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**Introduction** The water proton resonance frequency (PRF) based MR thermometry has been successfully used to map the temperature changes during thermal treatments. From a signal processing point of view, the temperature estimation with the PRF method intrinsically is a frequency difference estimation of damped complex exponential signal. By exploiting this characteristic, a spectrum model based temperature mapping with extended Prony algorithm was proposed recently to improve the accuracy of temperature estimation (1). To evaluate the noise performance of the algorithms used in frequency difference estimation, Cramér-Rao Lower Bound (CRLB) is examined since it provides the minimum variance of the unbiased estimator independent of the frequency estimation algorithm. The CRLB can be used to choose estimation algorithms and the imaging parameters such as number of echoes and echo times.

**Method** To derive the CRLB expression, we first model the received signal of multi-echo GRE sequence as  $s(t_n) = \sum \rho_i e^{i\theta_i} e^{(-i|T_{i_n}^++j2\pi f_i)t_n} + w(n), 0 \le n \le N-1$ , where  $\rho_i, \phi_i, T_{2,i}^*$  and  $f_i$  are the magnitude, phase,  $T_2^*$  and the chemical shift(Hz) of the species, respectively; w(n) is complex Gaussian white noise whose real and imaginary parts are independent identically distributed with zero mean and variance  $\sigma^2$ ;  $t_n$  is the echo time and N the number of echoes. For simplicity, we only consider a system containing two species, water and fat, which is reasonable in most cases of temperature mapping. Given the joint probability density function (pdf) as Eq.1, the elements of Fisher Information Matrix (FIM) can be expressed by Eq.2 The lower bound of the

variance of frequency difference(chemical shift) estimator between water and fat is then derived in Eq.3. By investigating Eq.3, we can expect that the lower bound depends on the imaging SNR, number of echoes, echo times, fat/water ratio and temperature. To evaluate the performance of different algorithms, Monte Carlo simulation experiment (5000 independent trials) was conducted. During the simulation experiment, the magnitude of fat and water is 1, the phase and  $T_2^{-}$  are all set to 0 and number of echoes is 8 with initial TE<sub>0</sub>=0s, echo spacing=1s, the frequencies of fat and water are 0 and 0.1, which are spaced closer than 1/N=0.125, the Fourier The resolution. SNR which is defined as

$$\begin{split} f(\mathbf{s} \mathbf{p}) &= \left(\frac{1}{2\pi\sigma^2}\right)^n \exp\left[-\frac{1}{2\sigma^2}\sum_{s=0}^{n-2} \left(S_s^n - \overline{S}_s^{-1}\right)^2 + \left(S_s^n - \overline{S}_s^{-1}\right)^2\right] & [Eq.1] \\ \text{S sample vector} \\ p: \text{ unknow parameter vector,} \left[-\frac{1}{2\sigma^2}\sum_{s=0}^{n-2} \left(S_s^n - \overline{S}_s^{-1}\right)^2 + \left(S_s^n - \overline{S}_s^{-1}\right)^2\right] & [Eq.1] \\ \text{S sample vector} \\ p: \text{ unknow parameter vector,} \left[-\frac{1}{2\sigma^2}\sum_{s=0}^{n-2} \left(S_s^n - \overline{S}_s^{-1}\right)^2 + \left(S_s^n - \overline{S}_s^{-1}\right)^2\right] & [Eq.1] \\ \text{S sample vector} \\ p: \text{ unknow parameter vector,} \left[-\frac{1}{2\sigma^2}\sum_{s=0}^{n-2} \left(S_s^n - \overline{S}_s^{-1}\right)^2 + \left(S_s^n - \overline{S}_s^{-1}\right)^2\right] & [Eq.1] \\ \text{S sample vector} \\ p: \text{ unknow parameter vector,} \left[-\frac{1}{2\sigma^2}\sum_{s=0}^{n-2} \left(S_s^n - \overline{S}_s^{-1}\right)^2 + \left(S_s^n - \overline{S}_s^{-1}\right)^2\right] & [Eq.1] \\ \text{S sample vector} \\ p: \text{ unknow parameter vector,} \left[-\frac{1}{2\sigma^2}\sum_{s=0}^{n-2} \left(S_s^n - \overline{S}_s^{-1}\right)^2 + \left(S_s^n - \overline{S}_s^{-1}\right)^2\right] & [Eq.1] \\ \text{S sample vector} \\ p: \text{ unknow parameter vector,} \left[-\frac{1}{2\sigma^2}\sum_{s=0}^{n-2} \left(S_s^n - \overline{S}_s^{-1}\right)^2 + \left(S_s^n - \overline{S}_s^{-1}\right)^2\right] & [Eq.1] \\ \text{S sample vector} \\ \text{S sample vector} \\ \text{S sample vector} \\ p: \text{ unknow parameter vector,} \left[-\frac{1}{2\sigma^2}\sum_{s=0}^{n-2} \left(S_s^n - \overline{S}_s^{-1}\right)^2 + \left(S_s^n - \overline{S}_s^{-1}\right)^2\right] & [Eq.2] \\ \text{S sample vector} \\ \text{F sher Information Matrix(FIM):} \\ \text{F sher Information Matrix(FIM):} \\ \text{F sher laft (sp)} = \left[\frac{1}{2}\frac{1}{n}\frac{f(sp)}{2}\frac{\partial \ln f(sp)}{\partial p}\right] = \mathbb{E}\left[\frac{1}{2}\frac{1}{n}\frac{f(sp)}{2}\frac{\partial \ln f(sp)}{\partial p}\right] \\ \text{e the dements of F are:} \\ \text{F sher laft (sp)} = \frac{1}{\sigma^2}\sum_{s=0}^{n-2} \left[\frac{1}{2\sigma^2}\sum_{s=0}^{n-2} \left(\frac{3\sigma_s^n}{2}\right)^2\right] & [Eq.2] \\ \text{variance of temperature estimation is } Var(Temperature) = \frac{Var(f_{\text{statistice}})}{(ap^2, B_0^n)^2}\right] \\ \text{e the dements of F are:} \\ = \left[0, 0, 0, 1, 0, 0, 0, -1\right]; \\ \text{variance of temperature estimation is } Var(Temperature) = \frac{Var(f_{\text{statistice}})}{(ap^2, B_0^n)^2}\right] \\ \text{variance of temperature estimation is } Var(Temperature) = \frac{Var(f_{\text{statistice}})}{(ap^2, B_0^n)^2}\right] \\ \text{variance of temperature estimation is } Var(Temperature) = \frac{Var(f_{\text{statistice}})}{(ap^2, B_0^n)^2} \\$$

