Frequency tuned bipolar oscillating gradients for mapping diffusion kurtosis dispersion in the human brain

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Abstract

**Purpose:** To introduce frequency tuned bipolar (FTB) gradients as a variation of oscillating gradients to measure frequency dependent differences in kurtosis.

**Methods:** An FTB oscillating gradient waveform is presented that provides encoding of 1.5 net oscillation periods to reduce the echo time of the acquisition. Monte Carlo optimization was performed to determine an optimal protocol based on simulated SNR of kurtosis dispersion maps - defined as the difference in apparent kurtosis between pulsed gradient and oscillating gradient acquisitions. Healthy human subjects were scanned at 7T using traditional pulsed gradient and an optimized 23 Hz FTB oscillating gradient protocol, which featured a b-value of 2500 \( s/mm^2 \). Test and re-test acquisitions were also acquired in each subject to validate optimization results and demonstrate repeatability.

**Results:** The optimized FTB gradient protocol demonstrated consistent reductions in apparent kurtosis values and increased diffusivity in generated dispersion maps from all subjects. Optimization results suggest SNR of kurtosis dispersion maps increases with diffusion weighting which was also apparent in subject data acquired at varied b-value.

**Conclusions:** This work demonstrates the feasibility of generating in vivo kurtosis dispersion maps in humans using oscillating gradients on modern clinical gradient systems.
1 Introduction

Diffusion MRI is traditionally performed using the well characterized pulsed gradient spin-echo (PGSE) sequence. While PGSE sequences enable efficient diffusion weighting, due to hardware constraints the range of accessible diffusion times remains limited to greater than $\sim 25$ ms. Complimentary to PGSE, oscillating diffusion gradients initially proposed by Stepišnik [1, 2], are utilized in oscillating gradient spin-echo (OGSE) sequences. While the effective diffusion time is not well defined for oscillating gradients, it is generally accepted that shorter effective diffusion times can be achieved with increasing oscillation frequency $\omega$ when compared to PGSE [3-5]. Consequently, OGSE has constituted a powerful tool in the investigation of time-dependent diffusion through monitoring of the ADC. As $\omega$ is increased, tracked water molecules diffuse shorter lengths and thereby have a reduced capacity to probe the surrounding environment; hence, the apparent diffusion coefficient (ADC) approaches the free diffusion limit. Deviations from this intrinsic limit, manifested as reductions in the ADC, can be instructive in providing information about physiological structures influencing diffusion such as cell membranes, cell density or extracellular components. Applications on this front include the probing of cell dimensions [6-11], surface-to-volume ratios [12, 13] and additional microstructural characteristics such as packing [14, 15], pore sizes [14] and extracellular space [16]. Recently, OGSE sequences utilized by Arbabi et al. [17] have also been used to investigate structural disorder in the human brain, confirming the predicted short-range disorder model [18] by demonstrating the square-root dependence of the ADC on oscillation frequency.

It should be noted that most ADC investigations and diffusion tensor imaging (DTI) protocols fundamentally rely on Gaussian diffusion approximations [19]. However, local inhomogeneity of the tissue microenvironment results in deviations from Gaussian diffusion. Such deviations are quantified by extending the DTI treatment to estimate the directionally dependent diffusion kurtosis tensor, formally introduced in diffusion kurtosis imaging (DKI) [20, 21]. Similar to the ADC, it has been proposed that the diffusion kurtosis is also a time-dependent quantity, approaching zero with vanishing effective diffusion
times \cite{22}. Studies by Lee et al. \cite{23} have used PGSE to explore time-dependent kurtosis in human gray matter in the context of exchange, while small animal studies \cite{24,25,26,27} in addition to ex vivo studies \cite{28,29} have benefited from advanced hardware to observe time-dependent kurtosis more thoroughly. Notably, Aggarwal et al. \cite{25} used both PGSE and OGSE methods to characterize the time-dependence of diffusion kurtosis in mice while Wu et al. \cite{24} demonstrated the use of OGSE kurtosis imaging of healthy and injured mouse brains. Moreover, both studies highlight the utility of comparing kurtosis measurements between PGSE and OGSE in the form of difference maps, indicating their sensitivity to demyelination \cite{25} as well as hypoxic-ischemic injury \cite{24}.

