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**A Proposal for Full-range Fat Fraction Estimation Using
Magnitude MR Imaging**

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A Proposal for Full-range Fat Fraction Estimation Using Magnitude MR Imaging

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**São Carlos
2018**

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“I’ve got to start listening to those quiet, nagging doubts.”

Bill Watterson

ABSTRACT

COSTA, Y. A. **A Proposal for Full-range Fat Fraction Estimation Using Magnitude MR Imaging**. 2018. 53p. Dissertação (Mestrado) - São Carlos School of Engineering, University of São Paulo, São Carlos, 2018.

Current methods for estimation of proton density fat fraction (PDFF) of the liver using magnitude magnetic resonance (MR) imaging face the challenge of correctly estimating it when fat is the dominant molecule, i.e. PDFF is more than 50%. Therefore, the accuracy of the methods is limited to half-range operation. We introduce a method based on neural networks for regression capable of estimating over the full range of fat fractions. We built a neural network based on the angles and distances between the data in the discrete MR signal (ADALIFE), using these as features associated to different PDFFs and as input for the network. Tests were performed assessing ADALIFE against dual echo, triple echo, and especially Multi-interference, a state-of-the-art method to estimate PDFFs, with simulated signals at various signal-to-noise (SNR) values. Results were compared in order to verify repeatability and agreement using regression analysis, Bland-Altman and REC curves. Results for Multi-interference were similar to its in-vivo literature, showing the relevance of a simulation. ADALIFE was able to correctly estimate fat fractions up to 100%, breaking the current paradigm for full-range estimation using only off-line post processing. Within half-range, our method outperformed Multi-interference in repeatability and agreement, with narrower limits of agreement and lower expected error at any SNR.

Keywords: Liver, magnetic resonance, neural networks, proton density fat fraction, quantification and estimation.

RESUMO

COSTA, Y. A. **Uma Proposta para Estimação de Fração de Gordura Hepática em Intervalo Completo Utilizando Imagens de Módulo de Ressonância Magnética**. 2018. 53p. Dissertação (Mestrado) - São Carlos School of Engineering, University of São Paulo, São Carlos, 2018.

Os métodos atuais para estimação de gordura hepática por densidade de prótons (PDFF) utilizando imagem de magnitude de ressonância magnética (RM) enfrentam o desafio de estimar corretamente quando a gordura é a molécula dominante, ou seja, PDFF é maior que 50%. Assim, a acurácia desses métodos é limitada a meio intervalo de operação. Apresentamos aqui um método baseado em redes neurais para regressão capaz de estimar pelo intervalo completo de frações de gordura. Construímos uma rede neural baseada nos ângulos e distâncias entre os dados do sinal discreto da imagem de RM (ADALIFE), usando esses atributos associados a diferentes valores de PDFF, com sinais simulados considerando diferentes relações sinal-ruído (SNR). Resultados foram comparados para verificar a repetibilidade e concordância através de análise de regressão, Bland-Altman e curvas de característica de erro de regressão (REC). Resultados para o método Multi-interferência (estado-da-arte) foram similares aos relatados *in vivo* pela literatura, ressaltando a relevância das simulações. ADALIFE foi capaz de estimar corretamente frações de gordura até 100%, quebrando o paradigma para intervalo completo de operação utilizando apenas processamento posterior à aquisição de imagens ou sinais. Considerando meio intervalo, nosso método superou o estado-da-arte em termos de repetibilidade e concordância, com limites mais estreitos e menor erro esperado em qualquer SNR.

Palavras-chave: Fígado, fração de gordura hepática, quantificação e estimação, redes neurais, ressonância magnética.

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LIST OF ABBREVIATIONS AND ACRONYMS

ppm	Parts per million
NAFLD	Nonalcoholic fatty liver disease
MRI	Magnetic resonance imaging
MR	Magnetic resonance
ROI	Region of interest
ANN	Artificial neural network
ADALIFE	Angle and DistAncE for LIver Fat Estimation
GRE	Gradient-recalled echo
PDFF	Proton-density fat fraction
IP	In-phase
OP	Opposed-phase, also out-of-phase
ReLU	Rectified Linear Unit function
SNR	Signal-to-noise ratio
BA	Bland-Altman
REC	Regression error characteristic
AOC	Area over the curve
SD	Standard deviation

