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Rapid simultaneous high-resolution mapping of myelin water fraction and relaxation times in human brain using BMC-mcDESPOT

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ABSTRACT

A number of central nervous system (CNS) diseases exhibit changes in myelin content and magnetic resonance longitudinal, T_1, and transverse, T_2, relaxation times, which therefore represent important biomarkers of CNS pathology. Among the methods applied for measurement of myelin water fraction (MWF) and relaxation times, the multicomponent driven equilibrium single pulse observation of T_1 and T_2 (mcDESPOT) approach is of particular interest. mcDESPOT permits whole brain mapping of multicomponent T_1 and T_2, with data acquisition accomplished within a clinically realistic acquisition time. Unfortunately, previous studies have indicated the limited performance of mcDESPOT in the setting of the modest signal-to-noise range of high-resolution mapping, required for the depiction of small structures and to reduce partial volume effects. Recently, we showed that a new Bayesian Monte Carlo (BMC) analysis substantially improved determination of MWF from mcDESPOT imaging data. However, our previous study was limited in that it did not discuss determination of relaxation times. Here, we extend the BMC analysis to the simultaneous determination of whole-brain MWF and relaxation times using the two-component mcDESPOT signal model. Simulation analyses and *in-vivo* human brain studies indicate the overall greater performance of this approach compared to the stochastic region contraction (SRC) algorithm, conventionally used to derive parameter estimates from mcDESPOT data. SRC estimates of the transverse relaxation time of the long T_2 fraction, $T_{2,l}$, and the longitudinal relaxation time of the short T_1 fraction, $T_{1,s}$, clustered towards the lower and upper parameter search space limits, respectively, indicating failure of the fitting procedure. We demonstrate that this effect is absent in the BMC analysis. Our results also showed improved parameter estimation for BMC as compared to SRC for high-resolution mapping. Overall we find that the combination of BMC analysis and mcDESPOT, BMC-mcDESPOT, shows excellent performance for accurate high-resolution whole-brain mapping of MWF and bi-component transverse and longitudinal relaxation times within a clinically realistic acquisition time.

1. Introduction

Alterations in myelin content and in magnetic resonance relaxation times T_1 and T_2 have been shown to be sensitive biomarkers for a number of central nervous system diseases. These include multiple sclerosis (Neema et al., 2007; Manfredonia et al., 2007; Ropele et al., 2000; Neema et al., 2009; Laule et al., 2004), brain atrophy (Nakamura et al., 2014; Vymazal et al., 1999), epilepsy (Pitkanen et al., 1996; Conlon et al., 1988; Townsend et al., 2004; Jackson et al., 1993), Parkinson's disease (Vymazal et al., 1999), Alzheimer's disease (House et al., 2006; Bartzokis et al., 2004), phenylketonuria (Sirrs et al., 2007; Vermathen et al., 2007), psychotic disorders (Wood et al., 2010), and schizophrenia (Supprian et al., 1997; Williamson et al., 1991; Pfefferbaum et al., 1999; Flynn et al., 2003). While it is most often assumed that relaxation within each imaging voxel may be described by a single T_1 or T_2 value, this assumption does not capture the structural and compositional complexity of brain tissue. In fact, previous studies have demonstrated the presence of multi-component T_1 and T_2 relaxation processes in brain as an indicator of compartmentation (Laule et al., 2004; MacKay et al., 1994; Bakshi et al., 2008; Alonso-Ortiz et al., 2015; Bouhrara et al., 2015; Bouhrara and Spencer, 2016; Dean et al., 2015; Deoni et al., 2013, 2008; Hwang et al., 2010; Kolind et al., 2015; Laule et al., 2006; Lenz et al., 2012; Zhang et al., 2015a, 2015b). Multicomponent relaxometry (MCR) analysis has characterized two main water pools, with distinct relaxation times and fractions. The pool exhibiting the more rapid transverse relaxation and smaller fraction size has been attributed to myelin-bound water, while the more slowly-relaxing pool has been assigned to relatively unbound intra- and

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Table 1
In-vivo acquisition parameters.

