Optimised Gradient Waveform Spin-Echo sequence for Diffusion Weighted MR in a Microstructure Phantom

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Introduction: There has been increasing interest in using diffusion MRI for probing tissue microstructure [1-4]. A microstructure parameter of particular interest is axon radius distribution in white matter regions of the brain, as this parameter has an abnormal distribution in a number of pathologies, such as amyotrophic lateral sclerosis (ALS) [5, 6] and schizophrenia [7, 8]. Traditionally, Pulsed Gradient Spin Echo (PGSE) sequences are used for diffusion weighting. However, reliable estimates of small axon radii (<5 µm) require high gradient amplitudes and short diffusion times, even using highly optimised parameters [9], which limit the suitability of PGSE sequences for microstructure estimates in a clinical setting. Previous studies have suggested greater sensitivity to axon radius estimates by replacing the trapezoid diffusion weighting gradients in PGSE sequences with sinusoidal [4] and chirp waveform [10]. A recent *in silico* study [11] compared protocols that used optimised general diffusion gradient (GEN) with trapezoid (PGSE) waveforms, showing that GEN provides improved axon radii estimates, particularly for radii <5 µm. In this study, we implement the optimised gradient waveform spin-echo sequence on a Varian pre-clinical system. A typical waveform can be found in figure 1. This sequence is used with water-filled microcapillary phantoms of various radii. Our findings show that there is a good agreement between the simulated signal and the measured signal which is a strong indication that these protocols can be practically implemented, thus potentially providing extra sensitivity to pore sizes <5µm.

Methods: **Optimisation**: The optimization framework was as described in ref [11]. The tissue model consisted of parallel fibres of a single radius filled with water at 18°C, with diffusivity of 1.93×10^{-6} m^2s^{-1}[12]. The pulse sequence used was a PGSE spin echo sequence except that the trapezoid gradients are replaced with the optimised gradient waveforms before the refocusing pulse; this waveform was played out in reverse after the refocusing pulse (i.e. gradients are symmetric about the refocusing pulse: see Figure 1). The 90° excitation and 180° refocusing pulses were slice selective and could be positioned independently. TE was set to 127ms and the duration of the waveforms was determined by maximising the time available within TE. The rate of change of gradient amplitude was constrained to a maximum of $5000Tm^{-1}s^{-1}$. The GEN waveforms were optimised for fibre radii of 1, 2.5, 5, 7.5 & 10µm for maximum gradient strengths of 40, 80, 200 mTm^{-1} (15 optimisations in total). The number of waveforms per optimized protocol was set to 4, thus producing 60 waveforms in total, each with unique shape. Gradients are applied perpendicular to the length of the fibres. **Simulation**: For each of the 60 waveforms and each fibre radius, we synthesize an expected signal using the matrix method [13]. **NMR**: An optimised gradient waveform spin echo sequence, identical to the sequence in the simulation, was implemented on a 9.4T Varian, Inc. pre-clinical system equipped with gradient capable of $1Tm^{-1}$ with a rise time of 200µs. A 26mm diameter Rapid Biomedical, GmBH r.f. coil was used. The microstructure phantoms consisted of silica microcapillary fibres with pore radius of 1±0.5, 2.5±1, 5±1, 7.5±1, 10±1 µm and outer diameter of 150±6 µm (Polymicro Technologies LLC). The fibres were cut to 4cm lengths, soaked in water for a minimum of two weeks, the outer surfaces were then dried, the fibres were packed in 10mm NMR tubes, and the NMR tubes were filled with Perflourosolv™ PFS-1 (Solvay Solexis, Inc.). Imaging parameters are as follows: TR = 3s, TE = 127ms, 10mm slice, 2 averages, 64 repetitions. Gradient waveforms were identical to those generated by the optimisation. Protocols optimised for all radii were used for each phantom: in total 300 measurements were taken, with 64 repetitions per measurement. The sample temperature was maintained at 18.0±0.5°C.

