A NOVEL METHOD OF G-RATIO MEASUREMENT IN WHITE MATTER WITH VALIDATION OF MONTE CARLO SIMULATION

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Purpose: The g-ratio is equal to the ratio between axon diameter and fiber diameter (axon plus myelin sheath). This ratio describes the microstructure properties of whiter matter and is able to reflect the nerve conduction velocity that is the speed at which an electrochemical impulse passes through a neural pathway. For a fixed axon diameter, conduction velocity increases with myelin thickness. For a fixed total fiber diameter, there is an optimal g-ratio at which conduction velocity is maximized [1]. Previous studies have shown that g-ratio can be a potential biomarker for white matter that is sensitive to the process of demyelination and remyelination after disease, as well as sex differences in the brain development of adolescences [2]. Imaging modalities like multi-component T2，diffusion MRI and magnetization transfer can provide information related to myelin and axon, which are potential methods to measure g-ratio non-invasively. Recently, a multi-modal method to measure g-ratio has been proposed [3, 4], in which g-ratio can be calculated by $g_1 = \sqrt{1/(1 + MVF/AVF)}$. In this method, multi-component T2 analysis and magnetic transfer is used to estimate myelin volume fraction (MVF), and NODDI [5] is used to estimate axon volume fraction (AVF). However, NODDI model ignores the signal from myelin water, which may potentially overestimate AVF. In this study, based on $g_2 = \sqrt{1 - MVF/FVF}$ where FVF is the fiber volume fraction, we propose another way to estimate g-ratio. In our method, the NODDI model is modified to account for signal from stationary water from myelin. So the hindered component is replaced with a stationary water component: $A = (1 - v_{iso})(v_{fiber}A_{fiber} + 1 - v_{fiber}) + A_{iso}v_{iso}$. To validate the accuracies of our method, we simulate the effect of multi-component T2 and diffusion on g-ratio with a three-compartment Monte Carlo model.

Methods: For the purpose of validation, the present work simulated a tissue model in which axons were regarded as a periodic array of cylinders with impermeable boundaries. The 3D tissue model was divided into three compartments: intra-axonal compartment with $T2_{in}$ and D_{in}, myelin compartment with $T2_m$ and D_m and extra-axonal compartment with $T2_{ex}$ and D_{ex} (Figure 1). Values for $T2_{in}$, $T2_m$ and $T2_{ex}$ were fixed at 20, 50 and 200ms respectively and D_{in}, D_m and D_{ex} at 1.7, 0.01 and 3.0 $\mu m^2/ms$ respectively. We chose fiber diameter as the variable corresponding to g-ratio changes in white matter, ranging from 1.91 to 2.88 and making g-ratio from 0.9 to 0.6. Simulations were conducted in Matlab, using number of spins and steps of 1×10^6 and 5×10^3 respectively. To estimate MVF, we first acquired T2 decay signal at multiple TE (from 10 to 300ms), then fit a multi-component T2 decay to the signal. The short T2 component (T2<50ms) was extracted as MVF. To estimate AVF and FVF, we employed a pulsed gradient spin echo sequence using a two-shell NODDI protocol. Then, the NODDI model and our model were fitted to the synthesized data. According to Zhang et al. [5], we used $v_{ic}(1 - v_{iso})$ to represent AVF. In our model, the FVF is represented by $v_{fiber}(1 - v_{iso})$. The same methods were also applied to in-vivo data. The MRI measurements were performed in the human corpus callosum, using a custom 20 head coil in a 3T Siemens Prisma scanner. Diffusion weighted imaging was performed over 64 direction at $b = 1000s/mm^{-2}$ and $b = 2000s/mm^{-2}$ with 2 averages. Multi-component T2 imaging was acquire at 12 echo times using spin echo, with TR equal to 500ms and TE ranging from 12 to 100ms. The image resolution is 1.875x1.875x4 mm for DWI and 0.86x0.86x4 mm for spin echo. Those voxels where MVF>FVF or AVF + MVF > 1 were removed from the final g-ratio mappings.

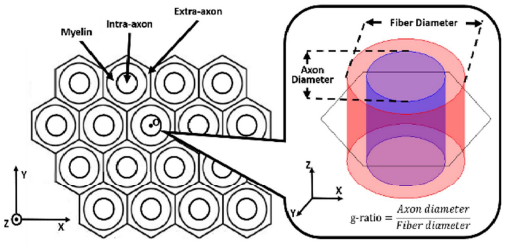

Figure 1 Tissue model and the definition of g-ratio.