LIST OF SYMBOLS

TE	Echo time, also time to echo
TR	Repetition time
$T1$	Longitudinal magnetization relaxation time
$T2^*$	Apparent transversal magnetization relaxation time constant
Δf_n	Precession frequency of fat moieties relative to that of water in parts per million
ρ_n	Proton density
k	Machine-dependent constant
S	Voxel signal
α	Flip angle in radians
f_n	Precession frequency of magnetization in Hz
γ	Gyromagnetic ratio of hydrogen in MHz/T
B_0	Main magnetic field in Tesla
δ	Chemical shift of a molecule in parts per million
θ	Angle
R_c	Repeatability coefficient
ρ_c	Lin's concordance coefficient
p	Statistical significance

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1 INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is characterized by hepatic steatosis unrelated to alcohol abuse and may lead to chronic liver disease. It has been estimated by a meta study that NAFLD has a prevalence of 25% among global population (1) and of 30% in the United States according to another study including 6000 subjects (2). Amongst noninvasive quantitative approaches for estimation of hepatic fat content, magnetic resonance imaging (MRI) has shown great reproducibility (3, 4) and good agreement to clinical and research gold standards, biopsy and spectroscopy, respectively (5, 6). Quantitative assessment of liver steatosis with MRI can be done by estimating the hepatic proton density fat fraction based on chemical shift images (from here on called fat fraction, PDFF), which may carry magnitude or complex information.

Complex imaging means obtaining magnitude and phase images. Whereas it allows full-range fat fraction estimation i.e., from 0 to 100% PDFF, phase errors must be accounted for as they can cause a bias of about 5% PDFF (7). Additionally, complex acquisition and correction algorithms are not standard on clinical MRI scanners, being sold separately as a vendor-dependent software (8). Magnitude-based images on the other hand, are clinical routine and do not include phase errors. However, fat fraction estimation is prone to their signal-dependent rician noise (9) and is assumed to be limited to estimations up to 50% PDFF due to an effect called water-fat dominance ambiguity (10, 11, 12) which could only be resolved using complex phase information as aforementioned or the acquisition of additional images with other parameters, which changes the clinical protocol (13). Current state-of-art method for fat fraction estimation using magnitude imaging is Multi-interference, which requires a set of multiple images and calculations can be performed offline. This method estimates tissue parameters within a set of registered voxels or regions of interest (ROIs). It calculates mainly water and fat proton densities and a single apparent transverse magnetization decay $T2^*$ by fitting the data using nonlinear least squares approximation. It is also limited to 0-50% PDFF.

MRI fingerprinting is the estimation of tissue parameters from a set of images acquired with variable settings (14). This is usually based on a dictionary containing reference values which are compared to the ones to be extracted from image signals, which limits the number of parameters and their discretization according to the computational power available, needing for compression methods (15). Recent works approached this problem from a machine learning perspective and obtained success using artificial neural networks and deep learning by first training a dataset with signals obtained from the reference parameters and then inverse mapping them from signals using the network (16, 17).

In this work we question the assumption that magnitude-based imaging is limited to half-range PDFF estimation when using standard protocol by proposing and simulating an estimation technique that we believe to work full-range, 0 to 100%. We trained an artificial neural network (ANN) for PDFF regression using shape features (angle, distance) extracted from simulated magnitude MRI signals and named the method Angle and DistAnc for LIver Fat Estimation (ADALIFE). Classical methods (10, 12), a state-of-the-art method (Multi-interference) and our method are compared in the task of estimating simulated PDFF values from signals contaminated with different levels of noise. Statistics are performed to verify their performance within the range of 0-50% for all methods and 0-100% PDFF for our method.

The chapters in this work are presented as follows: Chapter 2 will bring the literature review on the subject of MRI signal and fat fraction estimation focusing on signal processing. Chapter 3 presents materials and methods, introducing the proposed idea for full-range estimation, simulation and evaluation methods. Chapter 4 presents the results comparing estimation methods. Chapter 5 discuss the presented results, evaluating the present stage and proposing future improvements. Finally, Chapter 6 concludes this work.

1.1 Research Objectives

General objective: To propose and evaluate a method for full-range proton-density fat fraction estimation using magnitude MR images.

Specific objectives:

- a) To verify if simulations can appropriately reproduce *in vivo* behavior of estimation methods
- b) To test whether agreement and repeatability between ADALIFE and reference in half-range estimation is comparable to that of Multi-interference and reference.
- c) To test whether agreement and repeatability between ADALIFE and reference in full-range estimation is comparable to the one in half-range.

