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Original contribution

A data-oriented self-calibration and robust chemical-shift encoding by using clusterization (OSCAR): Theory, optimization and clinical validation in neuromuscular disorders

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ABSTRACT

Multi-echo Chemical Shift–Encoded (CSE) methods for Fat-Water quantification are growing in clinical use due to their ability to estimate and correct some confounding effects. State of the art CSE water/fat separation approaches rely on a multi-peak fat spectrum with peak frequencies and relative amplitudes kept constant over the entire MRI dataset. However, the latter approximation introduces a systematic error in fat percentage quantification in patients where the differences in lipid chemical composition are significant (such as for neuromuscular disorders) because of the spatial dependence of the peak amplitudes. The present work aims to overcome this limitation by taking advantage of an unsupervised clusterization-based approach offering a reliable criterion to carry out a data-driven segmentation of the input MRI dataset into multiple regions. Results established that the presented algorithm is able to identify at least 4 different partitions from MRI dataset under which to perform independent self-calibration routines and was found robust in NMD imaging studies (as evaluated on a cohort of 24 subjects) against latest CSE techniques with either calibrated or non-calibrated approaches. Particularly, the PDFF of the thigh was more reproducible for the quantitative estimation of pathological muscular fat infiltrations, which may be promising to evaluate disease progression in clinical practice.

1. Introduction

The applications of quantitative chemical shift-encoded (CSE) methods for fat/water separation are experiencing a growing interest due to the need of a robust and accurate lipid quantification in different body parts [1–3]. In the case of skeletal muscle, the estimation of fatty infiltration is important in analyzing the progression of neuromuscular disorders (NMDs) (i.e. Duchenne [4–7], myopathies [8,9]) assessing risk factors and monitoring therapy for metabolic abnormalities (like obesity and diabetes) [10], and in grading muscle degeneration after injuries [11]. The accurate evaluation of proton density fat fraction (PDFF) [12–15] requires the consideration of multiple confounding factors including: the field map variations [14–17], the complexity of fat spectrum [15,17], the effect of T_2^* decay [19,20], the T_1-weighting [21,22], the noise-induced bias [23], the eddy currents [18,24], the susceptibility [25] and also temperature effects [26].

Among them, the careful modeling of the fat spectrum complexity has been primarily accomplished by using a multi-peak spectrum model with three main approaches for the assessment of peak locations and their relative amplitudes [27,28], (i) magnetic resonance spectroscopy (MRS) measurements [15,17]; (ii) multi-echo Spoiled Gradient Recalled (SPGR) sequences [17,27,29] where it is assumed that the peak frequencies are known and do not change voxel by voxel while the variables related to the peak amplitudes are uncorrelated [17] or have to satisfy certain constraints imposed by the lipid chemical composition [30]; and (iii) multi-echo gradient-echo sequences with a high number of echoes [31]. All of those approaches are based on the hypothesis that fat spectral properties are spatial invariant. While this approximation for the frequency pecks is valid in almost most of the cases, in contrast, the lipid metabolites concentration (hence the amplitude of pecks) varies with the tissue, patient, anatomical site, composition and nature (i.e. metabolic or pathologic) of the fatty inclusions and this dependence is as large as in some pathologies linked to neuromuscular disorders (i.e. Duchenne, myopathies) progress [32–35]. Clinically, recent studies have demonstrated dissimilarities in lipid compositions of adipose tissues in different anatomical regions [36] [37–39]. Particularly, applications on muscular fat in vivo [40,41] showed marked intra- and inter-individual variability of the spatial distribution of lipids in the

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musculature of the lower body. Similar conclusions have been also drawn by analyzing leg muscles in subjects affected by Duchenne muscular dystrophy (DMD) [7,42,43] or in the study of whole body fat distribution [44,45]. In addition, MRI has revealed patterns of selective muscle involvement in muscular pathologies that in a number of cases appear to be reasonably disease-specific [9,46]. Finally, although most of such lipid accumulation in the liver and other organs usually does not exceed 50%, this is not in the case for degenerative muscle diseases, where higher FF values can be reached up to the complete substitution of the muscular tissue with fat and fibrosis [5,47–49] leaving the problem of the spatial variability of fat composition an open issue. According to this, the chance to perform a multi-regional self-calibration procedure on a given MRI dataset can be considered of interest in the study muscular dystrophies, being that the pathophysiological changes might spatially alter tissue relaxation properties [32,33] when evaluating affected from unaffected tissues. To this end, the signal model formulation with independent R_2^* decay as provided in Ref. [50] has been taken into account in our study, being that it has been shown to be unsusceptible to some artifacts that adversely affect single-decay formulation when large regional variations of transverse decay rate occur among biological species [50]. This is the key motivation of this work where we have generalized the implementations of CSE water/fat separation techniques in skeletal muscle [21,49,51] that use a spatially constant pre-calibrated multi-peak fat spectrum model [15,17] by considering a spatially-variable spectrum model of the fat. We exploit a clusterization technique to segment a multi-echo NMR image dataset into a number of partitioned areas (PAs). In other words, we develop an iterative self-calibration technique that for each PA enables the estimation of fat spectrum relative amplitudes to provide a PA-specific calibrated parameters and improve (i.e. reducing fitting error) overall CSE water/fat quantification process.

