RELAXOMETRY MODELLING

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HIGHLIGHTS

- Will provide a comprehensive overview of current approaches to multicomponent relaxometry analysis;
- Strengths and limitations of proposed methods and associated tissue models will be examined;
- Potential clinical utility and interpretability will be discussed.

TARGET AUDIENCE

The target audience of this presentation includes MR physicists as well as clinical researchers interested in the use of relaxometry data to interrogate tissue microstructure and composition.

OUTCOME/OBJECTIVES

By the conclusion of this presentation, viewers will have an improved understanding of the mathematical tissue models that are commonly applied to relaxation data, including their strengths and limitations.

PURPOSE

While the majority of routine clinical and diagnostic imaging comprises *qualitative* T_1, T_2 and/or proton density (PD)-weighted imaging, additional information related to tissue microstructure can be gleaned through *quantitative* voxel-wise evaluation of the T_1 and T_2 relaxation times. Such imaging, commonly referred to as quantitative relaxometry, can minimize or eliminate hardware, acquisition, and patient-specific confounds that exist within conventional qualitative images, such as coil sensitivity differences, or differences in acquisition pulse sequences and imaging parameters. As such, quantitative imaging can afford improved reproducibility (both between different imaging centers, as well as with longitudinal measures on the same patient) and, in some cases, improved image contrast (**Fig. 1**).

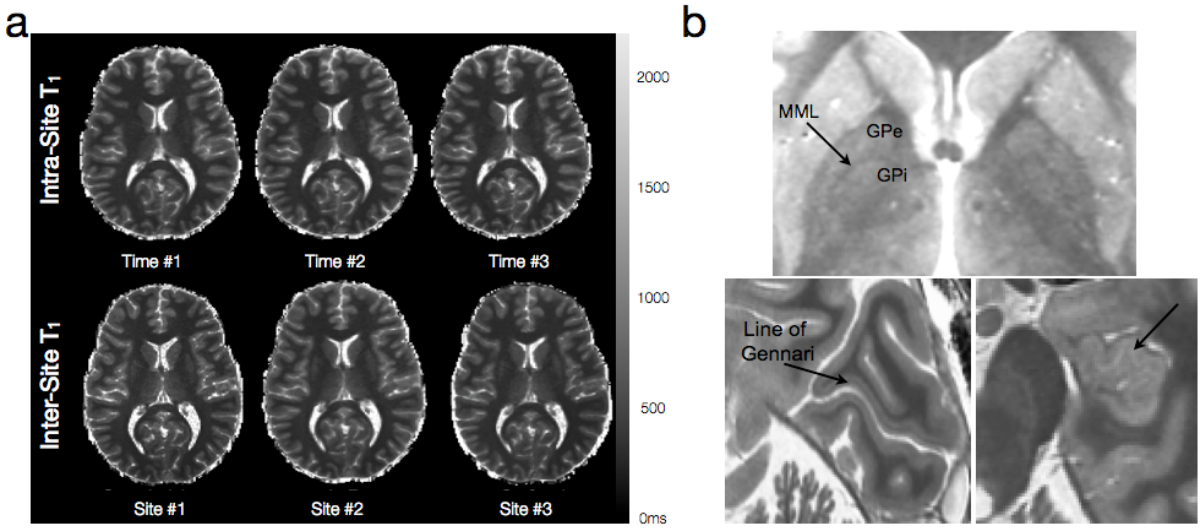

Figure 1: (A) Demonstrated intra and inter-site reproducibility of quantitative T_1 maps (Deoni et al. 2008). (B) Illustration of tissue contrast and detail revealed in high resolution quantitative T_1 maps throughout the basal ganglia (top), the visual cortex (bottom left), and hippocampus (bottom right).