Despite this however, at the time of writing only a single recent preliminary work by Yang et al. \cite{30} has explored the in vivo kurtosis in the human brain using oscillating gradients. The technical challenges associated with translation to clinical imaging systems have severely limited kurtosis measurements in humans using OGSE. In particular, limitations of gradient systems (both slew rate and gradient amplitude) restrict the range of frequencies and b-values available for protocol design. The recent advent of high-performance gradient hardware (as used by Yang et al.) has expanded this parameter space and made kurtosis measurements more feasible. Such gradient insert coils significantly outperform modern clinical gradient systems, routinely realizing max amplitudes of 200 mT/m and slew rates in excess of 500 T/m/s \cite{32,33,34} permitting both rapid slewing and increased gradient amplitudes to be achieved across a wider range of frequencies \cite{34}. Unfortunately, such hardware is not widely accessible and thus there remains a need to accommodate kurtosis measurements with OGSE to clinically relevant systems to further explore its utility for investigating restricted diffusion.

In this work we demonstrate the first frequency-dependent kurtosis measurements in humans using OGSE with a modern clinical gradient system. Our measurements, in conjunction with PGSE acquisitions, enable the generation of maps demonstrating the frequency dispersion of both the ADC and the diffusion kurtosis. This protocol is enabled by a novel frequency tuned bipolar (FTB) oscillating gradient waveform that reduces the TE of the diffusion acquisition while retaining the intrinsically high b-values required for
kurtosis imaging. In the sections that follow we present our waveform design, the optimization and validation of our acquisition protocol and preliminary results for diffusion kurtosis dispersion in healthy human subjects.

2 Methods

2.1 Gradient Waveform Design

Conventional OGSE is typically performed with trapezoidal cosine modulated waveforms (Figure 1B) to maximize the achievable b-value [35]. However, recently proposed by Hennel et al. [36], the conventional cosine sequence can be modified by optimizing ramp times and reducing the spacing between the two diffusion gradients to the minimum allowable, thereby effectively consolidating the two diffusion gradients into a single waveform. These changes were shown to produce more selective power spectra and increased diffusion weighting capabilities [36]. The framework presented by Hennel et al. enables the implementation of a non-integer number of periods introducing the $N = n + 1/2$ convention where $N$ constitutes the total number of periods and $n$ is an integer greater than 1.

Our proposed FTB waveform achieves shorter diffusion weighting durations by utilizing only $N = 1.5$ net oscillation periods over both sides of the refocusing RF pulse via two bipolar gradient waveforms that are tuned to achieve the desired net frequency. This approach functions as a variation of OGSE that reduces the duration of the diffusion gradients and thereby significantly reduces the TE of the acquisition. A comparison between this new FTB implementation and typical $N = 2$ cosine modulated OGSE is presented in Figure 1, where similar spectral selectivity is demonstrated between the two methods.

The waveform is constructed by initially determining the duration of the second lobe ($T$) using the expression:

$$T = \frac{1}{2} \left( \frac{1}{f} - \tau_{\text{RF}} - 2\tau \right) \quad (1)$$

where $\tau_{\text{RF}}$ is the separation required for the refocusing pulse, $\tau$ is the gradient rise time.
and \( f \) is the target frequency in Hz. This equation stems from an assumption that the central lobe of the three lobe k-space waveform will dominate the net frequency content of the diffusion weighting (see middle column of Figure 1). Constraining the integral of the zeroth moment to be zero to eliminate any DC spectral components, the duration of the first lobe \( (L) \) can then be calculated as:

\[
L = \frac{1}{2} \left( -2T - \tau_{RF} - 7\tau + \sqrt{8T^2 + 8T\tau_{RF} + \tau_{RF}^2 + 32T\tau + 14\tau_{RF}\tau + 33\tau^2} \right) \quad (2)
\]