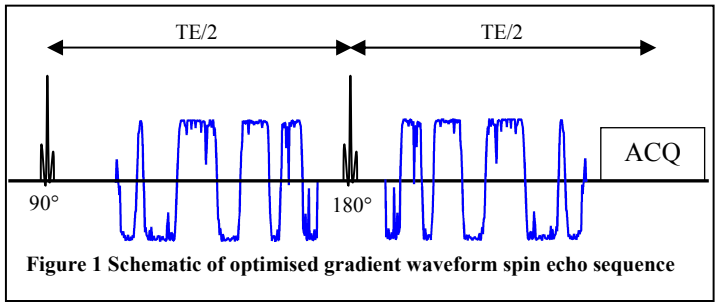

Figure 1 Schematic of optimised gradient waveform spin echo sequence

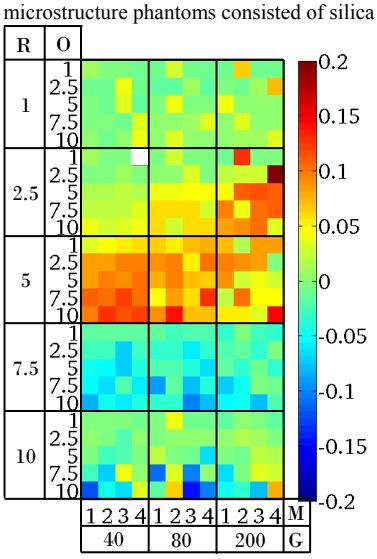

Figure 3 Normalised measured signal subtracted from normalised simulated signal: colour indicates this difference, ranging from -0.2 (blue) to 0.2 (red). One measurement is excluded due to incomplete execution of pulse sequence (white). R is the radius, in µm, of the fibres in the phantoms; O is the radius, in µm, for which the protocol is optimised for; M is the measurement number; G is the maximum gradient strength, in mTm^{-1}.

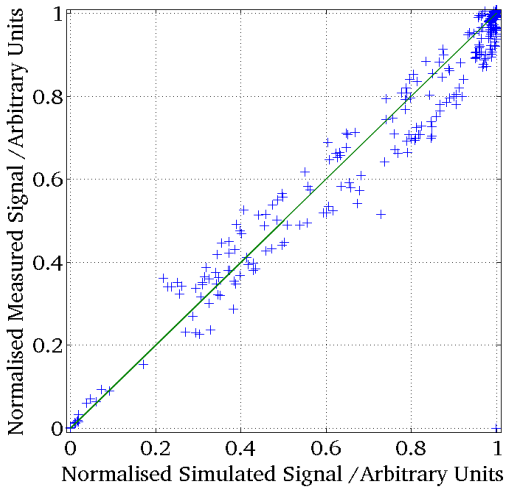

Figure 2 Simulated signal vs. measured signal for protocols that used GEN waveforms for phantoms of various radii and protocols optimised for various radii. Errorbars not shown for clarity

Results: Figure 2, a scatter plot of normalised simulated signal against normalised measured signal, shows that there is a good agreement between the measured and the simulated signal over all measurements. The difference between simulated and measured signal is shown in figure 3. The differences in the signals appear to be grouped by the radius of the fibres in the phantom; suggesting variation away from the quoted nominal pore radius. Further results (not shown) suggest that the simulated signal, for the range of radii within the quoted variation in pore radius, lies within one standard deviation of the measured signal.

Conclusions: We have shown that there is a good agreement between simulated and measured signal for protocols that are optimised for pore radii ranging from 1 to 10µm. This indicates that the diverse shape of gradient waveforms (for example, oscillating trapezoids, slow ramps, and waveforms that appear to be modulated by significant amounts of noise) can be practically implemented on a pre-clinical MRI scanner. Potentially, this good agreement between simulated and measured signal from the GEN optimised protocols could be closely reflected *in vitro* and *in vivo* scenarios, providing improved sensitivity to pore sizes of under 5µm (such as axon radius distributions) over the conventional PGSE optimised protocols that use waveforms consisting of single trapezoids.

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