Frequency difference mapping for measurement of white matter microstructure

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Introduction: Frequency difference mapping[1] (FDM) is a novel technique that takes advantage of the non-linear temporal evolution of the phase[2] in gradient echo (GE) sequences to obtain images that carry information about white matter (WM) microstructure. In contrast to other phase-based approaches for probing WM properties, such as quantitative susceptibility mapping and susceptibility tensor imaging[3], FDM can yield local contrast that is sensitive to microstructure without requiring sophisticated filtering of phase images. Here, we present a straightforward implementation of FDM, including the simple post-processing steps that eliminate the effect of initial phase offsets and frequency variation due to non-local sources. The application of this approach to measurement of the variation of microstructure across the corpus callosum in a study of 10 subjects is also described.

Theory: The effect of WM microstructure on the evolution of the GE signal can be characterised using a three-pool model[4],

$$F(t) = A_a e^{-(i\omega_a + R^*_{2a})t} + A_m e^{-(i\omega_m + R^*_{2m})t} + A_e e^{-(i\omega_e + R^*_{2e})t} \quad (1)$$

comprised of axonal (a), myelin (m) and external pools (e) where $A_{a,m,e}$, $\omega_{a,m,e}$ and $R^*_{2a,m,e}$ represent the amplitude, average frequency and relaxation rate of the different pools. $A_{a,m,e}$ and $\omega_{a,m,e}$ have a strong dependence on WM fibre properties including the fibre volume fraction (FVF), fibre orientation and g-ratio, and the relaxation rate of the myelin water signal, R^*_{2m}, is much larger than that of the external and axonal pools. The different frequency offsets of the different pools and the rapid decay of the signal from the myelin pool produces a non-linear phase evolution, which can be characterised by evaluating the change in the apparent frequency of signal evolution with echo time in FDM. In order to measure the microstructural effects, it is however necessary to eliminate the larger phase variation resulting from frequency variation, Ω, due to non-local field sources, as well as the time-independent phase offsets, ϕ_0, due to RF transmit phase variation and sequence imperfections, which together mean that the measured signal actually varies as

$$S(t) = S_0 e^{-i\Omega t} e^{i\Phi_0} F(t) \quad (2)$$

If we measure the signal evolution using a multi-echo GE sequence, with an initial echo time, TE_1, and an inter-echo spacing, ΔTE, such that the nth echo time is $TE_1 + (n-1)\Delta TE$, then we can eliminate the effect of ϕ_0, by dividing each echo by $S(TE_1)$

$$S'(TE_n) = \frac{S(TE_n)}{S(TE_1)} = e^{-i\Omega(n-1)\Delta TE} \times \frac{F(TE_n)}{F(TE_1)} \quad (3)$$

Non-local field effects are removed by dividing $S'(TE_n)$ by $\left(S'(TE_2)\right)^{n-1}$

$$S''(TE_n) = \frac{S'(TE_n)}{\left(S'(TE_2)\right)^{n-1}} = \frac{F(TE_n)}{F(TE_1)} \times \left(\frac{F(TE_1)}{F(TE_2)}\right)^{n-1} \quad (4)$$

yielding a signal which is predominantly sensitive to microstructure. Scaling the phase of $S''(TE_n)$ by $2\pi(TE_n - TE_1)$ gives the FD measure in Hz.

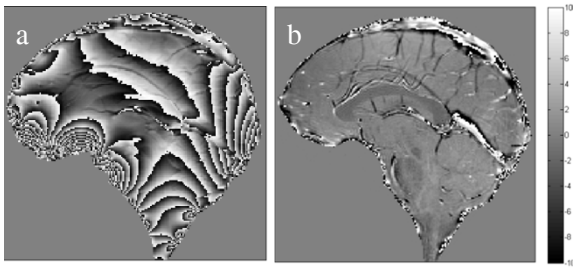

Fig 1: *a. Masked phase image & b. FD map in Hz (TE=23.4 ms).*

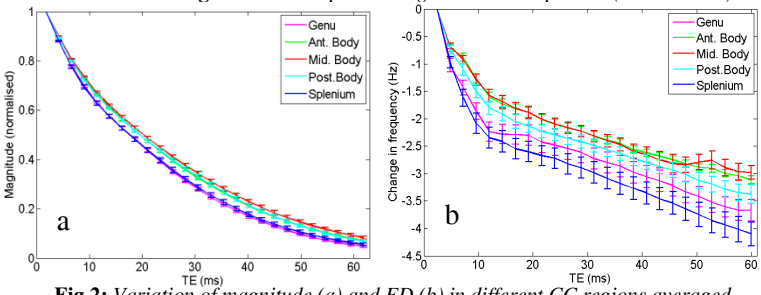

Fig 2: *Variation of magnitude (a) and FD (b) in different CC regions averaged over 10 subjects.*