2 LITERATURE REVIEW

Magnetic resonance imaging is a relatively new medical image modality. The first image of a human body was produced in 1977 by Raymond Damadian and his team (18) and took nearly five hours to complete, with eyes on disease diagnose. Damadian was one of the first physicians to show interest in MR: before him, the very first image was produced in 1973 by Paul Lauterbur (19) a chemist who imaged a clam, and later Peter Mansfield in 1977, a physicist who imaged the cross-section of a human finger (20), both using much smaller scanners and different MR imaging methods. Nowadays an abdominal MRI exam for assessment of liver steatosis generates a stack of slice images of the patient's abdomen. In a gradient echo (GRE) multiecho MRI sequence, for each slice position, multiple signals are repeatedly acquired within a time window of milliseconds. When combined, they form images spaced in time. A typical way to estimate liver fat fraction is by analyzing how these images change over that time window, an idea that has not changed much since its proposal by Dixon in 1984 (10). This chapter explores the concepts of these images, the properties of their signals and how methods in literature estimate fat fraction based on them.

2.1 Magnitude Gradient Echo Signal

A typical magnitude GRE in-phase (IP) and opposed-phase (OP) image set aims to explore the difference in water and fat content among tissues. For a fixed slice position, the test consists of a series of images acquired at different echo times (TE) after an excitation pulse. As the ^1H magnetization of distinct molecules precesses at characteristic frequencies, echo times are chosen such as to cause water and fat magnetizations to be in-phase or opposed-phase for each acquisition. That means, in a very simplistic way, magnitude IP images carry a signal that is proportional to the absolute value of the summation of proton densities of water and fat, whereas magnitude OP images carry the magnitude of their subtraction. A set of liver GRE IP-OP images and the corresponding plot of the average signal intensity (S) versus echo time TE of a region of interest in each image is shown in Fig. 1.

The signal of a voxel for a magnitude GRE image at different echo times such as plotted in Fig. 1 can be mathematically modeled according to the physical principles of magnetic resonance imaging as long as tissue properties and imaging parameters are known. Equation (2.1) represents the signal of the magnitude gradient echo sequence for n different molecules, where S is the voxel signal, k is a machine-dependent constant, ρ_n is the proton density of the given molecule, α is the flip angle in radians, TR is the repetition time in seconds, $T1_n$ is the longitudinal relaxation time of the molecule in seconds, TE is

Figure 1: Set of GRE OP and IP images and plot of corresponding average signal within ROIs at corresponding echo times

Source: author's own.

the echo time in seconds, $T2_n^*$ is the apparent transverse relaxation time of the molecule in seconds, and f_n is the magnetization precession frequency of the molecule in hertz. Tissue properties are ρ_n , $T1_n$, $T2_n^*$ and f_n . Imaging parameters are TR , TE and α . Equation (2.2) is an approximation of (2.1) for low α and short TR , which minimize T1 effects, as previously proposed in literature (12, 21). Therefore, equation (2.2) describes the signal intensity S in a voxel for the magnitude GRE sequence with small flip angle at a given TE as a constant k multiplied by the modulus of a sum of exponentially damped complex sine waves with different amplitudes ρ , frequencies f and decay rates $1/T2^*$.

Equation (2.3) defines the precession frequency in Hertz of a given molecule as used in (2.1) and (2.2). γ is the hydrogen gyromagnetic ratio in MHz/T, B_0 is the main static magnetic field in Tesla and δ_n indicates the chemical shift of the n molecule in parts per million, i.e. its precession deviation in relation to that of a reference (usually

tetramethylsilane, $\text{Si}(\text{CH}_3)_4$). The convenient echo times for in-phase and opposed-phase can then be calculated according to (2.4), where f_{water} and f_{fat} are water and fat frequencies, respectively, resulting in half the period of the difference in precession between those molecules. For IP-OP GRE imaging or spectroscopy as defined here, water and methylene (CH_2) chemical shifts are used ($\delta_{\text{water}} = 4.7$ and $\delta_{\text{fat}} = 1.3$ ppm, respectively) (10), the latter being the most abundant fat moiety in liver (22). However, fat is not a molecule as simple as water, and it may be formed by different combinations of glycerol and fatty acids which must be taken into account for a precise estimation.