This equation can also be further generalized to include additional periods, which we note then resembles the method presented by Hennel et al. [36] with the added condition of encoding only non-zero spectral components. However, the finite truncation of the gradient waveform - more prominent for our abbreviated FTB rendition, imposes a frequency limit based on the minimum permitted separation time \( \tau_{RF} \). In general this is not problematic for low frequencies when the period of the waveform is much larger than the separation time. However, when the period of the waveform approaches or exceeds the minimum separation time, the fidelity of the spectral components can become compromised as the gap between the gradients interrupts the periodicity. This can result in deviations from the target frequency in addition to significant spectral broadening. A useful empirical relationship for this limit proposed here is that this method is viable for frequencies that obey the relation \( T > \tau_{RF} \) such that the period of the waveform is greater than the separation time between gradients. For a separation time of \( 7 \) ms – the minimum permitted on our system, this limit is found to be \( \sim 50 \) Hz.

### 2.2 Monte Carlo Optimization

The signal when kurtosis is introduced by the fourth order cumulant expansion can be written as [20][22]:

\[
S(b) = S_0 e^{-bD+\frac{b^2D^2K}{6}e^{-\frac{TE}{T_2}}} \quad (3)
\]

where \( b \) is the b-value, \( D \) the apparent diffusion coefficient, \( K \) the kurtosis, \( T_2 \) the spin-spin relaxation time and \( TE \) the echo time. Monte Carlo simulations were used to
optimize the SNR of the difference in kurtosis between PGSE and OGSE acquisitions ($\Delta K$); we define this quantity as:

$$\Delta K = K_{OGSE} - K_{PGSE} = K(\omega) - K(0)$$  \hspace{1cm} (4)$$

The signal curve for both PGSE and OGSE acquisitions was generated using equation 3 at three different b-values of 0, a maximum b-value that was varied and a third intermediate b-value that was equal to half of the maximum. In order to maintain feasibility for clinical systems, the maximum frequency was limited to 45 Hz. Gaussian noise was added to the calculated PGSE and OGSE signals upon which the magnitude of the noisy signals were then fitted to equation 3 with a non-negative least squares algorithm to recover ADC and kurtosis values. These values were then used to calculate $\Delta K$ according to equation 4. This procedure was repeated for 2000 iterations per each frequency/b-value combination. Subsequently the SNR of $\Delta K$ was estimated as the mean of this set of values divided by the standard deviation. The b-values for OGSE and PGSE encoding were simulated for a gradient system with slew rate of 180 T/m/s and max gradient amplitude of 75 mT/m. To avoid the effects of higher order terms in the kurtosis signal expansion our simulations were limited to a maximum b-value of 2500 $s/mm^2$. The TE was chosen to be the minimum allowable for each frequency; accordingly the TE dependence is implicitly reflected through the varied frequency.

Accurate simulation of the diffusion signal required a priori knowledge of the frequency dependence of the diffusivity $D(\omega)$ and kurtosis $K(\omega)$ to capture the time-dependence of both quantities. The model of the diffusion dispersion presented by Arbabi et al. \cite{17} was used to infer $D(\omega)$ such that a unique diffusivity was assigned to each frequency. A similar relationship for $K(\omega)$ was also required, however no such characterization has yet been performed for the diffusion kurtosis. Rather, the multi-frequency measurements of mean kurtosis (MK) presented by Yang et al. \cite{30} were fitted to a power law model. This model, reported here as $K(\omega) = 0.93 - 0.0016\omega^{(0.78)}$ provided an empirical relationship between frequency and MK enabling simulation of the frequency dependent kurtosis.
The simulation was performed for FTB in addition to alternate OGSE encoding schemes including nominal N = 2 (Figure 1B) and N = 2.5 OGSE to observe the effects of adding additional periods. In addition to $\Delta K$ the SNR of $\Delta ADC$ (defined similarly as $\Delta ADC = ADC_{OGSE} - ADC_{PGSE}$), was also evaluated in a manner identical to $\Delta K$.

