Extracellular Fluid Volume Measurements with Complex Signal Analysis

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Introduction: The ability to measure the volume fraction of extracellular fluid could be a powerful tool for the analysis of hydrocephalus, as diffusion of Cerebral Spinal Fluid (CSF) into the periventricular white matter is a feature of all types of the condition. A recent study by Bender and Klose [1] introduced a non-invasive method of achieving this by exploiting the bulk dephasing of intra and extracellular fluid discovered by He and Yablonskiy [2,3]. This was achieved by fitting the signal from a Gradient Echo Sampling of a Free Induction Decay (GESFID) sequence with a model that describes the bulk dephasing of two components with differing relaxation rates. In this study we present a novel method of measuring extracellular fluid fraction and precession frequency shift using complex analysis.

Methods: All experiments were performed on a 3T Siemens scanner. The GESFID sequence had the following parameters: FOV 192x256x45mm, sampling matrix 96x128x9, TR=3500ms, NEX=4, GRAPPA=4 and as this is an adapted sequence there was also a spoiled inversion pulse at t=5 ms.
A total of 55 GEs with TEs ranging from 11.38 ms to 138.28 ms were acquired and movement corrected but the first 3 were discarded as they were in the non-linear decay regime as defined in ref. 2. The one component and two component models in Eq. 1 and 2 were then fitted to the complex data by minimizing the sum of the real and imaginary component sum-of-squares errors.

$$S_{1comp}(t) = S(0)\exp(-t/T_2^* + i(\Delta\omega\,t + \varphi)) \qquad [1] \qquad\qquad S_{2comp}(t) = S_1(0)\exp(-t/T_{2,1}^* + i(\Delta\omega_1 t + \varphi)) + S_2(0)\exp(-t/T_{2,2}^* + i(\Delta\omega_2 t + \varphi)) \qquad [2]$$

The $\Delta\omega$ terms describe the difference between the local precession frequency and the Larmor frequency at 3T and φ is the signal phase at the point of excitation. The T_2^* decay terms account for all intracompartmental dephasing and $T_{2,2}^*$ was fixed 500ms as observed in voxels of pure extracellular fluid. The human brain dataset was obtained from a healthy volunteer and the study was approved by the local ethics committee.

Results: An example of a signal timecourse from a representative voxel is given in fig. 1a,b . The single component model (dashed lines) is unable to fit the data as accurately as the two component fit (complete lines). Fitting the two component model to the entire brain we see that the relative signal contributions of the two components describe a fluid image (fig. 2b) and the precession frequencies of the components describe fieldmaps with a higher frequency in the compartment assigned to extracellular fluid (fig 2c,d).

