**METHOD**

1. Theory

In MRI, the excitation is achieved by tipping the magnetised spins initially aligned with the main magnetic field (longitudinal direction) towards the transverse plane with a flip angle (α) from the longitudinal direction and a phase shift (φ) in the transverse plane using a radiofrequency pulse. After the excitation, the spin’s magnetisation relaxes towards the longitudinal direction with the recovery of the longitudinal component (with the time constant T1) and decay of the transverse component, and the transverse magnetisation is measured for MR image formation. The time between excitation and acquisition of the signal is known as echo time (TE), and the time between adjacent excitations is repetition time (TR). The MRI signal acquisition is performed in Fourier space (known as k-space), and the resulting image will be obtained by performing an inverse Fourier transform of the k-space. [Method2]

图示

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* Multi-echo GRE

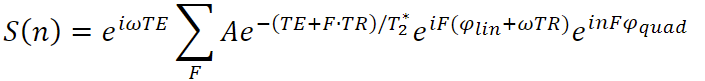
Using a gradient echo (GRE) based pulse sequence, the acquired MR signal decay with the time constant T2\* [Method1]. The gold-standard T2\* measuring method – multi-echo GRE is performed by simply measuring the MR signal at multiple TEs in one TR with GE sequence and fitting monoexponential decay to get the T2\* voxel by voxel as shown in Figure X.

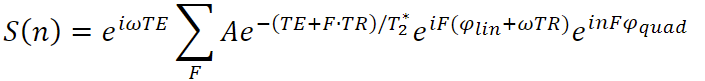
* N-periodic ka-SPGR

The N-periodic ka-SPGR sequence is based on fast GRE (short TR) [Method4] with TE = TR/2, which yields a steady-state signal behaviour. Additionally, quadratic radiofrequency-spoiling (RF-spoiling) and gradient-spoiling are required to perform the N-periodic ka-SPGR sequence. RF-spoiling is applied by constantly exciting the spins with a quadratic phase cycling given by the function [Method4] [Intro10],

  (for n = 0,1,2….) (1)

By adding RF-spoiling, N different and periodically repeating steady-state signals S(n) are yielded, each signal is the summation of quadratic phase modulation weighted T2\* decayed signal at the time (TE+F\*TR), the analytical solution of S(n) is below [Intro10],

 (2)

The T2\* related component, , in the equation is known as the configuration state or F-state and is denoted as F0 if F in the equation equals 0. Furthermore, gradient spoiling is added to shift and split the F-states away from the centre of the k-space by different amounts, as shown in Figure X.

The k-space of each F-state can be reconstructed by summing up N-acquired signals with reverse phase modulation followed by shifting the k-space back to the centre. An inverse Fourier transform is then performed to generate the F-states images, which is used to fit T2\*. An illustration of the procedure is shown in Figure X.

1. Model Simulation and analysis

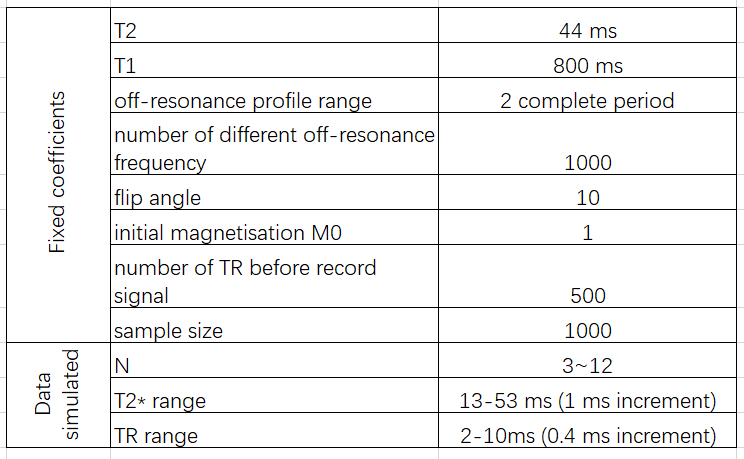
Based on the understanding of the N-periodic ka-SPGR sequence, a Python-based simulation is built to analyse its T2\* mapping performance when different TR and periods are used.

