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# On the $R_2^*$ relaxometry in complex multi-peak multi-Echo chemical shift-based water-fat quantification: Applications to the neuromuscular diseases

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ABSTRACT

*Purpose:* Investigation of the feasibility of the $R_2^*$ mapping techniques by using latest theoretical models corrected for confounding factors and optimized for signal to noise ratio.
*Theory and methods:* The improvement of the performance of *state of the art* magnetic resonance imaging (MRI) relaxometry algorithms is challenging because of a non-negligible bias and still unresolved numerical instabilities. Here, $R_2^*$ mapping reconstructions, including complex fitting with multi-spectral fat-correction by using single-decay and double-decay formulation, are deeply studied in order to investigate and identify optimal configuration parameters and minimize the occurrence of numerical artifacts. The effects of echo number, echo spacing, and fat/water relaxation model type are evaluated through both simulated and in-vivo data. We also explore the stability and feasibility of the fat/water relaxation model by analyzing the impact of high percentage of fat infiltrations and local transverse relaxation differences among biological species.
*Results:* The main limits of the MRI relaxometry are the presence of bias and the occurrence of artifacts, which significantly affect its accuracy. Chemical-shift complex $R_2^*$-correct single-decay reconstructions exhibit a large bias in presence of a significant difference in the relaxation rates of fat and water and with fat concentration larger than 30%. We find that for fat-dominated tissues or in patients affected by extensive iron deposition, MRI reconstructions accounting for multi-exponential relaxation time provide accurate $R_2^*$ measurements and are less prone to numerical artifacts.
*Conclusions:* Complex fitting and fat-correction with multi-exponential decay formulation outperforms the conventional single-decay approximation in various diagnostic scenarios. Although it still lacks of numerical stability, which requires model enhancement and support from spectroscopy, it offers promising perspectives for the development of relaxometry as a reliable tool to improve tissue characterization and monitoring of neuromuscular disorders.



## 1. Introduction

Potentially, relaxometry [1] offers multiple applications in MRI. Above all, fat/water quantification is considered a promising tool in modern healthcare and the premier non-invasive method for measuring both the amount and the distribution of lipids in biological tissues. Particularly in the last decade, MRI demonstrated its importance as a cost effective solution for diagnosis and monitoring of nonalcoholic fatty liver disease (NAFLD) [2–5], neuromuscular disorders (NMD) [6] (such as Duchenne Muscular Dystrophy (DMD) [7] and Pompe pathology [8]). To this end, it is well acknowledged that for a correct evaluation of the fat/water percentage it is necessary to take into account the right intrinsic relaxation properties $R_2^*$. As known, $R_2^*$ relaxation includes effects induced by spin–spin relaxation ($R_2$) and by $B_0$ inhomogeneities ($R_2'$), so that $R_2^* = R_2 + R_2'$. Nowadays, transverse relaxation times can be computed in many ways, such as via fast spin-echo (FSE), multiple spin-echo imaging [9,10], driven-equilibrium single-pulse observation time (DESPOT) [11] or spoiled gradient recalled (SPGR)

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multi-pulse acquisitions. Recent attempts to obtain an $R_2^*$ map considered the use of models which implement voxel-wise [12] or pixel-wise measurements [13]. For a given model, the parameter sensitivity and the reliability in species quantification depend on the repetition time (TR), the slice thickness, the number $N$ of images acquired with different inter-echo spacings (ΔTE), and the macroscopic $B_0$ inhomogeneity [14,15].

Currently, main chemical shift-based approaches can be broadly classified into: magnitude-based [16] and complex-based [4,17]. In the former, phase information is discarded and thus the contribution related to the field map inhomogeneity is not estimated. Therefore, water-fat ambiguity cannot be fully resolved and Fat Fraction (FF) can be uniquely estimated in a 0–50% range [18]. In the latter, the complex-based approach aims to mitigate more confounding effects, preserves the Gaussianity of the noise statistics of MR images [19] and enables measurement of the signal fat-fraction over a theoretical range of 0–100%. To improve the $R_2^*$ measurement in term of robustness, accuracy, precision [16,20,21] and signal-to-noise ratio (SNR) [22], different numerical formulations have been implemented [23,24]. The most sophisticated ones include a complex-based multi-peak fat signal representation [25] with $R_2^*$ correction that is modeled by using a single (1D) [26] or double decay (2D) approximation for the water and the fat species.

It has been recently demonstrated that 1D complex-fitting model [27] can provide results with high noise stability over a wide range of $R_2^*$ values (0÷600 $s^{-1}$) and TE combinations. On the other hand, the accuracy of $R_2^*$ quantification at larger rates [28,29] is currently debated because it is strongly sensitive to the type and timings (ΔTE) of the echo sequence. In addition, relaxometry methods have still notable limitations in obtaining reliable measurements in patients with iron overload in the liver [30,31] and in the myocardium [32–34], because of the significant different decay times of water and fat species. Hence, an optimized set of parameters is required to avoid biased reconstructions.

Latest achievements show the possibility to model separate decay rates for water and fat (2D model) [23,35] in order to improve the accuracy of relaxometry mapping and fat quantification [36]. However, they point out how this approach currently suffers of an increased noise sensitivity. For example, it is well known that, the inclusion of fat in tissues can lead to remarkable alterations in the signal amplitude of images acquired at increasing TE [37–42]. Although most of such infiltration in organs usually does not exceed 50%, this is not true in degenerative muscle diseases, where higher FF values can be reached up to the complete substitution of the muscular tissue with fat and fibrosis [43–46].

