**SESSION:** Imaging Microstructure

**TALK TITLE:** Multi-modal Modeling

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## HIGHLIGHTS

- the axon volume fraction (AVF) and myelin volume fraction (MVF) are related via the myelin g-ratio
- combining diffusion and myelin imaging sensitizes the MR measurement to the myelin g-ratio
- multi-modal imaging helps us gain insight into brain microstructure during development, aging, and disease

## TARGET AUDIENCE

Scientists and clinicians with a basic understanding of MRI physics, interested in modeling and non-invasive characterization of white matter microstructure.

## PURPOSE

Over the last ten years we have seen tremendous advances in the field of quantitative magnetic resonance imaging, enabling us to glean microstructural information on a scale that is orders of magnitude smaller than the native MRI resolution. Advances in hardware and pulse sequence design have enabled us to ask specific questions about the distribution of axons and myelin in the brain, but the answers will have to come from an interdisciplinary approach that combines multi-modal imaging and biophysical models of brain microstructure.

Let us imagine for a moment that all white matter in the brain is comprised of parallel, circular, concentric fibers, as shown in Fig. 1. Let us also imagine that the g-ratio (defined as the ratio of the inner to the outer radius of the myelin sheath) is constant for all fibers, and that there exists one qMRI measure specific to the axon volume fraction (AVF), and another specific to the myelin volume fraction (MVF). In this ideal world, there is a very simple formula relating the MVF to the AVF (Fig. 1), and the key to that relationship is the myelin g-ratio. For the first part of this lecture, we will look at the ramifications of this simplified model on the study of healthy and diseased brains. In the second part of the lecture we will look at several ways in which the ideal model breaks down, and we will explore what microstructural information about the real-world brain can be retained.

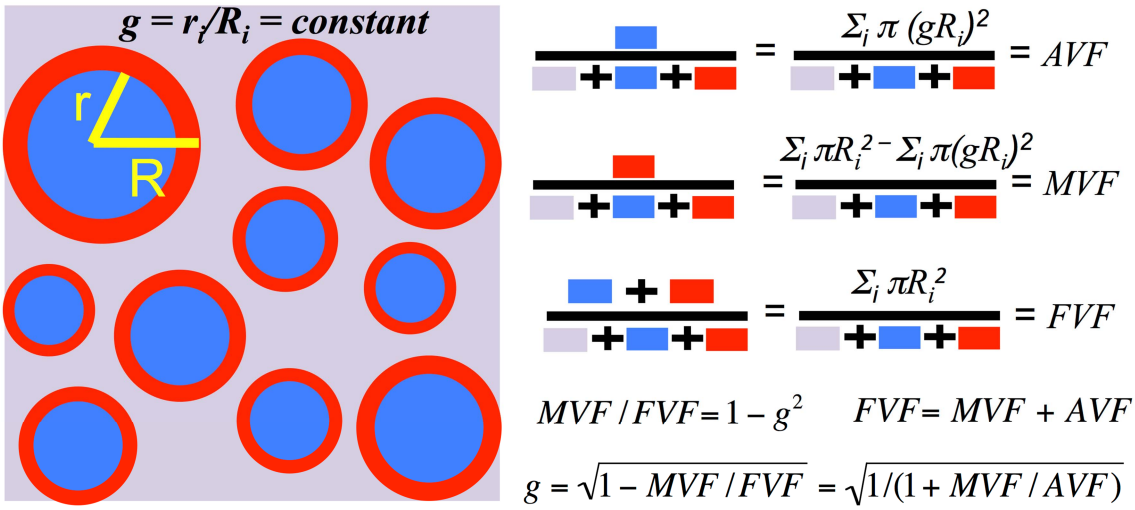


***Figure 1**: White matter model defining the axon volume fraction, myelin volume fraction, fiber volume fraction, and the myelin g-ratio*

## METHODS

While diffusion models have been used to describe the AVF, and there are a number of myelin models for characterizing the MVF, it is only through combining these two that we can obtain a more complete picture of the brain microstructure and the intricate relationship between axon caliber and myelin thickness.

Typical diffusion MRI acquisitions have relatively small signal contributions from myelin. This is because the transverse relaxation time $T_2$ of myelin water is short (10 - 30 ms [1]) and the echo time necessary to achieve sufficient diffusion sensitization is long (□100 ms). The lack of signal from the myelin compartment in diffusion imaging means that estimation of the true volume fractions of the other compartments is difficult.

Adding a complementary myelin imaging technique brings us one step closer to properly characterizing the brain microstructure. Absolute myelin content can be probed with techniques such as multicomponent $T_2$ imaging [2], magnetization transfer [3] or $T_1$ mapping [4].

## RESULTS

Several papers have shown that diffusion and myelin imaging are complementary techniques [5, 6], where the former is more sensitive to the AVF and the latter is sensitive to the MVF [7]. This suggests that combining the two can distill important information about the white matter microstructure, in particular about the relative myelin thickness, or the myelin g-ratio. [7]

Alexander et al. refer to a combination of different MR contrasts, including diffusion and magnetization transfer, as "quantitative stains" [8]. For instance, diffusion tensor imaging (DTI) and the magnetization transfer ratio (MTR) have been combined to look at regional brain changes in myelination and structural organization in early development

[9]. In general, any study that measures some quantitative parameters correlated with axon and myelin content (e.g., DTI and MTR) will be statistically sensitive to the myelin g-ratio.