* 1. Simulation setup

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* + 1. Bloch simulation



Based on the well know Bloch equation [Method2], the performance of the spin with certain tissue properties (T1, T2) under different applied pulse sequences (α, φ, TR, TE) can be modelled. As the project focused on SN region T2\* mapping, SN’s T1 (800ms) and T2 (44ms) are used in the computer simulation model, suggested by previous research on SN [Method7] [Intro5]. A 10°optimal flip angle calculated from the Ernst equation is used [Method3], and RF-spoiling is applied by implementing phase shift based on equation (1). Additionally, to ensure the steady state is fully reached, 500 times excitation is performed before the acquisition of the signal.

An off-resonance profile is then generated, which models the performance of spins under external disturbances by simulating spins with different extra phase shifts, and the Fourier transform of the off-resonance profile is equal to the configuration F-states [Method8].

* + 1. Magnetic field inhomogeneity modelling

A Lorentzian distribution is convolved with the off-resonance profile to model the field inhomogeneity effect caused by iron overload in the tissue [Method10]. With known T2\* and T2 (tissue-only dependent), the amount of field inhomogeneous used to build the Lorentzian distribution can be calculated by the relationship below [Method1],

 (3).

An equivalent operation supported by Fourier transform property is used in the simulation, which is multiplying the F-states signal by the Fourier transform of Lorentzian - an exponential curve with the time constant 1/T2’ = 1/γΔBinhomo.

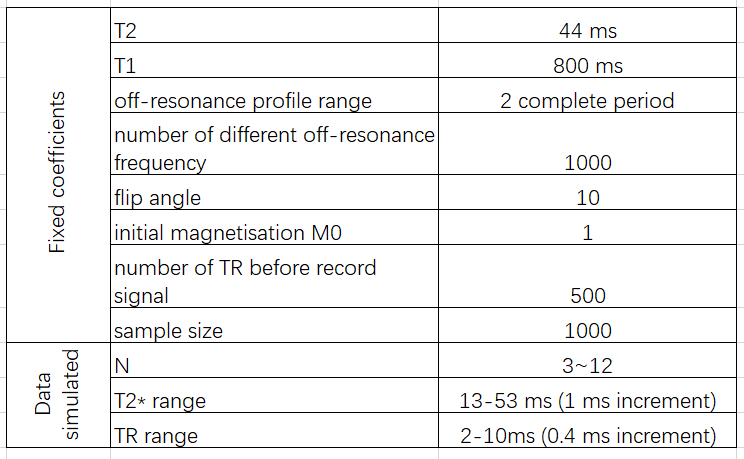
* + 1. Noise Modelling

Noise is introduced while acquiring the signal using an MRI scanner [Method9]. For ka-SPGR with different periods and TR, the acquisition noise is modelled using complex zero-mean Gaussian with s.d. = F0/sqr(N)\*5%, where the F0 is the F-state magnitude simulated for T2\* = 33ms (mean of the range of interest). And the generated Gaussian noise is added to the simulated F-states signals from 2.1.2.

* 1. Data Simulation

The model is simulated for a range of ground truth T2\* specific for PD detection, which is SN T2\* of PD patients (13ms) and healthy people (53ms). A range of ka-SPGR coefficient is also selected due to the following reason, a period less than 3 does not provide enough data points for fitting the exponential curve, and a TR smaller than 2ms is not achievable by a scanner, also, a period greater than 12 or TR greater than 10ms both resulting in a long acquisition time. Therefore, only the performance of spins with T2\* (13-53ms), when applying 3 to 12 periodic ka-SPGR sequences with different TRs in the range from 2ms to 10ms, are simulated.

To analyse the T2\* measurement performance of the ka-SPGR, Monte Carlo experiments are performed. The modelled noise is randomly generated and applied 1000 times on each F-states simulated with the period, TR and T2\* values within the range in Table X. By fitting each noise-added F-states, 1000 measured T2\* can be obtained for each ground truth T2\* value for different periodic ka-SPGR with different TR.



