] or to free and membrane-bound water [16]. In complex tissue structure, it is likely that the signal attenuation observed with DWI arises from a continuous distribution of diffusion rates [17–19]:

$$S(b) = S(0)\int_0^\infty P(D)e^{-bD}dD \tag{2}$$

where $P(D)$ is the PDF of the apparent diffusion rate D. The statistical distribution model postulates $P(D)$ as a truncated Gaussian distribution [18]. If the width of the distribution is smaller than the mean of the distribution, the signal decay at a low b-value (less than 2500 s/mm^2 in human brains) is approximated by:

$$S(b) = S(0)e^{-bD_{stat}+\frac{1}{2}b^2\sigma_{stat}^2} \tag{3}$$

where D_{stat} and σ_{stat} refer to the mean and width of $P(D)$ respectively. The approximation (Eq. (3)) is also valid for other choices of $P(D)$, e.g. gamma distribution [20,21]. The stretched exponential model [19] empirically describes the signal decay arising from the distribution of diffusion rates ($P(D)$). It has been used to measure structural heterogeneity in the brain with a high b-value: 4000–5000 s/mm^2 [19,22–24], and has been linked to fractal tissue microstructure [25,26].

Instead of making assumptions about the multiplicity of water diffusion rates, the Diffusion Kurtosis Imaging (DKI) model measures the deviation of water displacement PDF from a Gaussian distribution [27]:

$$S(b) = S(0)e^{-bD_{app}+\frac{1}{6}b^2D_{app}^2K_{app}} \tag{4}$$

where D_{app} is the apparent diffusion coefficient, and K_{app} is the apparent kurtosis, which quantifies non-Gaussian diffusion. The DKI model and the statistical distribution model (Eq. (3)) have an identical mathematical form, but their assumptions are different. The DKI model is derived from a truncated cumulant expansion based on the SGP condition. Nonzero kurtosis can arise from various physical environments [20], and it can be linked to the $P(D)$ [27] through:

$$\text{kurtosis} = 3v\text{ar}[\text{D}]/(\text{E}[\text{D}])^2 \tag{5}$$

where $var[D]$, $E[D]$ refer to the variance and mean of the apparent diffusion rate. Here, the kurtosis correlates with the width of $P(D)$.

The statistical distribution and the DKI models quantify non-Gaussian water diffusion with a relatively low b-value less than 2500 s/mm^2, and thus these models can be readily implemented in the clinic setting with a reasonable scan time and an adequate SNR. The models have been used to study biophysical and pathological changes [28–35], potentially exhibiting higher sensitivity and specificity compared to the ADC of the monoexponential model. However, the relation between these models of non-Gaussian water diffusion and tissue microstructure is still unclear.

To gain a better understanding of how these models related to healthy and diseased tissue, we investigated the relationship between two non-Gaussian water diffusion models (the statistical distribution and DKI models) and a simulated tissue microstructure. For this purpose, we created a 2-D Monte Carlo simulation of the DWI experiment and water diffusion in an intra- and extracellular microstructure with continuously distributed compartmental sizes. We varied three relevant microstructural parameters: cell size, volume fraction, and membrane permeability separately to study how the fitted parameters (D_{stat}, σ_{stat} of the statistical distribution model, D_{app}, K_{app} of the DKI model) correlated with the microstructural changes compared with the ADC. We compared the relative sensitivity between the diffusion models to the changes, and studied the dependence of the models on a realistic SNR. As each of the diffusion models exhibits different, specific sensitivity to microstructural changes, the models may be used together to better understand and identify the underlying biophysical mechanisms.

2. Methods

To simulate the MRI signal arising from tissue, a Monte-Carlo simulation was implemented in C++ and was simplified to a 2-D model to reduce computation time. 60,000 dimensionless spins were randomly placed in a 2-D plane of 0.4×0.4 mm^2 and performed a random walk at a rate $\Delta t = 2.5 \times 10^{-5}$ s per step within and between randomly packed cells (Fig. 1). The intracellular diffusivity (D_{in}) and extracellular diffusivity (D_{ex}) were set to be 1.0×10^{-3} and 2.5×10^{-3} mm^2/s [36] respectively, assuming that the intrinsic extracellular diffusivity is faster than the intracellular diffusivity. The step size of a spin was 3.2×10^{-4} mm in the intracellular compartment and was 5×10^{-4} mm in the extracellular compartment. Cell sizes were specified from a gamma distribution with a mean: 10 μm, (typical human cell size [37]), and a standard deviation (SD): 7 μm in diameter; the ratio (SD/mean) was 0.7 according to the axon size distribution in human corpus callosum [38,39]. The intracellular volume fraction was 0.65, which is within the range of measured values in rat brains (0.73 in gray matter, 0.60 in white matter [40]). The membrane permeability κ defined

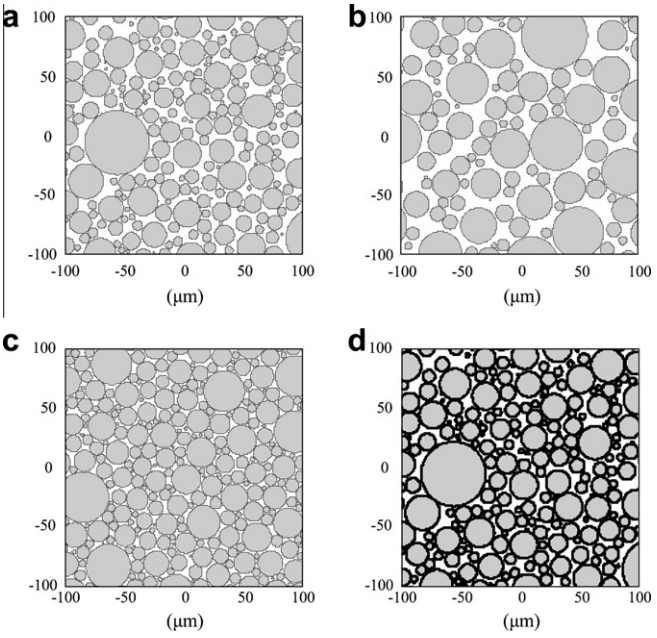

Fig. 1. Illustration of the simulated cell structure (a) with mean cell size: 10 μm in diameter and cell volume fraction: 0.65, and membrane permeability: 0.01 mm/s. (b–d) Simulated microstructural changes in mean cell size (increased to 15 μm) (b), cell volume fraction (increased to 0.80) (c), and membrane permeability (decreased) (d). All the changes (b–d) were made with other microstructural parameters kept the same as in (a). Intra/extra-cellular space is shown in gray/white color.