Conventionally, calculation of T_1 and/or T_2 within each imaging voxel is performed by fitting a known signal intensity model to appropriately acquired data. For example, T_1 may be obtained from a series of inversion recovery (IR) data, acquired with 3 or more incremented inversion times (TI), by fitting the governing expression,

$$SI(TI) = PD \times \left(1 - \beta e^{-\frac{TI}{T_1}} + e^{-\frac{TR}{T_1}}\right) e^{-\frac{TE}{T_2}}$$, [1]

for PD, T_1, and β (included to account for imperfect 180° inversion pulses). Similarly, T_2 may be calculated by fitting the equation

$$SI(TE) = PD \times \left(1 - e^{-\frac{TR}{T_1}}\right) e^{-\frac{TE}{T_2}}$$, [2]

to a series of spin echo (SE) data acquired with at two or more echo times (TE). While both these approaches (and many others) provide precise and reproducible T_1 and T_2 values, they impose an inherent tissue model onto the data. That being, all water protons within the voxel have the same relaxation properties (i.e, they are all governed by the same T_1 and/or T_2 relaxation time). Since T_1 and T_2 are exquisitely sensitive to their biophysical and biochemical environment (Bottomley et al., 1984), this model, therefore, assumes each voxel contains a single homogeneous water pool (i.e., single component relaxation). Unfortunately, observation of tissue structure on the microscopic scale reveals a more complex picture, with water compartmentalized into multiple distinct environments, with differing physical and biochemical structures, and passive and active transportation processes that shuttle water between them (Fenrich et al., 2001) (**Fig. 2**).

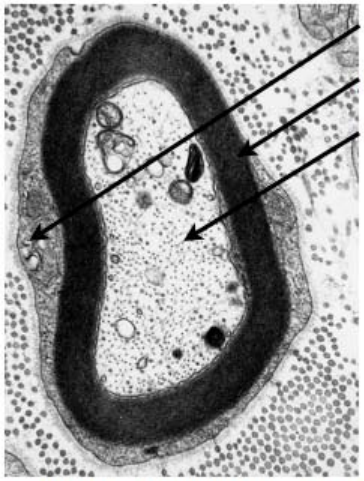

Figure 2: Electromicrogram of a myelinated axon detailing the numerous potential water compartments within brain tissue, and their differing physical and biochemical structure.

While the complexity of tissue microstructure raises concerns about the validity of single component relaxometry, the sensitive of relaxation to their environment offers the potential to glean additional microstructural information through the use of more complex relaxation (e.g., multicomponent) models.

METHODS

Multicomponent T_2 Relaxation

Proposed in the late 1980's and further refined through the 1990's, the first approach to tissue microstructure through relaxometry was through multicomponent analysis of T_2 relaxation (Fischer et al., 1990; MacKay et al., 1994). Expanding Eqn. [2] to include multiple T_2 relaxation species (each corresponding to a different water compartment) yields the general multicomponent SE equation

$$SE(TE) = PD \times \sum_{f=1}^{N} F_f e^{-\frac{TE}{T_{2,f}}}$$, [3]

where the index *f* denotes each T_2 species with $T_2 = T_{2,f}$ and relative volume fraction equal to F_f. (Here we have set TR much greater than T_1 to eliminate the middle $1\text{-}e^{-TR/T1}$ term.) While Eqn. [3] makes no assumption regarding the number of differing T_2 species within the voxel, it does present a formidable analysis problem in that unconstrained it presents an underdetermined system. To avoid this problem, a T_2 distribution consisting of M logarithmically-spaced T_2 values are fit to the M echo time SE data using non-negative least squares and imposing a smoothing function to ensure a continuous distribution (Whittall et al., 1997; Hwang and Du, 2009) (**Fig. 3a**).