2.3 In Vivo Protocol

Five healthy participants (3 male, 2 female, mean age 26±4 years) were scanned on a head-only 7 Tesla MRI scanner (Siemens Magnetom 7T Plus, Erlangen Germany). The scanner was equipped with a gradient system capable of a maximum gradient amplitude and slew rate of 80 mT/m and 400 T/m/s respectively, however to maintain clinical feasibility, the maximum gradient amplitude was limited to 75 mT/m and slew rate to 125 T/m/s. Approval for this study was granted by the Institutional Review Board at Western University; written informed consent was obtained from each participant prior to scanning.

The in vivo protocol consisted of an optimal (as determined from Section 2.2) and sub-optimal scan each conducted twice in a test and re-test fashion: subjects were scanned to acquire the test data and were subsequently removed from the scanner, repositioned and returned after a short period to obtain the re-test acquisitions. Diffusion weighted images (DWIs) were acquired with two diffusion weighting schemes each with three shells using b-values of 0, 1250 and 2500 $s/mm^2$ and 0, 1000, 2000 $s/mm^2$ constituting the optimal and sub-optimal scans respectively. Images were acquired at each shell using both PGSE ($f = 0 \text{ Hz}$) and 23 Hz frequency tuned bipolar OGSE encoding (see Figure 1A). PGSE and OGSE acquisitions were integrated into one scan such that all acquisitions required for $\Delta K$ map generation could be performed in a single scan. In addition to human subjects, a multi ADC diffusion phantom (CaliberMRI, Boulder Colorado, USA) was also imaged with the optimized in vivo protocol to validate dispersion measurements (see Figure S1).

Diffusion weighting was applied along 4-directions in a tetrahedral scheme to enable maximum achievable b-values [37]. The remaining acquisition details of both the optimal and sub-optimal scans were identical and were as follows: TE/TR = 91/6500 ms, FOV
= 200 × 200 mm², matrix size = 100 x 100, 2174 Hz/Px bandwidth, 38 slices, 2 mm isotropic resolution, 8 averages. Images were acquired with 6/8 partial Fourier phase encoding using a single shot EPI readout. The acquisition time per scan was 14 minutes for a total scanning time of 56 minutes not inclusive of the break between test/re-test sessions.

2.4 Image Analysis

Eddy current characterization was performed independently using a field-monitoring system (Skope MRT, Zurich Switzerland). Acquired k-space trajectories and higher-order field perturbations (up to third order) were utilized to correct for eddy current distortions through integration in an offline model-based image reconstruction algorithm. Principal component analysis based denoising [38] was also applied to the complex data during reconstruction. Following reconstruction, all diffusion-weighted images were processed with Gibbs ringing removal (MRtrix3) upon which FSL’s BET tool [39] was used to perform brain extraction and mask generation. Re-test images were registered to test images by applying rigid affine transforms generated from b = 0 s/mm² images from each acquisition; registration was performed using ANTs software [40].

DWIs from each shell were directionally averaged and fitted on a voxel wise basis to the natural logarithm of equation 3 with a non-negative least squares algorithm to extract ADC and kurtosis parameters; we note the use of a non-negative least squares fitting algorithm eliminates the potential for implausible negative kurtosis values. From the fitted data, mean ADC and apparent kurtosis maps were generated for the PGSE and OGSE acquisitions separately. We note the apparent kurtosis - as used here, is formally distinct from the mean kurtosis, the latter being derived from the diffusion kurtosis tensor.