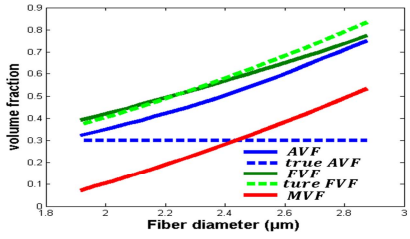

Figure 2 The volume fractions of three compartments

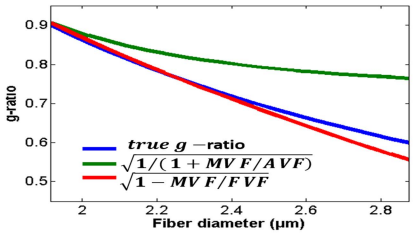

Figure 3 The plot of true g-ratio and estimated ones.

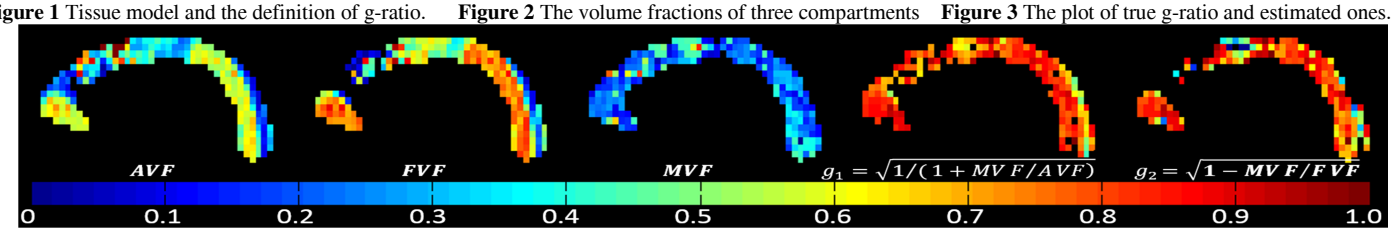

Figure 4 AVF, FVF, MVF and g-ratio maps (two kinds) in the human corpus callosum

Table 1 Pearson correlation coefficient between true g-ratio and the estimated g-ratios and other parameters

	AVF	FVF	MVF	g_1	g_2
r	-0.9804	-0.9888	-0.9867	0.9865	0.9985

Table 2 The mean value and standard deviation of volume fractions and g-ratio

	AVF	FVF	MVF	g_1	g_2
mean+std	0.44 ± 0.20	0.53 ± 0.26	0.26 ± 0.14	0.77 ± 0.12	0.74 ± 0.17

Results: Figure 2 shows the relation between different volume fractions and the fiber diameter, in which all the estimated fractions increases with the fiber diameter. Obviously, AVF (blue line) is overestimated as it is constant (0.3) in our simulation. As shown in Figure 3, the estimated g-ratios of both methods are well correlated to the true value but our method (red line) has a smaller deviation to the true g-ratio (blue line). Table 1 gives the Pearson correlation coefficient between the true g-ratio and the estimated ones as well as the estimated volume fractions. It turns out that FVF has a higher correlation than AVF and the estimated g-ratio from the combination of FVF and MVF has better correlation than any other parameters. As shown in Figure 4, although AVF, FVF and MVF vary along the CC, the g-ratio is relatively constant between 0.7 and 0.8. And the mean value for g_1 and g_2 are 0.7734 and 0.7454 respectively (table 2), which is consistent with simulation $g_1 > g_2$ in Figure 3.

Discussion & Conclusion: As shown in Figure 2, it is noticeable that the estimated value $v_{ic}(1 - v_{iso})$ standing for AVF in NODDI is larger than true value (0.3). The underlying reason is that NODDI takes myelin sheath as part of axon. This further leads to a g-ratio value with greater deviation calculated from $\sqrt{1/(1 + MVF/AVF)}$ than that from $\sqrt{1 - MVF/FVF}$, which also indicates that our modified model has a better estimation of FVF. As shown in table 2, the standard deviation of g-ratio is smaller in percentage than the other three parameters. This supports that, in spite of the variation of AVF, FVF and MVF, the g-ratio has a relatively constant value [1]. From the table 1, it can be concluded that g-ratio based on multi-modality MR signal has a better correlation than those from single modality, i.e., AVF, FVF and MVF. And our method further improves the accuracy of the g-ratio estimation. The preliminary result supports that ***the combination of short T2 component and anisotropic diffusion are able to better reflect true g-ratio***. Also, the g-ratio estimated with FVF is better correlated to g-ratio than that from AVF.

Reference: **1**. Waxman S G. MUSCLE NERVE, 1980, 3(2): 141-150. **2.** Tomáš Paus, Roberto Toro, FRONT NEUROANAT 2009. **3.** A Melbourne, et al., MICCAI 2014; **4.** Nikola Stikov1, et al., Proc. Intl. Soc. Mag. Reson. Med., 2014; **5.** Zhang et al. NeuroImage 2012, 61(4)