* 1. Simulation result analysis

The analysis is performed by comparing measured T2\* and ground truth T2\*.

* + 1. Bias

Because the x-coordinate of points used for exponential fit is TE+F\*TR, F = 0…(N-1), by using different periods and TRs, a different part and range of the exponential curve is sampled, which will affect the efficiency of exponential fit. Theoretically, there should be an ideal TR for different periodic ka-SPGR sequences which have the smallest bias T2\* measurement.

The percentage bias is calculated using the equation Mean (T2\* measured)-T2\* GT/T2\* GT \*100%, for different periods and TR at each ground-truth T2\*. Averaged T2\* percentage error in the PD biomarker range will then be calculated for each periodic ka-SPGR pulse sequence for different TR. By plotting the averaged percentage error against TR for each periodic ka-SPGR, the optimal TR and Period can be found and will be used in the MRI phantom scan test.

* + 1. Standard deviation

The standard deviation of the measured T2\* is also calculated to visualise the precision of the T2\* measurement, and to specifically check the measurement variation and verify the reliability of the method when using the optimised parameters. A plot of T2\* measured against T2\* ground truth is plotted for the data simulated using optimised parameters, with the error bar plotted for each ground truth T2\*.

1. MRI data acquisition and analysis

MRI scan using ka-SPGR sequence with optimised scan parameter is performed on a phantom. The quantitative T2\* values are calculated and compared with the ground truth T2\* value obtained using the gold-standard multi-echo GRE method. A comparison between the ka-SPGR and the gold-standard method with controlled variables is also carried out.

* 1. MRI scan setup
     1. Phantom

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(LHS: picture of NIST/ISMRM Premium System Phantom Model (SN:130-102), RHS: MnCl2-containing spheres layer being scanned)

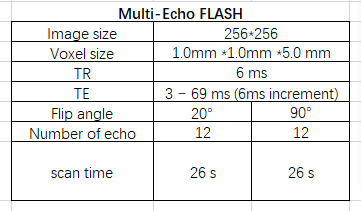
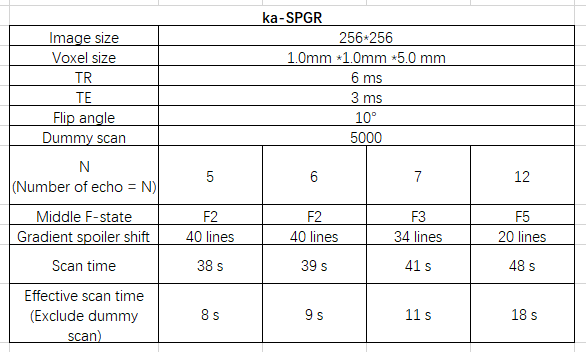
NIST/ISMRM Premium System Phantom Model (SN:130-102) is used as the scanning object, and a slice acquisition is performed at the MnCl2-containing spheres layer (Figure X). Multi-echo FLASH (Siemens, 3T), one commonly used multi-echo GRE sequence, is used as the gold standard T2\* mapping method to obtain the ground truth T2\* value for each phantom sphere.

* + 1. Scan parameters

7 and 12-periodic ka-SPGR sequences with TR = 6ms and 10° flip angle are used for scanning, which is the optimised result from the computer simulation. The middle F-state and amount of gradient spoiler shift are carefully selected (Table X) to make sure the required N F-states are within the k-space acquisition range.

For a fair comparison, the choice of the multi-echo FLASH parameters aims at matching with ka-SPGR.

In order to minimise the influence of the exponential fitting algorithm, the number and position of points used to fit the exponential curve should be the consist for the two methods. Therefore, to perform the match as shown in Figure X, the multi-echo FLASH TEs start with ka-SPGR’s TE and following by an increment equal to ka-SPGR’s TR as shown in Table X. And the number is kept consist by using first N echo of multi-echo FLASH to fit exponential fit when compare with N-periodic ka-SPGR. A 20° flip angle is used to match with ka-SPG aiming at comparing 2 method efficiency, and a 90° flip angle is used to obtain an accurate T2\* ground truth value. Also, the image size and voxel size are matched for all scanning performed.