At last year's ISMRM meeting (Milan 2014) there were a number of abstracts that complemented diffusion with a myelin metric to characterize the white matter microstructure. Barazany et al. showed a negative correlation between the T1 parameter and the mean axon diameter, indicating that bigger axons have a higher degree of myelination [10]. While the absolute myelin content may be higher in regions with large axons, this does not necessarily translate into greater relative myelin thickness (lower g-ratio) in those regions. As a matter of fact, super-axons found in the splenium of the corpus callosum tend to have a higher g-ratio [11], and this was recently measured in vivo [12, 13] by combining neurite orientation dispersion and density imaging (NODDI) [14] with quantitative magnetization transfer [15]. The ramifications of this approach are particularly interesting in the context of multiple sclerosis (MS), where variations in the g-ratio can be interpreted in terms of demyelination, remyelination, and axonal loss [16].

The field of MR tractometry is another example of a multi-modal approach that benefits from assigning quantitative MRI biomarkers to white matter pathways derived from diffusion tractography. One such biomarker is the magnetization transfer ratio, which is sensitive to the myelin content, and is used to evaluate the level of demyelination in MS. Combining MTR and diffusion imaging provides valuable information about the relationship between myelination and fiber geometry [17, 18]. Looking at the magnetization transfer along fiber tracts can help us identify the level of myelination of different fibers in the brain [19], as well as understand the patterns of (de)myelination in normal-appearing white matter in MS patients and healthy controls [20].

Computing $T_1$ along fiber tracts is another multi-modal approach that can be used to look at myelination along fiber tracts. A recent study found that each tract has a signature $T_1$ value that is consistent along its length for a subject [21]. While the $T_1$ value along a tract is nearly constant, the mean $T_1$ value of a tract often differs substantially from the $T_1$ values of neighboring tracts in the same hemisphere, and is consistent with myelination patterns during development and aging. $T_1$ tractometry in combination with the CHARMED model has also succeeded in resolving both axonal and myelin properties in the presence of multiple fiber populations within a voxel [22].

## DISCUSSION

Diffusion and myelin imaging are complementary techniques, and combining them sensitizes the measurement to the myelin g-ratio. While the AVF and MVF vary significantly in the brain, the myelin g-ratio has a much narrower dynamic range, which is theoretically predicted to be optimal for values around 0.7 [23-25]. Deviations in the g-ratio have been observed in several neurodegenerative diseases [26, 27], but to be sensitive to these deviations we need the qMRI biomarker for AVF to not be influenced by the MVF, and vice versa. However, this decoupling is impossible to achieve in a realistic MR experiment, thus raising the issue of which diffusion and myelin metrics,

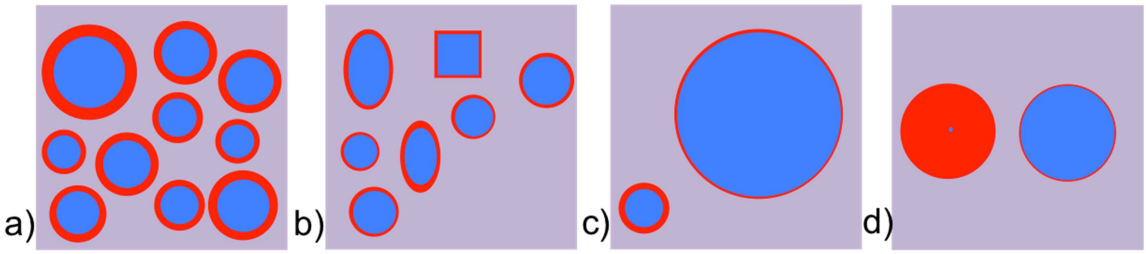


***Figure 2:*** *Illustration of the effect of various fiber arrangements on the aggregate g-ratio: a) parallel, concentric circles with uniform g-ratio b) arbitrary fiber shapes preserving uniform g-ratio c) two fibers with different caliber and g-ratio d) two fibers with equal caliber but different g-ratios*

when combined, provide the greatest specificity to the myelin g-ratio. That is why, in addition to NODDI and magnetization transfer, there is great value in exploring multi-modal imaging with other microstructural imaging techniques, such as AxCaliber [28], ActiveAx [29], and MTV [30].

The g-ratio framework in Fig. 1 holds for many deviations from the ideal model. Figures 2a) and 2b) illustrate several fiber arrangements for which the framework holds, including non-parallel arbitrarily shaped fibers, uniform thinning of the myelin sheath, and significant fiber loss. However, the framework hinges on assuming concentric isomorphic shapes with a uniform g-ratio. Figure 2c) demonstrates a configuration with non-uniform g-ratios, where the measurement will be biased towards the fiber with larger caliber. Figure 2d) is an extreme (and unrealistic) example with only two fibers, one with $g \sim 0$ and another with $g \sim 1$. The average g-ratio in this configuration is $g = 0.5$, but the g-ratio obtained with the formula from Fig. 1 is $g = 0.7$. This discrepancy should not come as a surprise, as the g-ratio framework assumes homogeneity of the g-ratio within the voxel, much like every other qMRI model that assigns a single number (and not a distribution) to a voxel. Fortunately, histology shows that the g-ratio is significantly more uniform within a voxel compared to AVF and MVF, justifying the uniformity assumption [12]. However, to remove any ambiguity arising from calling the computed metric an 'average' g-ratio, we recommend referring to it as the 'aggregate' g-ratio.

## CONCLUSION

The promise of combining qMRI measurements to characterize tissue is at the core of the newly emerging field of *in vivo* histology. Being able to map the g-ratio non-invasively opens up a wide range of possibilities for the study of white matter. Combined with measurement of the axon diameter distribution, which is possible with techniques such as "AxCaliber" [28] and "ActiveAx" [29], the g-ratio will allow us to see a more complete picture of white matter microstructure from imaging data. Thanks to its potential for tracking microstructural changes during development, aging, disease and treatment, multi-modal imaging has the promise to become an invaluable tool in the *in vivo* histology toolbox.

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