BEHAVIOR OF THE STATISTICAL DISTRIBUTION AND DIFFUSION KURTOSIS MODELS IN HUMAN ISCHEMIC STROKE

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INTRODUCTION: The apparent diffusion coefficient (ADC) of the monoexponential model has been shown to decrease following ischemic stroke [1,2]. The underlying mechanisms of the reduction in the ADC remain unclear. The increased cell volume fraction is suggested to be one mechanism that results in more hindered extracellular diffusion [3,4]. However, intracellular diffusion was found to decrease [5] or increase [6] in separate studies. Reduced membrane permeability was shown to have a minor impact on reduced ADC [7]. Recently, with a b-value of up to 2500 s/mm^2, the statistical distribution model [8] and diffusion kurtosis model (DKI) [9] have been used to study biophysical and pathological changes, potentially exhibiting higher sensitivity compared to the ADC [10-13]. The aim of this study was to investigate the relationship between the non-monoexponential models and microstructural changes in ischemic stroke. For this purpose, we studied the fitted parameters: σ_{stat} of the statistical distribution model (width of the distribution of diffusion rates) and K_{app} of the DKI model (measure of non-Gaussian diffusion) in response to simulated microstructural changes. We compared our simulation results to the *in vivo* measurements of human ischemic stroke (n = 6). The results suggest that the non-monoexponential models may be useful in identifying the biophysical mechanisms in ischemic stroke.

METHOD: *Simulation*: We performed a Monte Carlo simulation of 2-D water diffusion inside simulated tissue consisting of semi-permeable cells and a variable cell size and inter-cell distance [14,15]; mean cell size: 10 μm, cell volume fraction: 0.65, and membrane permeability: 0.01 mm/s. We generated DWI signals using a simulated PGSE sequence [15], and fitted the models to the simulated DWI signals with b = 2500 s/mm^2 in increment of 500 s/mm^2. For comparison, we calculated the ADC of the monoexponential model (b-value = 1000 s/mm^2). To simulate possible microstructural changes in ischemic stroke, we decreased or increased intracellular diffusion by varying cell size (5-10-15 μm) [7]. In addition, we increased cell volume fraction (0.65-0.80) [4], and decreased membrane permeability (0.01-0.001 mm/s) [7] in separate experiments to study how the fitted parameters varied with these changes. *In vivo experiments*: We collected DWI images from six patients with ischemic stroke within 48 hours after the onset of neurological deficits. No patients had hemorrhages. The maximum b-value was 2500 s/mm^2 in increment of 500 s/mm^2 with diffusion gradients applied respectively on x, y, and z axes. Other imaging parameters were: SENSE: 2, TR/TE = 4000/104 ms, NEX = 4, slice thickness = 4.5 mm, FOV = 240 × 240 mm^2, and matrix = 128 × 128. We defined two ROIs (Fig. 2): lesion ROI on DWI images with hyper-intensity, and contralateral white matter ROI on T2-weighted images segmented using SPM (University College London, UK). We compared the differences between these two ROIs using the paired Student's t-test with significance level: $p < 0.05$.

RESULTS: *Simulation*: The ADC was sensitive to all microstructural changes except to the decrease in membrane permeability (Fig. 1). The ADC increased with larger cell size, and decreased with smaller cell size, larger cell volume fraction, and smaller membrane permeability. The σ_{stat} of the statistical distribution model decreased specifically with the increase in cell volume fraction (Fig. 1). The K_{app} of the DKI model increased specifically with the decrease in cell size. *In vivo* experiments: All the fitted parameters showed significant differences between white matter and lesion ROIs (Fig. 3). Compared with white matter ROI, the stroke lesion showed a decrease in the ADC by 37 % and a decrease in the σ_{stat} by 26 % (Fig. 3). However, the stroke lesion showed an increase in the K_{app} by 53 %.

DISCUSSION: Our *in vivo* study of human stroke showed a 26 % decrease in the σ_{stat} of the statistical distribution model compared with white matter ROI. This agrees with our predicted increase in cell volume fraction in ischemic stroke using our simulation, where the σ_{stat} showed a 29 % decrease (Fig. 1). Our *in vivo* study showed a larger percentage change in the K_{app} of the DKI model than that in the ADC (53 % increase in the K_{app} vs. 37 % decrease in the ADC). This larger percentage change in the K_{app} is consistent with previous studies applying the DKI model on human stroke [12,13]. We suggest that this observed larger increase of the K_{app} may arise from a decrease in cell size, as our simulation showed that the increase of the K_{app} was sensitive to the decreased cell size and was relatively insensitive to the increased cell volume fraction and decreased membrane permeability (Fig. 1).

