Flip angle optimisation using an in-vivo T1 distribution-weighted approach based on the Cramer-Rao lower bound theory for accurate T1 quantification

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Introduction: Spoiled gradient echo (SPGR) images acquired using different flip angles can be used to estimate the spin-lattice relaxation rate ($R_1 = 1/T_1$) by fitting data to the SPGR signal equation: $S_{SPGR} = S_0 \cdot \frac{\sin\alpha\left(1-e^{-TR.R_1}\right)}{1-e^{-TR.R_1}\cos\alpha} = S_0 \cdot f(\alpha, R_1)$ where α and TR are flip angle and repetition time respectively and S_0 is a constant including the proton density, machine-dependent gain factor and the echo term. Optimisation of flip angles when imaging samples with a large R_1 range of values has been far from trivial and little work has been published on this subject [1, 2]. During the optimisation, it is important that the actual distribution of R_1 values in the image sample is taken into account. We propose a novel flip angle optimisation approach, based on the Cramer-Rao lower bound (CRLB) theory, which is weighted by the probability distribution of the R_1 range of interest.

Theory: The CRLB states that the variance of a parameter of an unbiased estimator is equal to or greater than the iith element of the inverse of the Fisher information matrix: $\sigma^2(\theta_i) \le (F^{-1})_{ii}$. θ_1 and θ_2, in our case, are S_0 and R_1 respectively. The bound on the variance of R_1 is given by the following expression:

$$\sigma^2_{R_1,R_1} \ge (F^{-1})_{22} = \frac{\sigma_G^2}{S_0^2} \frac{\sum f(\alpha,R_1)^2}{\sum f(\alpha,R_1)^2 \cdot \sum f'(\alpha,R_1)^2 - (\sum f(\alpha,R_1).\sum f'(\alpha,R_1))^2} = V_{R_1}$$

where S_0/σ_G is the signal-to-noise ratio. We will use V_{R1} as a surrogate of σ^2_{R1} in the optimisation procedure. The estimation errors are typically proportional to R_1, so the optimality criterion is based on a relative measure, V_{R1}/R_1^2. In order to account for a range of R_1, the overall optimality criterion (OC) is the integral of the relative variance over the range of interest, weighted by the R_1 probability distribution (i.e. the expectation). The integral is calculated for different flip angle combinations and the combination that corresponds to the minimum integral is defined to be the optimum. Only flip angles between 1° to 90° are considered in the optimisation. In the case of two different flip angles, there is a single minimum in this cost function within the constraints imposed. When there are more than two different flip angles, however, there are multiple minima. It is therefore necessary to ensure the global minimum is found.

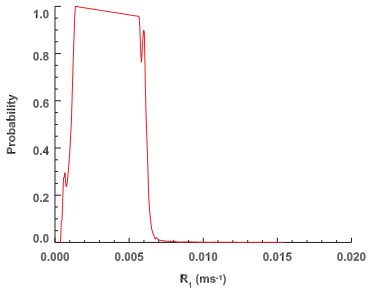

Figure 1: Probability distribution of R_1 used in the optimisation. Pre-contrast R_1 distribution was extracted on a pixel-by-pixel basis from whole liver ROIs in 20 patient datasets.

Materials and Methods: Our application of interest is dynamic contrast enhanced (DCE-) MR imaging in the liver. As the paramagnetic contrast agent passes through the organ, R_1 changes linearly with contrast agent concentration. The distribution of pre-contrast R_1 values were extracted on a pixel-by-pixel basis from regions-of-interest drawn around the whole liver in 20 clinical DCE-MR pre-contrast R_1 maps of patients with liver metastases. Maximum-contrast R_1 values were calculated by assuming the peak organ concentration to be 1mM. To obtain the R_1 distribution for the optimisation algorithm, the initial and maximum-contrast R_1 distributions were combined and the peaks of the two distributions were connected. A minimum of two different flip angles are required to quantify R_1. Different numbers of measurements (N = 2 – 10) were analysed in order to investigate whether it is more desirable to have many different flip angles or to have more repetitions of the same flip angles. For every N, the optimal flip angle combinations were calculated using a simplex algorithm for different TR values (3, 4, 5 and 6 ms) and S_0 and σ_G of 2000 and 10 respectively.

Results: The final R_1 distribution used in the optimisation is shown in figure 1 with R_1 ranging from 0.0003 to 0.015 ms^{-1} (equivalent to T_1 = 65 – 3000 ms). The optimal flip angle combinations for different N and TR are summarised in the table. The number in brackets, preceded by x, represents the number of repetitions of the flip angle measurement. OC corresponding to every optimal flip angle combinations in the table are plotted in figure 2 for varying TR and N.

