Optimization of the MR acquisition parameters for quantitative measurement of brain iron in Alzheimer's disease

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Introduction: Alzheimer's disease (AD) is estimated to affect approximately 22 million people globally and accounts for more than 60% of all dementia cases [1]. AD is typically identified after the onset of neuropathological symptoms. Biomarkers whose manifestation precedes the symptoms can enable preemptive intervention. Neuroscience research points towards the role of iron in the pathogenesis of AD, and accurate quantification of brain iron would be useful in early diagnosis [2, 3] . Iron accumulation alters the MR characteristics of the brain tissue which is assessed through the quantitative measurement of surrogate biomarkers such as T_2, T_2^* and T_1 [4, 5]. The purpose of this work is to optimize the MR acquisition parameters for quantitative measurement of brain T_2 values through the use of Cramér-Rao bound (CRB) analysis [6]. CRB theory allows the determination of the smallest possible variance on the parameter estimates from any unbiased estimator [6, 7]. The noise performance (minimum standard-deviation on T_2 estimates) at different acquisition parameters was analyzed at different signal-to-noise ratios (SNR) and at different T_2 values to determine the optimal echo-times for measuring brain iron.

Theory and Methods: The signal model, $s(t)$, considered for the CRB analysis is shown in Equation 1, where M is the bulk magnetization vector, T_2 is the transverse relaxation time and η is additive noise. The analysis shown in the reminder of this work is independent of magnet field strength and is applicable for both spin-echo and gradient-echo imaging, with the replacememt of T_2 with T_2^* for gradient-echo. The distribution of noise in an MR magnitude image is Rician (square root of sum-of-squares of the Gaussian noise on the real and imaginary channels) in nature. However, for a SNR greater than 10, Rician noise can be approximated to have a Gaussian distribution. In this work noise performance was analyzed for SNR greater than 10; hence, for the CRB computations a Gaussian noise model was assumed.

$$s(t) = M\exp(-t/T_2) + \eta \quad [1]; \quad \mathbf{S} = \mathbf{A\Gamma} + \boldsymbol{\eta} \quad [2]; \quad \mathbf{S} = [s(TE_1) \quad s(TE_2)]^T \quad [3]; \quad \mathbf{\Gamma} = [M \quad M)]^T \quad [4]; \quad \boldsymbol{\eta} = [\eta_1 \quad \eta_2)]^T \quad [5];$$

$$\mathbf{A} = \begin{bmatrix} e^{-TE_1/T_2} & 0 \\ 0 & e^{-TE_2/T_2} \end{bmatrix} \quad [6]; \quad \mathbf{FIM}_{11} = \frac{1}{\sigma^2}[\mathbf{A}^T\mathbf{A}]_{11} \quad [7]; \quad \mathbf{FIM}_{12} = \mathbf{FIM}_{21} = \frac{1}{\sigma^2}[\mathbf{A}^T\frac{\partial \mathbf{A}}{\partial T_2}\mathbf{\Gamma}]_1 \quad [8]; \quad \mathbf{FIM}_{22} = \frac{1}{\sigma^2}\mathbf{\Gamma}^T\frac{\partial \mathbf{A}^T}{\partial T_2}\frac{\partial \mathbf{A}}{\partial T_2}\mathbf{\Gamma} \quad [9];$$

Equations 2-6 show the matrix representation of signal model for two measurements at first-echo time (TE_1) and second echo-time (TE_2). The equations for the four elements (indexed 11, 12, 21, 22) of the Fisher information matrix (**FIM**) used for CRB computations are shown in Equations 7-9. The Cramér-Rao lower bound (CRLB) of T_2 was obtained by calculating the inverse of **FIM**. The CRLB for T_2 was computed with varying inputs of TE_1, TE_2, SNR and T_2 values. In this work, SNR of X means an M value of X and noise with unity standard-deviation (SD) on the signal acquired at the first and second echoes.