 $SNR = 10\log_{10} \frac{1}{\sigma^2} dB$  varies from 0dB to 40dB. Two algorithms are compared, one is the extended Prony algorithm, and the other is Maximum Likelihood (ML) estimation performed by trust region Levenberg-Marquardt (LM) algorithm which is widely used in the nonlinear least-squares problem.

**Results** / Discussion The Mean Square Error (MSE) results of Monte Carlo simulation with the two algorithms are shown in Fig.1, along with the CRLB. At relatively high SNR (>7dB), the ML estimator achieves the CRLB while the MSE of Prony algorithm is higher than CRLB, which may probably be attributed to the inappropriate linearization modeling. But the Prony algorithm is acceptable in high SNR cases because of its simple computation. However, when the SNR is lower, the MSE of ML estimator increases and oscillates rapidly due to the LM algorithm occasionally converging to a local rather than global minimum of ML criterion. This phenomenon can be termed as "threshold effects" which generally is a plague in nonlinear estimation. Fig.2a shows the CRLB dependence on the number of echoes. As expected, the more number of echoes are acquired, the lower the CRLB is. Nevertheless, the more number of echoes may sacrifice the temporal resolution which is a critical issue in temperature mapping. Thus there is a trade-off between the number of echoes and the accuracy of temperature estimation increases rapidly, which is the major problem that using fat as internal reference encounters (2). Then our model is reduced to only one damped exponential signal. Incorporating the baseline subtraction method or referenceless method (3), our model with the Prony or LM algorithm can handle this case to improve the accuracy of temperature estimation. However, in the opposite extreme case when fat dominates the signal, all the methods based on PRF method fail, including our method. Other MR parameters sensitive to temperature should be utilized to measure temperature, such as T1 (4). The CRLB dependence on echo times can also be examined. Interestingly, the choice of TE which is equivalent to  $T_2^*$  in the conventional PRF method with one echo (5) is a special derived result from the CRLB.

**Conclusion** In this work, the expression for CRLB for PRF temperature mapping is derived. With the CRLB, the noise performance of two algorithms to estimate the temperature, Prony algorithm and LM algorithm based on ML criterion, is evaluated and compared; By carefully examining the CRLB dependence on the imaging SNR, number of echoes, echo times, fat/water ratio, the choice of imaging parameters is discussed. In sum, the CRLB analysis theoretically provides insight into how the imaging parameters and estimation algorithm affect the noise performance in temperature mapping.

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Fig.1 Comparison of the estimation algorithms

Fig.2 CRLB dependence on (a) number of echoes, (b) fat/water ratio