Fig 1. (a) Raw signal Argand diagram. (b) Real and imaginary signal timecourses with 1 & 2 component fits. (c) 1 & 2 component model fitting residuals.
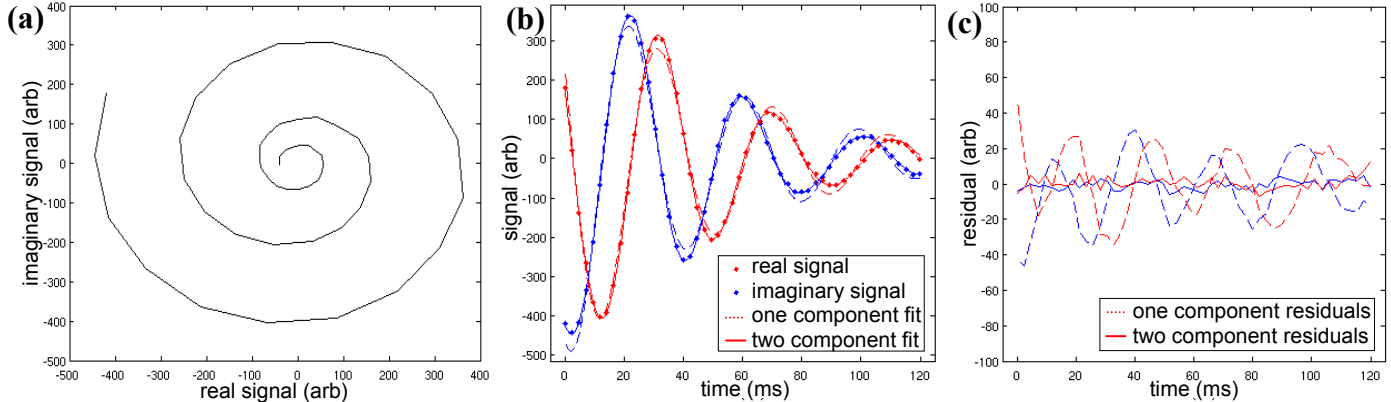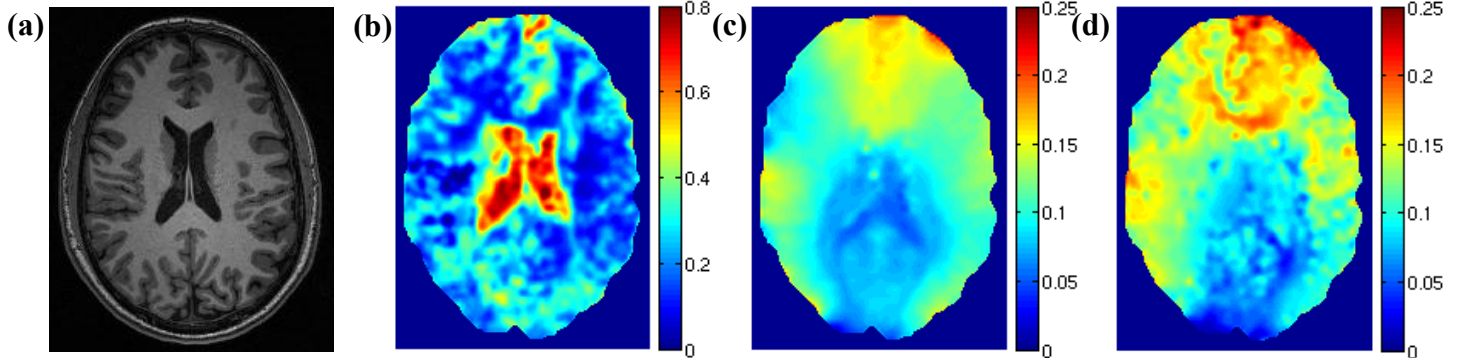

Fig 2. (a) MPRAGE image. (b) Extracellular fluid volume fraction. (c) $\Delta\omega_1$ (rad ms^{-1}). (d) $\Delta\omega_2$ (rad ms^{-1})

Discussion: In all voxels tested, the one component model failed to fit the data. The form of the one component fitting residuals in fig. 1c supports the theory of a second component with a higher precession frequency and a lower relaxation rate. Further, the two component model fitted the data accurately and provided quantitative measures of both the volume fractions and the precession frequencies of intra and extracellular fluid. The mean frequency difference between components observed in this study was 2 Hz. This is lower than was observed in the magnitude fitting studies in ref. 1 (3.5-3.8 Hz) and ref. 2 (5.4 Hz). This discrepancy could be a result of differences in model fitting protocol or it could be due to intersubject variation in protein/lipid concentrations.

Conclusion: This study has provided direct evidence for the existence of bulk dephasing between intra and extracellular fluid spins. By fitting a complex signal model to GESFID data we have introduced a novel method of making quantitative measures of the extracellular fluid fraction and precession frequency shift. This method is more efficient than fitting the magnitude data as it also utilizes the phase information acquired.

References: [1] Bender and Klose, *MRM*, 2009. 61(4): p.834-841. [2] He and Yablonskiy, *MRM*, 2007. 57(11): p.115-126. [3] He and Yablonskiy, *PNAS*, 2009. 106(32): p13558-13563.