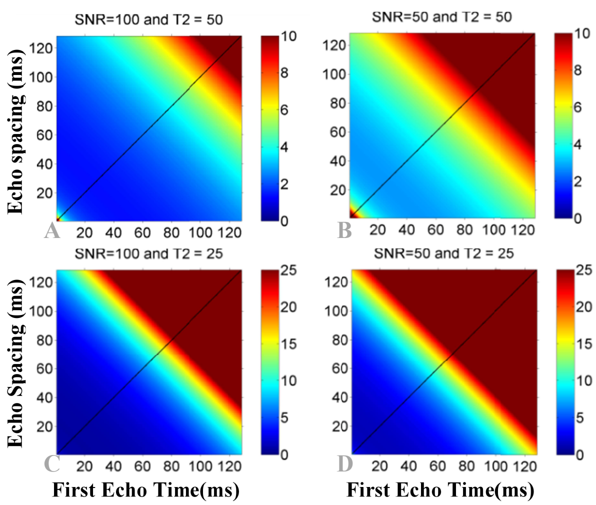

Figure 1*: Cramér-Rao lower bounds (ms) for T_2 estimation, computed at different first echo-times (TE_1) and echo-spacing (ΔTE): (A) SNR=100, T_2= 50; (B) SNR = 50, T_2= 50; (C) SNR = 100, T_2= 25; (D) SNR = 50, T_2= 25. Line of Symmetry (black solid) shows that the second echo-time (TE_2) is the determining factor for noise performance in the estimation of brain iron.*

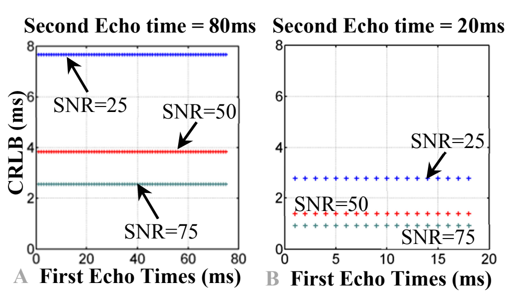

Figure 2*: CRLB for T_2 estimation computed at different TE_1 with the TE_2 of (A) 80ms and (B) 20ms for T_2 of 25ms at three different SNR. Results show that change in TE_1 does not change the standard-deviation in the estimation of T_2.*

Results and Conclusions: Figure 1 shows the CRLB in the estimation of T_2 for different TE_1 and echo-spacing ($\Delta TE = TE_2 - TE_1$) conducted at four different combinations of SNR and the T_2 values. The line of symmetry is shown as a dark line on the images. For a typical TE_1 and TE_2 of 18ms and 80ms used in earlier works [4] there would be a minimum SD of 3.85ms in the estimation of T_2 of 25ms at a SNR of 50. Symmetry of the CRB values around the line with $\Delta TE = TE_1$ on images A-D of Figure 1, and plots shown in Figure 2 demonstrate that TE_2 is the determining factor for the noise performance in the estimation of T_2. The CRLB is independent of the variation of the TE_1 values except for the limiting cases (ΔTE needs to be finite positive value). Computations were conducted over different sets of values for SNR and T_2 other than shown in Figure 2, and the pattern of results were similar to those in Figure 2. Figure 3 shows the CRLB computed at different TE_2 values, choosing $TE_1 = TE_2/2$, over a range of T_2. These results show that the TE_2 which provides optimal noise performance differs with changing T_2 values. However, there exists a line of optimality around which the optimal TE_2 values are clustered. Hence, the TE_2 needs to be chosen according the brain region for which optimal noise performance is desired. For example, for regions such as hippocampus with T_2 values between 55 to 65ms at 3T [4], a TE_2 of 25 to 30ms would be optimal.

References: [1] Prince M et al, World Alzheimer Report 2011, Alzheimer's Diesease International. [2] Leskovjan AC et al, *NeuroImage*, 2011, 55(1): 32-38. [3] Zhu W et al, *Radiology*, 2009, 253(3): 497-504. [4] Schenck JF et al, *Top MRI*, 2006;17(1):41-50. [5] Schenck JF et al, *NMR in Biomed.* 2004; 17(7): 433-445. [6] Cavassila S et al. *NMR in Biomed.* 2001; 14(7): 278-283. [7] Pineda AR et al, *MRM*, 2005; 54(3): 625-635.

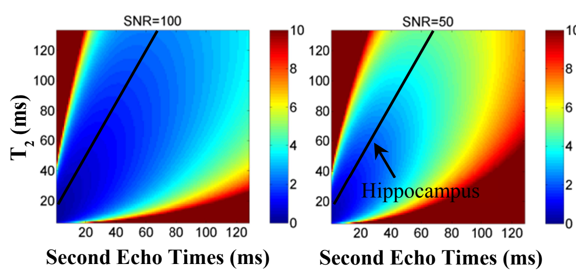

Figure 3*: CRLB (ms) for T_2 estimation computed at different TE_2 and T_2 at SNR=100 and SNR=50. The dark line shows the relation between T_2 and the corresponding TE_2 that provides the optimal noise performance.*