$$S = | k \sum_n \rho_n \frac{\sin(\alpha) [1 - \exp(-TR/T1_n)]}{1 - \cos(\alpha) \exp(-TR/T1_n)} \cdot \exp(-TE/T2_n^*) \exp(2\pi i f_n TE) | \quad (2.1)$$

$$S = | k \alpha \sum_n \rho_n \exp(-TE/T2_n^*) \exp(2\pi i f_n TE) | \quad (2.2)$$

$$f_n = \gamma B_0 \delta_n \quad (2.3)$$

$$TE = \frac{1}{2} \frac{1}{f_{\text{water}} - f_{\text{fat}}} \quad (2.4)$$

2.2 Fat Fraction Estimation in Literature

Proton density fat fraction, or simply fat fraction PDFF is defined according to (2.5), where ρ_f and ρ_w are fat and water proton densities, respectively. In order to obtain those values, the first method was proposed by Dixon in 1984 (10) using a pair of opposed-phase and in-phase images at echo times calculated for water and methylene, which allowed for estimation of only this fat moiety. Calculation is performed arithmetically according to (2.6). Later magnitude-based methods added a third echo to include the effects of a single $T2^*$ exponential decay (13, 23), thus called triple echo and shown in Equation 2.7.

Studies of the *in vivo* liver fat spectrum (24) using high resolution spectroscopy identified not only CH_2 but six fat moieties in fixed proportions across subjects. Three of them are considered more prominent in humans, located at 0.9, 1.3 and 2.1 ppm, accounting for about 91% total liver fat (22). The other peaks are located at 2.75, 4.2, and 5.3 ppm. These last two fat peaks and water (4.7 ppm) partially overlap, making it difficult to characterize them. Based on those studies, Yokoo et al. proposed the Multi-interference method (25) which took into consideration the three major peaks and a single $T2^*$ value. They showed it was possible to use non linear least squares to calculate ρ_f and ρ_w by fitting the signal of six echoes to (2.8), a reduction of the previously presented GRE

equation. As the convergence of such fitting method depends on a number of initialization parameters, we recently proposed optimal values for increasing the chances of converging to a correct approximation (26). Equation (2.8) results in a signal S that is $k\alpha$ times the magnitude of the water proton density (ρ_w) and the weighted sum (ρ_f) of three complex sinusoids with different, fixed amplitudes c_n (contributions adjusted to sum up a total of 100%) and frequencies Δf_n relative to water, and the result multiplied by an exponential decay dependent on a single $T2^*$ value. The presented methods for estimation using magnitude images at low flip angles and fixed echo times undergo water-fat dominance ambiguity. This effect is the inability to tell whether water or fat proton density is greater when phase information is discarded and modulus operation is applied in (2.1), as single data point cannot give information to resolve if its value is due to the subtraction of fat from water or vice versa, resulting in underestimation of high values of PDFF, as shown in Figure 2. Water is then assumed to be dominant based on *in vivo* findings (27) and magnitude estimation is usually limited to 0-50% PDFF when using standard clinical protocols. However, a thorough analysis of the signal across the echo times may show other relevant clues on this issue.

Figure 2: Simulation of PDFF estimation from 0 to 100% using Multi-interference

Source: author's own.

$$PDFF = \frac{\rho_f}{\rho_w + \rho_f} \quad (2.5)$$

$$\begin{aligned} \rho_w &= (S_{IP} + S_{OP})/2 \\ \rho_f &= (S_{IP} - S_{OP})/2 \end{aligned} \quad (2.6)$$

$$\begin{aligned} \rho_w &= [S_{IP} \exp(TE_{IP,1}/T\mathcal{Z}^*) + S_{OP} \exp(TE_{OP,1}/T\mathcal{Z}^*)]/2 \\ \rho_f &= [S_{IP} \exp(TE_{IP,1}/T\mathcal{Z}^*) - S_{OP} \exp(TE_{OP,1}/T\mathcal{Z}^*)]/2 \\ \text{where} & \\ T\mathcal{Z}^* &= \frac{(TE_{IP,1} - TE_{OP,1})}{\log(TE_{IP,1}/TE_{IP,2})} \end{aligned} \quad (2.7)$$

$$\begin{aligned} S(TE, \alpha) &= k \alpha \left| \rho_w + \rho_f \sum_{n=1}^3 c_n \exp(2\pi i \Delta f_n TE) \right| \\ &\cdot \exp(-TE/T\mathcal{Z}^*); \quad \sum_{n=1}^3 c_n = 1 \end{aligned} \quad (2.8)$$

3 MATERIALS AND METHODS

In this section we introduce the idea behind full-range estimation using machine learning, and how we evaluated the proposed model against classical and state-of-the-art models using simulations, as presented at the 2018 World Congress of Medical Physics & Biomedical Engineering (28, 29).