	TR (ms)			
N	**3**	**4**	**5**	**6**
2	2.6 (x1), 16.1 (x1)	3.0 (x1), 18.5(x1)	3.4 (x1), 20.7 (x1)	3.7 (x1), 22.6 (x1)
3	2.0 (x1), 3.0 (x1), 15.1 (x1)	2.3 (x1), 3.5 (x1), 17.5 (x1)	2.6 (x1), 3.9 (x1), 19.5 (x1)	2.8 (x1), 4.2 (x1), 21.3 (x1)
4	2.5 (x1), 2.8 (x1), 16.1 (x2)	2.9 (x1), 3.2 (x1), 18.5 (x2)	3.2 (x1), 3.6 (x1), 20.7 (x2)	3.5 (x1), 3.9 (x1), 22.6 (x2)
5	2.2 (x2), 3.5 (x1), 15.8 (x2)	2.5 (x2), 4.0 (x1), 18.2 (x2)	2.8 (x2), 4.6 (x1), 20.3 (x2)	3.1 (x2), 5.0 (x1), 22.2 (x2)
6	2.4 (x2), 3.1 (x1), 16.2 (x2)	2.8 (x2), 3.6 (x1), 18.7 (x3)	3.1 (x2), 4.0 (x1), 20.8 (x3)	3.4 (x2), 4.4 (x1), 22.8 (x3)
7	2.3 (x3), 3.9 (x1), 16.1 (x3)	2.7 (x3), 4.5 (x1), 18.5 (x3)	3.0 (x3), 5.1 (x1), 20.6 (x3)	3.3 (x3), 5.5 (x1), 22.6 (x3)
8	2.4 (x3), 3.4 (x1), 16.3 (x4)	2.8 (x3), 4.0 (x1), 18.8 (x4)	3.2 (x3), 4.4 (x1), 20.9 (x4)	3.5 (x3), 4.9 (x1), 22.9 (x4)
9	2.4 (x4), 4.2 (x1), 16.2 (x4)	2.7 (x4), 4.9 (x1), 18.7 (x4)	3.1 (x4), 5.4 (x1), 20.8 (x4)	3.3 (x4), 6.0 (x1), 22.8 (x4)
10	2.5 (x4), 3.7 (x1), 16.4 (x5)	2.8 (x4), 4.3 (x1), 18.8 (x5)	3.2 (x4), 4.8 (x1), 21.0 (x5)	3.5 (x4), 5.2 (x1), 23.0 (x5)

Discussion: For a given number of measurements (N), the optimal flip angles increase with TR. Simple calculations using the SPGR signal equation show that a consistent signal is maintained by this parallel increase in the two parameters. It is seen that a maximum of three different flip angles are required to quantify the particular R_1 distribution of interest, with greater emphasis on the two outer flip angles; the numbers of repetition on these flip angles increase incrementally with N, whilst the repetitions of the middle flip angles remain at 1. For odd numbers of N, all three optimal flip angles increase with N. For even numbers of N greater than 2, the two larger optimal flip angles increase with N whilst the lowest optimal flip angles remain largely unchanged. Having greater repetitions (i.e. NSA) of the largest flip angle measurement is impractical in DCE-MR studies since these flip angle data are used in the rapid dynamic data acquisition and increasing the NSA will worsen the temporal resolution. Future optimisation work needs to investigate the case where the repetition of the largest flip angle measurement is fixed at 1. Plots in figure 2 show that the OCs corresponding to the optimal flip angle combinations tend to decrease with increasing number of measurements and with increasing TR.

Conclusion: This work has shown that optimal flip angles for R_1 quantification can be derived using a R_1 distribution-weighted optimisation approach based on the CRLB theory. This optimisation approach is an objective method which takes into account the actual distribution of R_1 in the imaging sample. The variable flip angle method allows accurate and efficient R_1 quantification which is important in many fields of MR. An effective flip angle optimisation approach, therefore, is essential and much needed.

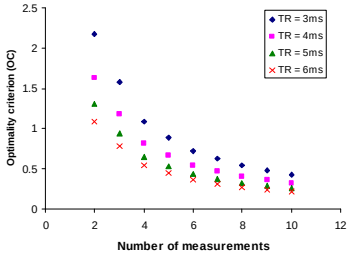

Figure 2: Variation of optimality criterion corresponding to optimal flip angles for varying TR and N

References: [1] Deoni SC, *et al.* Magn Reson Med (2004), [2] Cheng H-LM, *et al.* Magn Reson Med (2006)

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