Dispersion maps of the ADC (ΔADC) and kurtosis (ΔK) were generated for each subject as the difference between PGSE and OGSE acquisitions; as previously defined: ΔK = K_{OGSE} - K_{PGSE} and ΔADC = ADC_{OGSE} - ADC_{PGSE}. 
2.5 Re-test Analysis

$\Delta K$ maps generated from registered re-test DWIs were compared to test $\Delta K$ maps through a Bland-Altman analysis \[41\] for both the optimal ($b = 2500 \text{ s/mm}^2$) and sub-optimal ($b = 2000 \text{ s/mm}^2$) protocols. A minimum kurtosis threshold of 0.9 was applied to isolate white matter voxels upon which volumes from each subject were combined and were used to generate Bland-Altman plots of $\Delta K$ measurements. Coefficients of variation (CoVs) and standard deviations were calculated for both the optimal and sub-optimal scans to infer relative differences in SNR.

3 Results

3.1 Optimization Results

Optimization results in Figure 2 indicate the optimal frequency of 23 Hz was most influenced by differences in maximum b-value between frequencies. The optimal protocol to acquire $\Delta K$ maps was found to consist of 23 Hz FTB OGSE with a b-value of 2500 $\text{s/mm}^2$ and a corresponding TE of 91 ms. The proposed FTB waveform (Figure 1A) achieves higher SNR for both $\Delta K$ as well as $\Delta ADC$ maps compared to traditional $N \geq 2$ OGSE encoding as seen in Figure 2B. We note the distinction in scaling in Figure 2B, with $\Delta ADC$ maps having approximately 4 times higher SNR than $\Delta K$.

3.2 In Vivo Results

A trend of decreasing kurtosis and increasing ADC is observed when comparing OGSE to PGSE images as seen in Figure 3. In frontal white matter ROIs (see Figure 3C) mean differences between OGSE and PGSE of approximately 10% and 14% are observed across subjects in apparent kurtosis and ADC values respectively. These differences constitute the contrast of the dispersion maps generated from PGSE and OGSE shown in Figure 3E and 3F. Comparable image quality is observed across all subjects in both $\Delta K$ and $\Delta ADC$ maps as seen in Figure 4. Consistent measurements of $\Delta K$ were also
observed across participants in the genu, splenium and body of the corpus callosum and are presented in Figure 5B. No statistically significant differences were observed between the regions.

The effect of applied diffusion weighting on $\Delta K$ is exhibited in Figure 6, showing $\Delta K$ maps generated from both the optimal and sub-optimal protocols. A noticeable qualitative difference is observed when comparing the optimal and sub-optimal scans, with the lower b-value protocol exhibiting reduced SNR.

Bland-Altman plots comparing the test and re-test $\Delta K$ measurements across all WM volumes from each subject are shown in Figure 7. Mean CoVs from $\Delta K$ maps across all subjects are reported as 0.60 and 0.69 for the optimal ($b = 2500 \text{s/mm}^2$) and sub-optimal ($b = 2000 \text{s/mm}^2$) scans respectively. The lower variation in the $b = 2500 \text{s/mm}^2$ images suggests a higher SNR of $\Delta K$ which is also qualitatively observed in Figure 6 and consistent with the optimization results of Figure 2A. Moreover, mean CoVs for $\Delta ADC$ maps were considerably lower and calculated to be 0.50 and 0.54 for the optimal and sub-optimal protocols respectively, demonstrating increased SNR relative to $\Delta K$. This is supported by observations from Figure 2B that suggest an increased SNR of $\Delta ADC$ maps when compared to $\Delta K$. The trends observed in the coefficients of variation were mirrored in the standard deviations, which are also shown on the Bland-Altman plots in Figure 7.