3.1 Signal Shape and Feature Extraction

By simulating the liver signal at several fat fractions we observed interesting particularities in the geometric distribution of the data points. For the next examples we used (2.2) for the simulations considering the frequencies and proportions of water molecule and six lipids as described in (12, 22, 30). All molecules had the same $T2^*$ value of 0.082 seconds and no noise was added. Each signal was calculated for seven echo times considering water and methylene interaction for setting IP and OP times and a main static magnetic field of 3 Tesla.

Fig. 3 explores four cases depicting particularities we found to highlight differences in signals at different fat fractions. Case I in Fig. 3a is an example of two fat fractions far apart within the range of 0-50% in which we observe an evident increase in the y-axis distance between IP and OP points. This is expected within this range where water is dominant and IP represent $\rho_w + \rho_f$ and OP is $\rho_w - \rho_f$. Distances decrease back after 55% PDF, as expected when fat becomes dominant. The reason for being about 55% is that at that point the three major fat moieties account for about 50% of total signal (and as most estimation methods only consider these moieties, it is said to be 50% fat). Case II in Fig. 3b shows a line connecting IP points (dotted line, orange points) and another for OP points (dashed line, blue points). The concavity of the dashed line aims downward if PDF is less than 55% and then changes to upward if greater. Pointing downward becomes more evident at fat fraction close to 50% and pointing upward when close to 90%. The connection between IP points seems to change only in terms of steepness. Case III as depicted in Fig. 3c demonstrates that for the latter echoes their relative position (to each other) is practically reversed. The angle θ between y-axis and a line between two consecutive data points shows this change. Moreover, in this fat-dominant example it can be observed that the y-axis distances are shortened in the initial echoes, as commented before. Lastly, Case IV was simulated using two different common $T2^*$ values for all molecules and the same fat fraction. It can be seen a difference in slope, represented by the change in angle for a line connecting the first and last echoes. Evidently, applying different relaxation values for each molecule would result in different signals, but the overall effect is a change in slope.

Figure 3: Shape particularities in geometric distribution of signal as fat fraction varies

Case I (a) describes how distance changes for IP-OP echoes as fat fraction increases. Case II (b) shows a change in the concavity of OP points as fat becomes dominant. Case III (c) shows a swap in the position of latter echoes as PDFF increases around 90 to 100%. Case IV explicits the change in overall decay caused by parameter $T2^*$. Source: author's own.

Considering a normalized signal, we can compute the Euclidean distance between any pair of points A and B at echo times TE_A and TE_B and with signal intensities SI_A and SI_B . We can also compute the angle between the y-axis and the straight line that connects both points, as shown in Fig. 4a. If we calculate these features for all possible connections between the seven echoes we end up with a network such as the one in Fig. 4b, which results in a descriptor containing 42 features that can be used in a machine learning approach. Intuitively, distances between in-phase and opposed-phased points will reflect the height, distances and angles within IP or OP between inner and outer points will reflect the concavity, and connections between extremity points will reflect decay, which should suffice to differentiate between fat fractions. The distance between points A and B can be calculated using (3.1) and the angle using law of cosines for a triangle with points A, B and an auxiliary point C located at $(TE_A, 2)$ for convenience. The set of equations presented in (3.2) allows the calculation of the sides D_{AC} and D_{BC} of the

Figure 4: Features considered in the signal

(a) Distance and angle as shape features to be computed for each pair of data points.

(b) All the connections for a single 7-echo signal, totalizing 42 features (21 distances and 21 angles).

Source: author's own.

triangle, and the angle $\theta_{C\hat{A}B}$. It is useful simply use the index of the echo times instead of the actual values to make it independent of main magnetic field strength but keep the order. In order to scale the resulting distance and angle to values between zero and one, we must figure out maximum and minimum possible values for distance and angle. Distance is minimum when two points are consecutive and horizontally aligned, and maximum when they are distant by the maximum number of echoes and greatest difference in signal (considering the signal to be between zero and one). Angle is minimum when two points are consecutive and the earlier and latter points have minimum and maximum signals, respectively. The maximum value can be obtained by subtracting the minimum value from π , which represents consecutive points and swapped signal values.

$$D_{AB} = \sqrt{(S_B - S_A)^2 + (TE_B - TE_A)^2} \quad (3.1)$$

$$\begin{aligned} D_{BC} &= \sqrt{(2 - S_B)^2 + (TE_B - TE_A)^2} \\ D_{AC} &= 2 - S_A \\ \theta_{C\hat{A}B} &= \arccos\left(\frac{D_{AC}^2 + D_{AB}^2 - D_{BC}^2}{2D_{AC}D_{AB}}\right) \end{aligned} \quad (3.2)$$