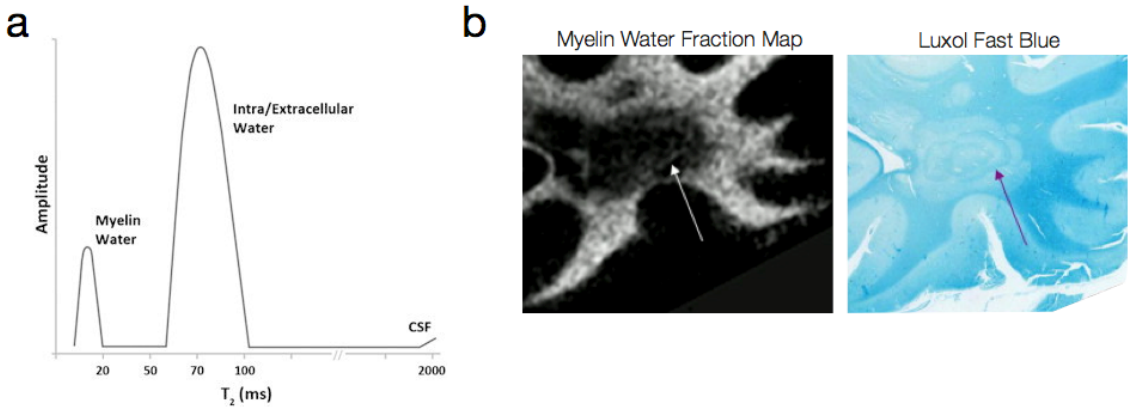

Figure 3: (A) Graphical T2 distribution calculated by fitting a N-component model to 32 echo spin echo data. **(B)** Comparison between a high resolution myelin water fraction map, centered about an MS lesion, and the same region stained for myelin using Luxol Fast Blue. Laule et al. 2008.

Peaks within the T_2 distribution are believed to correspond to unique physical environments (MacKay et al., 2006). In brain, for example, the short T_2 peak (T_2 < 50ms) corresponds to water trapped within the lipid bilayers of the myelin sheath; the intermediate peak (80ms < T_2 < 200ms) to intra/extra-cellular water; and the longer peak (T_2 > 250ms) to unrestricted free water. These assignments have been collaborated through histological comparison studies (**Fig. 3b**), as well as examination of their changes in known demyelinating diseases (such as multiple sclerosis, MS) (Laule et al., 2008). The ratio of the area under the short T_2 peak to the area under the full distribution has been termed the myelin water fraction (MWF), which has seen increased research activity of late due to its ability to provide improved sensitivity and specificity to myelin changes in MS and other degenerative disorders (Mackay et al., 2009).

In addition to neuroimaging applications, multicomponent T_2 analysis has also been performed, and found utility, in musculoskeletal applications, including changes in muscle composition following training and creatine supplementation (Saab et al., 2002); and in the analysis of cartilage degradation (Reiter et al., 2009).

Multicomponent T_1 Relaxation

Initial attempts to replicate results from T_2 analysis in the context of T_1 were, unfortunately, unsuccessful. This failure is believed to be due to the relative difference in the timescales between T_1, T_2, and the rate of water exchange between the various water compartments (Li et al., 2012). Eqn. [3] makes no mention of water exchange between, for example, the myelin-associated water and the intra/extra-cellular water pools, assuming instead that T_2 is short relative to the exchange time, , such that each component can be considered in isolation. In contrast, T_1 is long with respect to , such that the components appear as one “well-mixed” container. Thus, while T_2 may be analyzed using multicomponent analysis, T_1 appears to be mono-exponential.

However, in combined T_1 and T_2 analysis of peripheral nerve, Does et al., have shown unique T_1 times associated with each T_2 component (Does et al., 1998). Though difficult to observe and quantify directly, this underlying multicomponent T1 has led to the development of novel imaging methods designed to selectively isolate the T1-weighted signal associated with the myelin water (Travis and Does, 2005).

Combined Multicomponent T_1 and T_2 Relaxation

While the conventional approaches to visualizing and quantifying multicomponent relaxation rely on spin echo or inversion recovery methods, any imaging sequence is sensitive and susceptible to these effects. Recently, a more rapid approach for quantifying multicomponent relaxation, termed mcDESPOT, has been proposed that utilizes rapid and time efficient steady-state imaging methods (Deoni et al., 2008). This approach differs from spin echo based measures in that water exchange and cross-relaxation effects are implicitly included within the signal model. This inclusion, however, requires knowledge of the tissue system (i.e., what water pools are in each with each other), which forces an upper limit on the number of tissue pools that can be modelled (3) (**Fig. 4**) (Deoni et al., 2013).