4 Discussion

4.1 Waveform Remarks

This article demonstrates the first measurements of kurtosis in the human brain using oscillating gradients on a conventional gradient system. The work was facilitated by the introduction of a frequency tuned bipolar OGSE gradient waveform that significantly reduces the TE of the acquisition. By reducing the minimum number of oscillation periods to 1.5, significant gains in SNR were realized through the reduction of the echo time. Optimization results confirm this configuration to be ideal for measurements of
\(\Delta K\) and \(\Delta ADC\) providing higher SNR for both compared to OGSE performed with additional periods (see Figure 2B). This result agrees with previous findings from Arbabi et al. [17] that suggest a waveform with less than 2 periods would provide higher SNR than conventional \(N \geq 2\) OGSE for \(\Delta ADC\) maps. Moreover, this reduction in echo time may also prove useful in future investigations by facilitating the implementation of lower oscillation frequencies without excessive signal loss previously incurred due to extensive TEs. This may find particular applications in future studies exploring PGSE and OGSE sensitivities with comparable diffusion times.

Despite these advantages, the shorter duration of the FTB waveform further limits the range of possible b-values and as such our method is likely best suited for lower oscillation frequencies \((f < 40 \text{ Hz})\) where the reduction in b-value due to oscillation is negated by the longer period of the waveform. This effect further justifies the use of the tetrahedral direction scheme, which critically enables the maximum gradient amplitude to be exploited in each direction simultaneously thereby maximizing the applied diffusion weighting [37]. While the tetrahedral scheme also prevents the use of DKI derived metrics associated with the diffusion kurtosis tensor and may introduce rotational variance [42], the directionally averaged kurtosis has been shown to be a useful and accurate reflection of MK derived from tensor fitting [43].

In addition, the method presented here inherently includes first-moment nulling to eliminate any spectral component at 0 Hz. While this change also provides flow-compensation to avoid perfusion effects, it may also be vital when performing \(\Delta K\) or \(\Delta ADC\) map generation using PGSE and OGSE acquisitions. Spectral overlap between the two acquisitions may result in signal loss when a difference is taken and hence eliminating overlapping components mitigates this potential issue.

### 4.2 In Vivo Findings

Generated \(\Delta ADC\) maps exhibit comparable diffusion dispersion to previously reported studies. Using the model from Arbabi et al. [17] and the oscillation frequency of 23 Hz, the mean diffusion dispersion rate (across all subjects) can be estimated to be 10
This is consistent with mean rate of 11 $\mu m^2/s^{1/2}$ reported by Arbabi et al. [17] in addition to the rate of $\sim 10$ $\mu m^2/s^{1/2}$ inferred from Baron and Beaulieu’s data [5,17].

In contrast to $\Delta ADC$ maps, $\Delta K$ maps demonstrate consistent differences between white (WM) and gray matter (GM) regions across all subjects as seen in Figure 4B. The larger negative $\Delta K$ in WM suggests that, somewhat surprisingly, 23 Hz is a sufficiently high frequency to be in a regime where diffusion becomes increasingly Gaussian and kurtosis begins to vanish, similar to findings at short diffusion times in the ex vivo spinal cord and mouse brain [25,28]. Expectedly however, our frequency is not high enough to observe significant changes between regions of the corpus callosum where microstructural differences are more subtle. While the proximity to the ventricles may make measurements in the corpus callosum more susceptible to cerebrospinal fluid partial volume effects [44], given the high diffusion weighting cerebrospinal fluid is not anticipated to contribute to these results. Moreover, lack of trends in the $\Delta K$ of the corpus callosum suggests higher frequencies may be required to observe finer structural changes even in dominant WM tracts [45]. Conversely, at even lower frequencies (i.e., longer diffusion times), it is expected that the trend of kurtosis with frequency will reverse due to the effects of permeability, contributing to predicted [25,46] and observed [25,27,29] non-monotonic behavior. Notably, this transition frequency may be larger here compared to previous ex vivo samples due to axon shrinkage that is known to occur with sample fixation. Given that the diffusion times accessible through OGSE are shorter than typical exchange times derived from the Kärger model, our measurements lie in the short diffusion time regime where exchange and permeability effects that act to reduce the apparent kurtosis likely do not have a significant role in these results [23,47]. Moreover, for this reason a monotonic model is likely appropriate to describe $K(\omega)$ in the context of OGSE measurements.