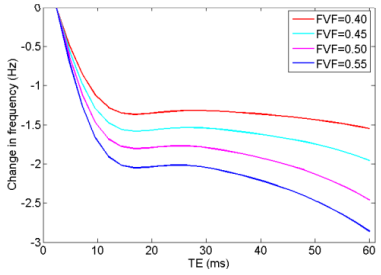

Fig 3: *Modelled FD variation with TE for different FVF values.*

Method: Using a Philips Achieva 7T MR scanner, 10 subjects underwent a single-slice, sagittal multi-echo GE scan (slice thickness=5mm, resolution=1mm, FOV=224×224 mm^2, TE_1=1.8 ms, ΔTE=2.4 ms, # of echoes=26, TR=138 ms, flip angle=25°, # of averages=20). The slice was positioned on the mid-line, thus spanning a portion of the corpus callosum where the fibres are oriented perpendicular to B_0. The data was processed as detailed in the Theory section, with an additional step involving fitting and subtraction of a term describing linear phase variation in the read direction (foot-head), which results from small differences of echo position in the acquisition window. A T_1-weighted image was acquired from the same slice and used in segmenting the CC of each subject into 5 regions[5,6] (genu and splenium, plus anterior-, mid- and posterior-bodies). The variation of the signal magnitude and FD with TE was evaluated in each region for individual subjects and averaged across the group. Repeatability of the measurements was characterised by imaging a single subject four times (removing from scanner between measurements). The signal variation due to microstructure, characterised by Eq. (1) was simulated using a geometrical multi-fibre model and expressions characterising frequency offsets in a hollow cylinder model of myelinated nerve fibres[1,2].

Results: Figs. 1a and 1b shows a raw phase image acquired from one subject at TE=23.4 ms (10th echo) and the corresponding FD map. Fig. 2 shows the variation of the FD and signal magnitude with TE from the five regions of the CC, averaged over the 10 subjects. Fig. 3 shows the simulated variation of the FD with TE for different values of FVF (other parameters taken from literature[1]).

Discussion: Comparison of Figs. 1a and 1b shows that the processing steps described in the Theory section eliminate the effects of non-local field sources and ϕ_0, yielding a FD map that is sensitive to microstructure. The CC is clearly depicted as hypointense compared with the surrounding tissue (along with other WM structures such as the superior cerebellar peduncle in which fibres run perpendicular to B_0). Comparison of Figs. 2b and 3 (and of Fig. 2a and simulated magnitude data – not shown) indicates that the three-pool model of WM well characterises the signal behaviour. The early decrease of frequency with TE results from the rapid decay of the myelin contribution, which has a positive frequency offset relative to the axonal and external pools for fibres that are perpendicular to B_0. Interplay between the signals from the axonal and external pools contributes to the continuing reduction in frequency at larger TE-values. Fig. 2 reveals an ordered variation of signal behaviour across the CC, with the splenium and genu displaying faster magnitude decay and a larger change in frequency with TE than is found in the mid-regions of the CC. The magnitude & FD curve ordering across the CC was consistent in the 4 repeats on a single subject. The number of small fibres (<0.4 μm dia.) per unit area increases when moving from the mid-region of the CC towards the splenium or genu[5], while large fibres (>3 μm dia.) show an opposite distribution[5]. Our data is consistent with an increase in FVF (Fig. 3) or g-ratio with the number density of small fibres such that the largest FD and greatest rate of signal decay occurs in the splenium and genu.

Conclusion: FDM offers a simple approach for producing images with contrast that is sensitive to WM microstructure and which does not require complicated signal processing (e.g. solution of an inverse problem). Measurements from 10 subjects provide evidence that the FD is sensitive to variation in microstructure across the CC.

References: 1. Wharton, S. and Bowtell, R. *PNAS* **109**, 18559-18564 (2012)., 2. Sati, P. et al, *NIMG* **77**, 268-278, (2013)., 3. Liu, C. *MRM* **63**, 1471-1477 (2010)., 4.Van Gelderen, P. et al. *MRM* **67**, 110-117 (2012)., 5. Aboitiz, F. et al. *Brain Research* **598**, 143-153 (1992)., 6. Stikov, N. et al. *NIMG* **54** 1112-1121 (2011).