THE SENSITIVITIES OF THE PHENOMENOLOGICAL DWI MODELS IN THE PRESENCE OF CELLULAR COMPARTMENTS

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INTRODUCTION: The distance of water movement during a DWI experiment is beyond the microstructural dimension (4-100μm), a fact that is demonstrated as a non-monoexponential decay when b-value is high. Considering the complex physical compartmentation in tissues, there can be multiple diffusion components. More generally, the signal can be given by a summation of a statistical distribution of diffusion rates. The stretched exponential (α-DWI) [1] and diffusion kurtosis imaging (DKI) [2] models can be used to characterize the distribution of diffusion rates. Another approach is to model the signal decay with a statistical distribution: the truncated Gaussian distribution [3] and gamma distribution [4] models. Those phenomenological models fit the data well with only two free parameters within a certain range of b-value. Their fitted parameters can quantify the diffusion heterogeneity, related to the width of the distribution of diffusion rates. However, their theoretical underpinnings are very different and how to infer the tissue structures from measured diffusion heterogeneity is unclear. In this work, we created a simulation where cell sizes were statistically distributed, and the cellular volume fraction, mean intra-cellular sizes, and membrane permeability were varied to study how the measured diffusion heterogeneity correlated with the changes. We focused on three fitted parameters: α, Kapp, and σ_{gamma} (standard deviation of gamma distribution) of α-DWI, DKI, and gamma distribution models. The diffusion models were also applied to one clinical case of recurrent tumor.

METHOD: Simulation: We implemented a random walk model and simulated a PGSE DWI experiment in Matlab (Mathworks, Inc.) with max. gradient strength 40 mT/m and $\delta \approx \Delta \approx 32$ ms. 60'000 spins were randomly placed in a 1-D space, assuming an isotropic diffusion, with randomly packed intra- and extra-cellular compartments. The cell sizes were statistically distributed to simulate the tissue heterogeneity, as shown in Fig. 1a. The intra- and extra-cellular diffusivity were $1.0/2.5 \times 10^{-3}$ mm^2/s, and the membrane permeability was defined in [5]. The b-value was set to be 0-2500 in increments of 500 s/mm^2 by changing the gradient strength g. The diffusion models were fitted to the data using the Levenberg-Marquardt algorithm in Matlab (Mathworks, Inc.). The ADC values were calculated for comparison.

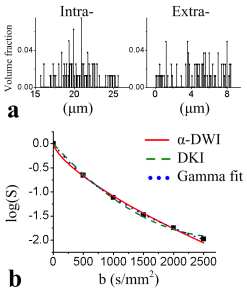

Figure 1a: *Histogram of the simulated intra- and extra-cellular sizes.* ***1b:*** *DWI signal generated with cell volume fraction: 0.8, membrane permeability: 0.05 mm/s, mean intra-cellular size: 20 μm (fixed parameters).*

Human experiment: The Institutional Board approved this study, and the informed consent was obtained from a patient (44 yr, male), who went through the combined chemo-radiation therapy after surgical resection and was diagnosed with recurrent high-grade gliomas. Echo planar imaging (EPI) sequences were implemented on a GE 3T scanner with 40 mT/m gradients. DWI images were acquired with directions: X, Y, and Z axes using maximum b-value: 2500 in increments of 500 s/mm^2. 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. Three ROIs were defined [6] (Fig.3): enhancing region on T1, peri-enhancing region defined on the T2 abnormal signals outside of the enhancing regions, and the normal appearing white matter (NAWM), which was segmented on T1 images using SPM. The fitted parameters were compared using the Student's t-test with significance level: $p < 0.05$.