* 1. Image processing
     1. Raw data to DICOM

The F-states images of ka-SPGR are reconstructed from raw data as described in 1.2 using MATLAB (Code provided by Pete) and exported as DICOM files for further processing in Python. For consistency, the images obtained by multi-echo FLASH are also reconstructed from raw data using MATLAB (Code provided by Pete), instead of directly using the default DICOM file from the scanner.

* + 1. T2\* mapping

As the region we are interested in is only the fiducial spheres of the phantom, a mask is generated for the phantom as shown in Figure X, to only perform T2\* mapping for the pixels inside each sphere. Exponential fitting using decay time-related images (multi-echo FLASH), or F-states (ka-SPGR) is performed as shown in Figure X to obtain T2\* values for each pixel. As we are only interested in T2\* range around 13ms to 53ms, the phantom spheres with T2\* largely outside this range are excluded for further analysis.

* + - T2\* mapping images generated for both gold-standard and ka-SPGR to compare the result images. Colour coding the T2\* value for each sphere on top of a greyscale average image of multiple acquisition MRI data.

* 1. Result analysis
     1. Percentage error

This analysis is based on comparing 7 and 12-periodic ka-SPGR T2\* results with the ground truth T2\* obtained using 90° flip angle multi-echo FLASH. Percentage error is calculated for each voxel, and a dot plot of percentage error in different spheres (different T2\*) is used to visualise the distribution and variation of T2\* measurement percentage errors. Therefore, analyse the 7 and 12-periodic ka-SPGR sequences PD biomarker measurement accuracy.

* + 1. Effective T2\* Signal-to-Noise ratio

This analysis is based on comparing 7 and 12-periodic ka-SPGR T2\* results with the T2\* measured using 20° flip angle multi-echo FLASH, to keep the environment maximally align. Effective T2\* SNR is calculated for each sphere for both ka-SPGR and multi-echo FLASH using the equation,

The ka-SPGR and multi-echo FLASH sequences’ effective T2\* SNR at different T2\* will be compared using a bar plot. The efficiency of two method is compared while maintain

Method Reference:

1. Principles, techniques, and applications of T2\*-based MR imaging and its special
2. Principle of MR imaging (that book)
3. Principles of nuclear magnetic resonance in one and two dimensions (check for Ernst angle)
4. Steady state effects in fast gradient echo magnetic resonance imaging
5. Steady state of echo-shifted sequences with radiofrequency phase cycling
6. A motion-robust, short-TR alternative to multi-echo SPGR (Intro10)
7. MRI characteristics of the substantia nigra in Parkinson's disease: A combined quantitative T1 and DTI study
8. Extended phase graphs: Dephasing, RF pulses, and echoes - Pure and simple
9. The rician distribution of noisy mri data
10. Theory of NMR signal behavior in magnetically inhomogeneous tissues: The static dephasing

**RESULT**

1. Model Simulation
   1. Averaged percentage bias

图示

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Each plot shows the variation of the averaged T2\* percentage bias with different TR used in different periodic ka-SPGR sequences. The optimal point is around XXX for XX period, however, due to the limitation of the MRI scanner used for this project, the minimum TR able to achieve is 6ms, therefore, 7-periodic and 12-periodic ka-SPGR with TR = 6ms is chosen based on the simulation.

* 1. Standard deviation of the optimal coefficient

The T2\* measured against the ground truth plot for the optimised coefficient is shown in the figure, and it clearly indicates the measured T2\* aligns quite well with the ground truth and the variation of measurement is acceptable. The increase in standard deviation when measuring a larger T2\* value is because the exponential fit is more sensitive to sampling in a specific region. With larger T2\*, the sampling is not at the sensitive region of the slower exponential decay curve, so it is less tolerant to noise.

* + 1. Standard deviation contour plots

图表, 折线图

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* + 1. Average standard deviation for different TR and Period

1. MRI data acquisition and analysis
   1. Quantitative T2\* mapping image

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* 1. Performance analysis
     1. Percentage error

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* + 1. Effective T2\* Signal-to-Noise ratio

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