Volunteers	Acquisition parameters	
	Low-resolution (LR) protocol	**High-resolution (HR) protocol**
Volunteer #1 Healthy 23 year-old male **Volunteer #2** Healthy 22 year-old male	3D SPGR: α_{SPGR} = [2 4 6 8 10 12 14 16 18 20]°, TE_{SPGR} = 1.2 ms, TR_{SPGR} = 6.5 ms. 3D bSSFP: β_{bSSFP} = [2 6 14 22 30 38 46 54 62 70]°, TE_{bSSFP} = 3.2 ms and TR_{bSSFP} = 6.5 ms. FoV = 230×180×130 mm^3, matrix size = 116×90×65, acquisition voxel size ≃ 2 mm×2 mm×2 mm, total acquisition time ≃ 10 min.	3D SPGR: α_{SPGR} = [2 4 6 8 10 12 14 16 18 20]°, TE_{SPGR} = 1.2 ms, TR_{SPGR} = 6.5 ms. 3D bSSFP: β_{bSSFP} = [2 6 14 22 30 38 46 54 62 70]°, TE_{bSSFP} = 3.2 ms and TR_{bSSFP} = 6.5 ms. FoV = 230×180×130 mm^3, matrix size = 153×120×86, acquisition voxel size ≃ 1.5 mm×1.5 mm×1.5 mm, total acquisition time ≃ 17 min.
Volunteer #3 Healthy 29 year-old male	–	3D SPGR: α_{SPGR} = [2 4 6 8 10 12 14 16 18]°, TE_{SPGR} = 0.83 ms, TR_{SPGR} = 6 ms. 3D bSSFP: β_{bSSFP} = [2 4 7 11 16 24 32 40 50]°, TE_{bSSFP} = 2.8 ms and TR_{bSSFP} = 5.8 ms. FoV = 230×190×140 mm^3, matrix size = 154×127×94, acquisition voxel size≃1.5 mm×1.5 mm×1.5 mm, total acquisition time≃15 min.
Volunteer #4 Healthy 22 year-old male	3D SPGR: α_{SPGR} = [2 4 6 8 10 12 14 16 18 20]°, TE_{SPGR} = 0.83 ms, TR_{SPGR} = 6 ms. 3D bSSFP: β_{bSSFP} = [2 6 14 22 30 38 46 54 62 70]°, TE_{bSSFP} = 2.8 ms and TR_{bSSFP} = 5.8 ms. FoV = 200×216×140 mm^3, matrix size = 100×108×70, acquisition voxel size≃2 mm×2×mm×2 mm, total acquisition time≃11 min.	–

FoV: Field of view. The bSSFP images were acquired twice, once with RF phase increment, θ_{RF}, of 0 ($bSSFP_0$) and once with θ_{RF} of π ($bSSFP_\pi$). All images were acquired with SENSE factor = 2. LR images were reconstructed to voxel volume = 8 mm^3 while HR images were reconstructed to voxel volume = 1 mm^3.

extracellular water (MacKay et al., 1994; Alonso-Ortiz et al., 2015; Deoni et al., 2008; Rioux et al., 2015).

A variety of approaches to MCR have been applied to *in-vivo* clinical studies (Deoni et al., 2008; Hwang et al., 2010; Lenz et al., 2012; Whittall et al., 1997; Akhondi-Asl et al., 2015; Prasloski et al., 2012a, 2012b; Nguyen et al., 2015; Oh et al., 2007; Armspach et al., 1991; Vargas et al., 2015; Baranovicova et al., 2016), and have been reviewed recently by Alonso-Ortiz et al. (2015). Among these methods, the multicomponent driven equilibrium single pulse observation of T_1 and T_2 (mcDESPOT) method, based on steady-state magnetic resonance imaging (MRI) sequences, is of particular interest (Deoni et al., 2008; Deoni, 2011). mcDESPOT allows simultaneous mapping of multicomponent T_1 and T_2 relaxation times and myelin water fraction (MWF), providing improved sensitivity and specificity to tissue changes associated with development or pathology. Moreover, mcDESPOT permits the use of a relatively short echo time, TE, thereby allowing improved detection of the short-T_2 component of the signal, representing the MWF. Finally, mcDESPOT makes use of conventional MR acquisition sequences, namely, fully balanced steady state free precession (bSSFP) and spoiled gradient recalled echo (SPGR), widely available on clinical MRI systems. Overall, then, mcDESPOT is particularly attractive for clinical investigations (Dean et al., 2015; Kolind et al., 2015; Croteau-Chonka et al., 2016).