RESULTS: Simulation: Fig. 1b illustrate DWI signals generated by the simulation. The signals were fitted by three diffusion models with sum-of-residuals (SSR) < 5×10^{-4}. The fitted parameters correlated with the simulated changes of the cellular structures (Fig. 2). The reduced diffusivity measured by ADC, and the increased diffusion heterogeneity measured by α, Kapp, and σ_{gamma} were related to the increased intra-cellular fraction, reduced mean cell sizes and membrane permeability. The variations of each fitted parameter were dependent on the changes of the cellular structures. The variations of ADC with the volume fraction were larger than the variations with the mean cell sizes and the membrane permeability by 50 %. The variations of Kapp with three cellular changes were similar (the differences were less than 15 %). The variations of α with the cell size and the membrane permeability were larger than the variations with the volume fraction by 30 %. The variations of σ_{gamma} with the cell size and the membrane permeability were larger than the variations with the volume fraction by 75 %. This suggested the fitted parameters have different sensitivities to the changes of cellular structures.

Human experiment: The enhancing region showed the significantly lower diffusivity measured by ADC and significantly higher diffusion heterogeneity measured by α, Kapp, and σ_{gamma} than the peri-enhancing regions (p<0.001) (Fig. 3). Comparing the enhancing/peri-enhancing with the normal white matter ROIs, we found different overlaps in the values of fitted parameters. This suggests diffusion models reacted differently to the modulated cellularity.

DISCUSSION: The results from the simulation showed that the ADC was more sensitive to the changes of cell volume fraction, which is consistent with the previous work by Szafer et al. [5]. The diffusion heterogeneity measured by α and σ_{gamma} was more sensitive to the changes of cell size and membrane permeability. The differences in the model sensitivities were observed in the results of human experiment. This work demonstrated that the phenomenological DWI models correlated with the changes of the cellular structures, but had different sensitivity to the changes, suggesting that diffusion models may be used together to study and further identify the underlying pathological mechanisms.

REFERENCES: [1] Bennett KM, et al, MRM (50), 727-34. [2] Jensen JH, et al, MRM (53), 1432-40. [3] Yablonskiy DA, et al, MRM(50), 664-69. [4] Yablonskiy DA, et al, NMR Biomed, in press, Jun 3, 2010. [5] Szafer A, et al, MRM (33), 697-712. [6] Khayal IS, et al, NMR Biomed (22), 449-55, 2009.

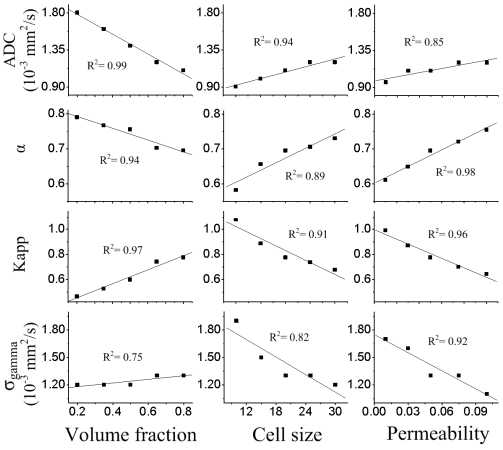

Figure2: *The variations of the fitted parameters with the specified changes of the cellular structures.*

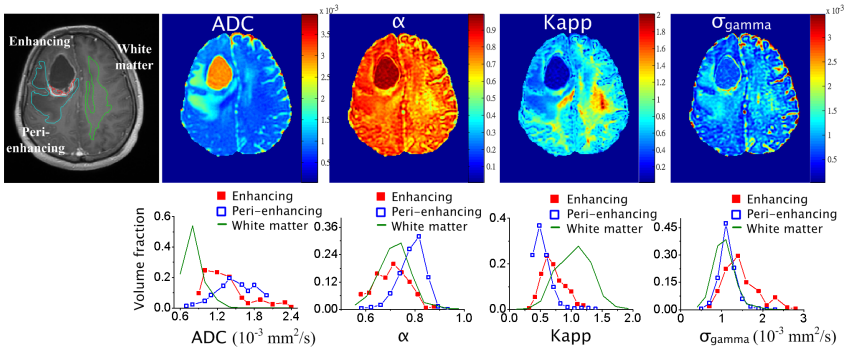

Figure3: *Illustration of selected ROIs and the calculated parametric maps of one case of recurrent tumor (first row). The histogram of the fitted parameters in the selected ROI (second row).*