To this end, $R_2^*$-corrected fat quantification is particularly important in subjects affected by progressive Neuromuscular Disorders (NMD) for the careful assessment of disease severity at the time of diagnosis and for longitudinal monitoring of their response to therapy [47]. The purpose of this study is to analyze the ability of MRI to obtain robust $R_2^*$ quantification by investigating the use of a complex multi-echo chemical-shift based $R_2^*$ estimation method that contemporarily evaluates independent relaxation rates for biological species.

A comparison between 2D and 1D decay models is presented in order to focus on the following challenges: (*i*) reproducibility of results across different FFs, (*ii*) dependence on imaging parameters and protocols, (*iii*) identification of numerical artifacts, (*iv*) requirements to achieve optimal performance. The approach employed concerns to an attempt to extend investigation on previously reported techniques for 1D $R_2^*$ mapping [27] following a systematic approach [48] where the effects of parameter changes are independently investigated. In details, we evaluate the performance of different complex multi-peak fat-corrected relaxometry models in terms of SNR and bias in order to study the limits of each theoretical formulation, such as the weaknesses in $R_2^*$ mapping associated with increasing fat infiltration and for different relaxation rates. In any case, the unknown parameters (e.g. water and fat signal amplitudes, $B_0$ field inhomogeneity, relaxation rates) are evaluated at the same time via the nonlinear least squares (NLLS) estimation algorithm for simulated and in vivo data. Systematic analyses ranging from the theoretical characterization of different models to simulations and clinically significant examples are presented.

## 2. Methods

### 2.1. Theoretical models

The fat/water quantification from a signal $s_n$ measured on a given voxel at $TE_n$ ($n=1, \ldots, N$) is achieved by considering a theoretical model. The complex formulation of a single $R_2^*$ decay (1D) including $B_0$ field inhomogeneity is given by:

$$s_n(\rho_W, \rho_F, \phi_0, f_B, R_{2C}^*) = \left(\rho_W + \rho_F \sum_{p=1}^{P} \alpha_p e^{i2\pi f_{F,p} TE_n}\right) e^{i(\phi_0 + 2\pi f_B TE_n)} e^{-R_{2C}^* TE_n} + \eta_n \quad (1)$$

where $\rho_W$ and $\rho_F$ are the amplitudes of water and fat signals, respectively, with initial phase $\phi_0$, $f_B$ is the frequency shift due to local magnetic field $B_0$ inhomogeneities, $R_{2C}^* = 1/T_{2C}^*$ is the common decay for both species, while $f_{F,p}$ are the known frequencies for the multiple spectral peaks of the fat signal relative to the water peak and $\alpha_p$ are the relative amplitudes of the fat signal that satisfy the condition $\sum_{p=1}^{P} \alpha_p = 1$. The values of $\alpha_p$ and $f_{F,p}$ can be directly estimated from the data by means of spectrum self-calibration algorithms [2] or well known multipeak spectral configurations [49,50]. It has been recently demonstrated that fat quantification techniques using multipeak fat models [51] provide comparable results. Therefore we will use the method proposed in Ref. [25], with the data reported in Ref. [49] where the relative amplitudes (%) are $\alpha_p$= (4.7, 3.9, 0.6, 12, 70, 8.8) whereas the relative frequencies (expressed in ppm) of fat peaks are (0.6, −0.5, −1.95, −2.6, −3.4, −3.8), respectively. The noise $\eta_n$ can be modeled as a complex white Gaussian distribution. Relaxation rate $R_{2C}^*$ can be estimated from Eq. (1) using NLLS that, according to Ref. [52], provides the maximum-likelihood estimation. Above equation assumes a common decay rate for the water and fat signals, which has been shown to be effective for fat quantification [12,21,27] in previous phantom [53], and clinical studies [4].

Nonetheless, we stress the fact that a 1D $R_2^*$ model is intuitively not appropriate for an accurate estimation of water and fat compound percentages when they exhibit very different decay rates, such as in the presence of a non-negligible iron concentration in muscular tissues [54] or liver [55].

In general, water and fat have different $R_2^*$ decays (and even the multiple fat peaks will have independent decay rates, but this is typically ignored being that it leads to a significant complication of the model [25]). This has led to methods that employ independent $R_2^*$ decay rates [23]. Although multiple $R_2^*$ correction may reduce bias by more accurately modeling the underlying physics, recent studies pointed out the higher numerical instability [25] that requires further investigation. The Eq. (1) can be rewritten for a 2D formulation as follows:

$$s_n(\rho_W, \rho_F, \phi_0, f_B, R_{2W}^*, R_{2F}^*) = \left(\rho_W e^{-R_{2W}^* TE_n} + \rho_F \sum_{p=1}^{P} \alpha_p e^{i2\pi f_{F,p} TE_n} e^{-R_{2F}^* TE_n}\right) e^{i(\phi_0 + 2\pi f_B TE_n)} + \eta_n \quad (2)$$

In this case, independent relaxation rates for water $R_{2W}^*$ and fat $R_{2F}^*$ are considered assuming also the same decay rate $R_{2F}^*$ for all the