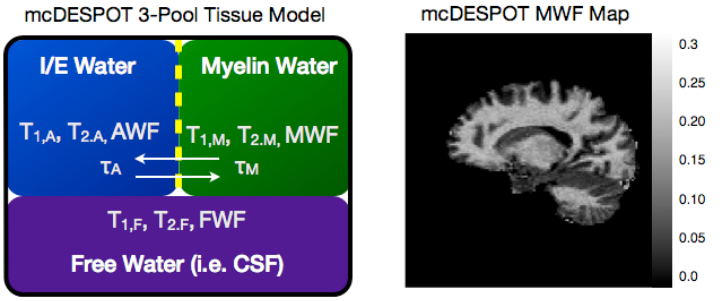

Figure 4: Graphical Illustration of the mcDESPOT 3-pool tissue model and a corresponding mcDESPOT myelin water fraction map of a healthy adult male.

While offering a potentially rapid approach to myelin water imaging (as well as potential application to cartilage imaging (Liu et al., 2014)), mcDESPOT remains to be fully understood. MWF values derived using mcDESPOT are universally higher than those obtained using spin-echo methods, though they are correlated with each other (**Fig. 5a**), and have been qualitatively validated against histology (**Fig. 5b**). Further, the effect of magnetization transfer remains to be fully addressed (Zhang et al., 2014).

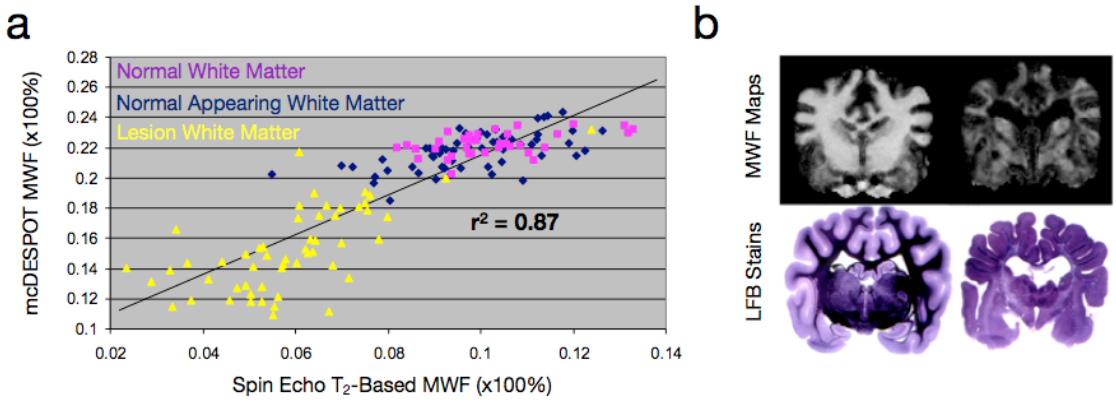

Figure 5: (A) Comparison of regional mean healthy WM, normal appearing WM, and lesion WM mcDESPOT and Spin Echo T_2-based MWF measures from 15 patients with early-stage relapsing remitting multiple sclerosis (unpublished, Kolind SH 2014). **B).** Qualitative comparison of mcDESPOT MWF images and corresponding Luxol Fast Blue histologic stains in a shaking pup dysmyelination model (Hurley SA et al. 2010).

METHODS & RESULTS

MRI relaxation data offers a potential wealth of information with increased specificity and sensitivity to tissue microstructure and composition. While numerous acquisition methods have been presented, and several mathematical tissue models and analysis approaches described, there remains significant limitations and voids in our knowledge regarding the ideal approach or the interpretation of derived results. Nevertheless, with more recent methodologies offering the potential for multicomponent relaxometry within clinically realistic scan times, the field is experiencing renewed interest and rapid growth. Once relegated to research studies of known myelin disorders, multicomponent relaxometry and MWF imaging is now being applied to studies of neurodevelopment (Deoni et al., 2011; 2012), aging (Lamar et al., 2014), and other neurological disorders (Spader et al., 2013).

Throughout this talk, we will discuss the various models and acquisition approaches commonly employed for multicomponent relaxometry, and detail the strengths and limitations of each model.

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