As observed in Figure 6 even relatively small decreases in b-value (20%) for the same frequency have noticeable impact on the SNR of produced $\Delta K$ maps. This effect is consistent with previous studies focusing on the optimization of kurtosis measurements [48,49] and suggests the optimal $\Delta K$ protocol will favor increasingly larger diffusion weighting. That said, future protocol designs should be attentive to the validity of equation 3 for $b \geq $
3000 \( s/mm^2 \) beyond which higher order effects begin to emerge. Such limitations may be avoided by recalling the relation proposed by Jensen et al. \cite{22}, indicating that equation 3 remains valid so long as the condition \( b < \frac{3}{2K_D} \) is satisfied. These effects were assumed to be conservatively avoided in this study by limiting the b-value of the acquisitions to 2500 \( s/mm^2 \). However, the general increase in \( \Delta K \) values for the sub-optimal (lower b-value) acquisition observed in Figure 6 may suggest some higher order effects are still present in our optimized protocol due to the increased b-value.

4.3 Applications

Observations of the frequency/time dependence of the kurtosis may constitute a novel biomarker, enabling further insight into physiological conditions influencing the degrees of diffusion restriction and heterogeneity - similar to the utility of \( \Delta ADC \) \cite{17, 50, 52}. Aggarwal et al. \cite{25} observed significantly reduced \( \Delta MK \) in regions of local demyelination due to increased permeability while Wu et al. \cite{24} noted increases in \( \Delta MK \) corresponding to regions of severe edema in a mouse model of hypoxic ischemic injury demonstrating the sensitivity of the frequency dependent kurtosis to various pathologies. Wu et al. \cite{24} also noted significantly larger differences in kurtosis relative to differences in ADC between PGSE and OGSE, suggesting \( \Delta K \) may be an equally prominent indicator of pathology.

Since our method does not require rapid slewing or extremely large gradient amplitudes our protocol can be easily adapted to full body scanners without exceeding the specifications of modern clinical gradient systems. However despite this, the method presented here is still likely ill-suited to fully characterize the relationship between kurtosis and frequency, \( K(\omega) \). The range of frequencies remains limited by the b-values required for observing kurtosis while the tetrahedral scheme prohibits the calculation of the diffusion kurtosis tensor. Consequently, a multi-frequency investigation would benefit from the performance presented by recent advancements in gradient hardware \cite{31, 83}. As a result, our optimized protocol does not aim to replace high-performance gradient measurements but rather to compliment them, providing an efficient method to make frequency dependent kurtosis measurements more efficient and accessible on a wider variety
of systems.

The primary limitation of this study however, remains the low SNR of the generated $\Delta K$ maps. Since the results of Figure 7 demonstrate large single-voxel CoVs for both the optimal and sub-optimal protocols, the use of ROI-based analysis for investigations of diffusion kurtosis dispersion is recommended. Moreover, while our study avoids the use of high-performance gradients, it does benefit from the additional SNR that arises due to imaging at ultra-high field (7T). Equivalent measurements conducted at 3T would require more than twice as many averages thereby further elongating the scan time. However, our technique will benefit from recent and on-going advancements in the field including non-cartesian readouts such as single-shot spirals [53] or 3D multi-slab acquisitions [54] to provide increased SNR. Future work may also include the in-depth anatomical characterization of $\Delta K$ in addition to multi-frequency investigations of the time dependent kurtosis in the short diffusion-time regime that is accessible with oscillating gradients.