In mcDESPOT analysis, SPGR and bSSFP datasets are acquired over a range of flip angles (FAs), with very short repetition times, TRs. Two different bSSFP datasets are acquired respectively with radio-frequency (RF) phase increments equal to 0 or π ($bSSFP_0$ and $bSSFP_\pi$) to correct for off-resonance effects (Deoni, 2011). Although this formalism has been extended to include a third pool to account for either partial volume effects (Deoni et al., 2013) or magnetization transfer (Liu et al., 2015), mcDESPOT modeling is generally restricted to a two-pool model. Even with this restriction, quantitative parameter estimation from mcDESPOT is problematic, especially at the low-to-moderate signal-to-noise ratios (SNRs) typical of high-resolution imaging (Bouhrara and Spencer, 2016; Bouhrara et al., 2016; Lankford and Does, 2013). In recent studies, Zhang et al. (2015a, 2015b), Lankford and Does (Lankford et al., 2015) and Bouhrara et al. (2016) showed that for a two-component implementation of mcDESPOT using stochastic region contraction (SRC) with nonlinear least squares (NLLS), determination of relaxation times was problematic due to the flatness of the parameter least-squares energy surfaces. It was found, for example, that estimates of T_1 for the more rapidly relaxing T_1 component, and of T_2 for the more slowly relaxing T_2 component, showed a tendency to cluster respectively at the upper and the lower limits of the specified parameter spaces (Zhang et al., 2015a, 2015b).

In a recent study, we showed that the quality of MWF estimates from the two-component mcDESPOT signal model was greatly enhanced through use of a new Bayesian Monte Carlo (BMC) analysis (Bouhrara and Spencer, 2016). However, that work was limited to MWF analysis and did not address the important issue of relaxation time estimation. In this work we therefore extend BMC-mcDESPOT analysis to the simultaneous estimation of MWF and relaxation times over the whole brain with a voxel volume of 1 mm^3, with an acquisition time of under 15 min. In addition, we directly demonstrate the superior performance of BMC compared to the conventional approach using SRC.

2. Materials and methods

2.1. Experimental analysis

2.1.1. Data acquisition

All experiments were performed on a 3 T whole body Philips MRI system (Achieva, Best, The Netherlands) using the internal quadrature body coil for transmission and an eight-channel phased-array head coil for reception. Data were collected at low-resolution (LR) or high-resolution (HR) from four volunteers, from whom written informed consent was obtained prior to participation. All examinations were performed with approval of the local Institutional Review Board. Table 1 summarizes the experimental acquisition and reconstruction parameters of mcDESPOT imaging data for each volunteer. LR images were obtained with an acquisition voxel size of 2 mm × 2 mm × 2 mm and reconstructed to this same voxel volume of 8 mm^3 while all HR images were acquired with an acquisition voxel size of 1.5 mm × 1.5 mm × 1.5 mm and reconstructed to a voxel volume of 1 mm^3 using zero-filling to improve visual quality.

In our *in-vivo* studies, SNR was estimated as the mean signal value within a large region in SPGR images obtained over all non-zero FAs divided by the mean signal value for FA = 0°. These SNR values were ~30 and ~50 for the HR and LR protocols (Table 1), respectively.

2.1.2. Data analysis

We assumed a two-component non-exchanging system consisting of short, *s*, and long, *l*, T_1 and T_2 components (Bouhrara and Spencer,