This algorithm is organized as follows (further details are provided in Section 3.2): (*i-ii*) segmentation of the input MRI space into a finite number of partitions by using the Gap-statistics, (*iii*) self-calibration on each partition, to extract corresponding fat spectral components, (*iv-v*) independent fat/water quantification on each partition using calibrated fat relative amplitudes, and consolidation of intermediate results and finally, (*vi*) generation of the output maps. The validation of the method has been performed by evaluating the numerical results as obtained from a cohort of enrolled patients, and analyzed in terms of accuracy, robustness and reproducibility. Accuracy is assessed by taking in consideration the Mean Squared Error (MSE) and cumulative MSE. Robustness has been evaluated by examining the occurrence of artifacts (i.e. fat-water swaps). Reproducibility has been investigated by analyzing multiple datasets from a subset of patients which agreed to undergo a supplemental examination after a 1-week period, and by calculating the Intra-Class Correlation (ICC). In the second part of the work the performance of the proposed approach are validated and compared with state-of-the-art CSE methods (in Section 4) focusing in the field of NMD and by considering ad-hoc and public MRI datasets. The structure of the paper is the following: Section 2 describes the key theoretical elements behind the proposed methodology. In Section 3 we introduce the full reconstruction technique for fat/water quantification based on clustering and gap statistics and provide details about the subjects involved in the study and the reference metrics used to compare the results. Experimental findings are thoroughly presented in Section 4, whereas discussions are provided in Section 5. Finally, we draw conclusions in Section 6. Further results and explanations are included in the Supplementary material and in the Appendix A, respectively.

2. Theory

2.1. Chemical shift methods without clusterization

A CSE model for the fat/water quantification from a signal s_q measured on a given voxel q ($q = 1, \ldots, Q$, where Q is the number of voxels) at time TE_n ($n = 1, \ldots, N_{echo}$) is given by the following equation [17,20,27,31]:

$$s_q(t_n) = \left(\rho_{W,q} + \rho_{F,q}\sum_{p=1}^{P}\alpha_p e^{i2\pi f_{F,p}TE_n}\right)e^{i(\phi_{0,q}+2\pi f_{B,q}TE_n)}e^{-R^*_{2C,q}TE_n} \quad (1)$$

where $\rho_{W,q}$ and $\rho_{F,q}$ are the amplitudes of water and fat signals, respectively, with initial phase $\phi_{0,q}$, $f_{B,q}$ is the frequency shift due the spatial inhomogeneities of the bias magnetic field B_0. The terms $f_{F,p}$ are the known frequencies for the multiple spectral peaks of the fat signal relative to the water peak. Each fat peak p has a different unknown amplitude α_p and $\sum_{p=1}^{P}\alpha_p = 1$ (being P the number of fat peaks, here fixed as $P = 6$) and it is supposed that in Eq. (1) $f_{F,p}$ and α_p once defined, are spatially invariant. The usual approximation of a common relaxation rate (single-decay), $R_{2C,q}{}^*$, is used for both water and fat species, although there is no physiologic basis for this assumption [20]. A refined variant is constituted by the following equation:

$$s_q(t_n) = \left(\rho_{W,q}e^{-R^*_{2W,q}TE_n} + \rho_{F,q}\sum_{p=1}^{P}\alpha_p e^{i2\pi f_{F,p}TE_n}e^{-R^*_{2F,q}TE_n}\right)e^{i(\phi_{0,q}+2\pi f_{B,q}TE_n)} \quad (2)$$

Here, independent relaxation rates for water $R_{2W,q}{}^*$ and fat $R_{2F,q}{}^*$ are modeled [50]. Either signal models with single-decay approximation $R_{2C,q}{}^*$ as in Eq. (1) or independent decay ($R_{2W,q}{}^*$,$R_{2F,q}{}^*$) as in Eq. (2) can be calculated using Non-Linear Least Square method (NLLS) which provides the maximum-likelihood estimation [52] and are considered valid for each voxel [53]. On a general basis, the relative amplitudes $\{\alpha_p\}_{p=1,\ldots,P}$ are among the unknowns to be estimated. In this research, we will consider the solution of Eq. (2) as the core of our self-calibration technique which will be described further.

2.2. Clustering

Clusterization is an important technique in data analysis and mining. The goal of clustering is to split a set of elements into subsets with some criteria of similarities. The elements of the same subset are more similar to each other than the elements from different subsets [54]. As the clustering problem requires an unsupervised approach, the definition of reliable parameters is a key ingredient in the segmentation process. Thanks to its manifold applications, recent efforts in the processing of MRI data are documented [55–58], including unsupervised assessment of fat distribution [59–63], segmentation [62,64–69] and whole-image optimization [70]. In Kullberg et al. [62], a fully automated algorithm for segmentation of the visceral, subcutaneous, and total adipose tissue (TAT) depots has been presented. In Berglund et al. [64] a simple segmentation of adipose tissue was performed, in order to quantify TAT, although such technique leverages on a traditional Three-Point Dixon [71,72] acquisition scheme, which generally provides limited information on relaxation maps if compared with modern multi-echo sequences [20,73,74]. Among several different clustering schemes, the *k*-Means [54] is an iterative partitioning algorithm that, given a positive, finite and discrete number k, it is able to subdivide a dataset of Q data points into k groups (or clusters), by attempting to minimize the distance (we choose the Euclidean distance as the reference metric) between data points within a cluster and a point designated as the center of that cluster (intra-cluster distance). As a result, k clusters are found representing a set of input data objects, such that each object has the lowest intra-cluster distance (highest intra-cluster similarity) and the highest inter-cluster distance (lowest inter-cluster similarity), at the same time. A complete description of the algorithm is out of the scope of the paper and is provided in Ref. [75]. The *k*-Means is a favorable choice because it has demonstrated to be more computationally efficient than other methods [76–81]. Here, the role of the