5 Conclusion

In this work we present a method for the generation of differential kurtosis maps on the basis of the kurtosis dispersion probed using a more efficient design for frequency-selective diffusion weighting. This frequency tuned bipolar gradient waveform demonstrates highest SNR for both $\Delta K$ and $\Delta ADC$ maps when compared to traditional OGSE encodings. Our findings demonstrate the feasibility of frequency dependent kurtosis measurements on modern clinical gradient systems. Moreover, our optimized protocol constitutes a viable method for exploring the increasingly compelling evidence from rodent studies suggesting the role of the frequency dependent kurtosis as a multi-purpose biomarker.

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6 Figures

Figure 1: Frequency tuned bipolar (FTB) \(N = 1.5\) OGSE waveform (A), conventional \(N = 2\) cosine OGSE (B) and PGSE (C) waveforms. Corresponding power spectra are shown in (G-I) demonstrating comparable spectral selectivity between FTB and \(N = 2\) OGSE for the same target frequency. Also shown is the zeroth moment of each waveform (D-F). Uninterrupted periodicity of the zeroth moment is apparent in the FTB waveform (D) compared to \(N = 2\) (E) due to the reduction of the gradient separation time.
Figure 2: SNR of $\Delta K$ for varying b-value and frequency combinations using frequency tuned bipolar (FTB) OGSE (A) and comparisons of maximum possible SNR for FTB ($N = 1.5$), $N = 2$ and $N = 2.5$ OGSE for both $\Delta K$ and $\Delta ADC$ maps (B). The masked region in the upper right of (A) denotes experimentally prohibited parameters combinations.

Figure 3: Generated ADC maps (A,B) and apparent kurtosis maps (C,D) from a healthy subject using both PGSE (A,C) and OGSE (B,D). An increase of ADC in parenchyma is observed in OGSE relative to PGSE while a reduction is demonstrated in apparent kurtosis maps. Also shown in (C) is an example region of interest used to calculate mean WM differences between OGSE and PGSE. Difference maps of the ADC, $\Delta ADC$ (E) and kurtosis, $\Delta K$ (F) are also shown, demonstrating positive dispersion of the ADC and negative dispersion of the kurtosis.
Figure 4: Generated $\Delta ADC$ (top) and $\Delta K$ (bottom) maps from each subject. Comparable image quality is observed across participants though some $B_0$ inhomogeneity induced distortions are apparent.
Figure 5: Sagittal slices of kurtosis dispersion maps showing the corpus callosum of each subject (B) and magnitude of negative $\Delta K$ values from different regions of the corpus callosum averaged across all subjects (B); error bars indicate the standard deviation. There is no statistically significant difference between regions. Also shown (as the rectangular inset in (A)) are typical regions of interest used for region specific measurements.

Figure 6: Comparison of optimal ($b = 2500 \text{ s/mm}^2$, top row) and sub-optimal ($b = 2000 \text{ s/mm}^2$, bottom row) $\Delta K$ maps from the same subject. A qualitative increase in noise is apparent in the sub-optimal scans supporting the optimization results of Figure 2A.
Figure 7: Bland Altman plots comparing test and re-test acquisitions for the $b = 2000$ (left column) and $b = 2500$ $s/mm^2$ scans (right column) across all volumes from each subject; rows correspond to different subjects, columns correspond to the sub-optimal and optimal protocols. Also shown are the coefficients of variation (CoV) and standard deviations (Std). The dashed lines on each plot denote ±1.96 standard deviations and the solid black line denotes the mean difference between the test and retest measurements.
Figure S1: Mean ADC and kurtosis measurements obtained in a multi-ADC diffusion phantom (CaliberMRI, Boulder Colorado, USA) with both PGSE and frequency tuned bipolar OGSE (23 Hz) using a protocol identical to the in vivo scans. Equivalent ADC measurements are observed between OGSE and PGSE acquisitions (a) while zero kurtosis is also demonstrated for both acquisitions (b). Here error bars denote the standard deviation of the ROIs.