CONCLUSION: We simulated the three important microstructural changes in ischemic stroke and have demonstrated that the non-monoexponential models of water diffusion have different, specific microstructural sensitivities. Our simulated microstructure is a simplistic physical system. Nonetheless, we suggest that these different sensitivities of the diffusion models may contribute to the observed differences in the *in vivo* experiments. More importantly, a combination of these models may give insights into the microstructural underpinning of ischemic stroke.

REFERENCES: [1] Moseley ME, et al, MRM (14), 1990. [2] Schaefer PW, et al, Radiol (217), 2000. [3] van der Toorn A, et al, MRM (36), 1996. [4] Syková E, et al, Physiol Rev (88), 2008. [5] Silva MD, et al, MRM (48), 2002. [6] Harkins KD, et al, MRM (66), 2009. [7] Szafer A, et al, MRM (33), 1995. [8] Yablonskiy DA, et al, MRM (50), 2003. [9] Jensen JH, et al, MRM (53), 2005. [10] Zhao L, et al, MRM (59), 2008. [11] Raab P, et al, Radiol (254), 2010. [12] Jensen JH, et al, NMR Biomed (24), 2011. [13] Hui ES, et al, Stroke, 2012. [14] Lee CY, et al, 2011 ISMRM Proc, p. 414. [15] Lee CY, et al, 2012 ISMRM Proc, p. 1839.

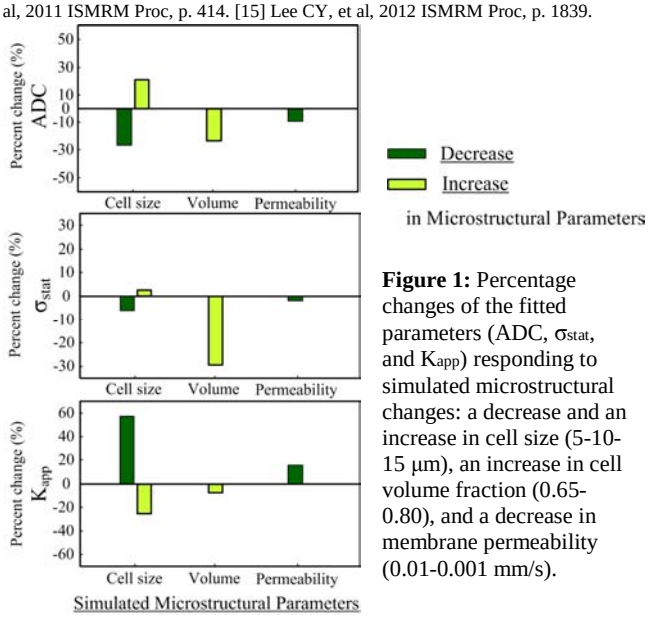

Figure 1: Percentage changes of the fitted parameters (ADC, σ_{stat}, and K_{app}) responding to simulated microstructural changes: a decrease and an increase in cell size (5-10-15 μm), an increase in cell volume fraction (0.65-0.80), and a decrease in membrane permeability (0.01-0.001 mm/s).

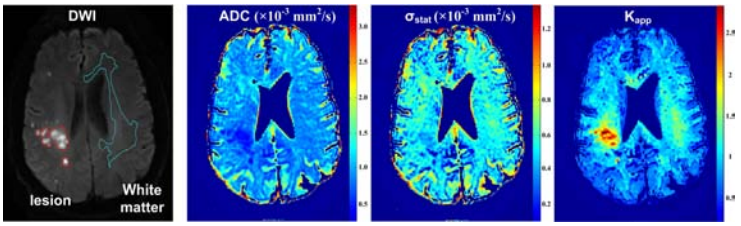

Figure 2: Example of ROI selection and calculated parametric maps of a 63 year old male with ischemic stroke. The region of cerebrospinal fluid was excluded to avoid partial volume effect.

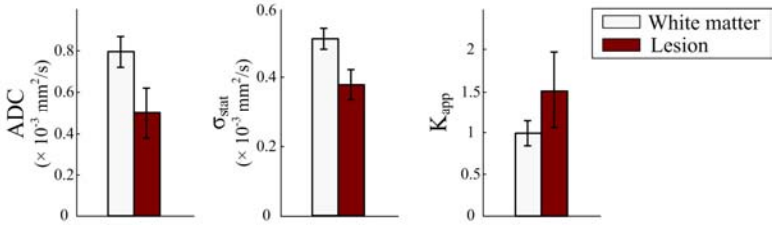

Figure 3: Mean fitted parameters in white matter and lesion ROIs averaged across six patients with ischemic stroke (3 females, 3 males, age: 63 ± 18 years old).