3.2 Obtaining a Complete GRE Signal

Signals with seven echoes were generated based on (2.2) considering the interaction effects of water molecule and six fat moieties, at echo times chosen for water and methylene to be in-phase and opposed-phase in a 3 Tesla magnetic field, according to (2.4). It has been suggested that the proportion between fat moieties tends to be similar regardless the fat fraction (22). That means that fixed ρ_n values for each fat moiety can be used and

then multiplied by a desired overall fat proton density ρ_f . Thus, values 0.088, 0.7, 0.12, 0.006, 0.039, and 0.047 (total equals 1) were used for fat peaks at 0.9, 1.3, 2.1, 2.75, 4.2, and 5.3 ppm, respectively (22). $T2^*$ values are known to vary according to their molecular surrounding, presence or iron deposits in the liver and magnetic field inhomogeneities. However, typical values have been described in literature (30, 22, 12), allowing us to simulate the variability of these values using truncated normal distributions. Lower limit was 0.001 and upper limit was 1 second. The following average values in seconds were used: $T2^*_{water} = 0.027 \pm 0.007$, $T2^*_{fat0.9} = 0.083 \pm 0.016$, $T2^*_{fat1.3} = 0.061 \pm 0.011$, and $T2^*_{fat2.1} = 0.052 \pm 0.030$, where the $\pm$ sign indicates standard deviation. Fat peaks located at 2.75, 4.2, and 5.3 ppm were assigned fixed $T2^*$ values of 0.051, 0.025 and 0.039 seconds, respectively, due to lack of information in literature for a proper distribution. The frequency of each molecule was determined by (2.3), terms k and α were set to 1, and ρ_f and ρ_w were set using random positive numbers between 0 and 1 that would satisfy a given fat fraction value, according to (2.5). Finally, Rician distributed noise (31) was added with signal-to-noise ratios (SNR) between 25 and 200, values we experienced in clinical images and similar to previously reported in literature for liver and water-fat separation imaging (32, 33). Simulations were performed using Python 3.

3.3 Building the Artificial Neural Network

The model consisted on a fully connected regression neural network of the type multilayer perceptron (MLP), with 42 inputs, three hidden layers with sizes 32, 16, and 2, and one output. Activation function was Rectified Linear Unit function (ReLU) and optimizer method was ADAM (34) with default settings (learning rate = 0.001, $\beta_1 = 0.9$, $\beta_2 = 0.999$, $\epsilon = 1e - 7$, and decay = 0.0). The size of the training batches was 400 and the network was trained during 2000 epochs using separate train and validation datasets. The model was built and trained using Keras with TensorFlow backend in Python 3.

3.4 Datasets for Training, Validation and Testing

Datasets for training, validation and testing differ in size and in how data is distributed. The training dataset consisted of 50000 signals with 1000 different fat fraction values linearly distributed between 0.1 and 100%. In this way, each PDF is presented in 50 random combinations of ρ_w , ρ_f , $T2^*_n$ and SNR values. A validation dataset is used during the learning process of the network for fine tuning. For this task, we used a dataset containing 20000 signals with single, random fat fraction values uniformly distributed between 0.1 and 100%, random $T2^*_n$ and SNR values. Test datasets are the ones used to finally evaluate the performance of the trained network and Multi-interference methods. There were 16 test datasets, each consisting of 5000 instances of signals with fixed SNR values of 25, 50, 100 and 200 and PDF ranging from 0 to 45 or 100%. For a given range

of PDFF, the dataset corresponding to each SNR had random and unique fat fraction values uniformly distributed within its range. For each dataset, a repetition set with same fat fractions was generated from different parameters for repeatability analysis. When the datasets were meant to be used by the neural network, there was a conversion step to calculate the distances and angles for each signal as explained before.

3.5 Statistical Analysis

We performed an initial analysis to verify if known methods respond as expected and compare to our method, comprising Dual-echo, Triple-echo, Multi-interference, and ADALIFE using least squares linear regression of True PDFF versus their respective estimations (range limited 0-40%) and in full range for ADALIFE at different SNRs. Next, a more detailed analysis included only Multi-interference and ADALIFE. For each test dataset (SNR 200, 100, 50, and 25), Multi-interference estimated fat fractions ranging from 0.1-45% and ADALIFE within ranges 0.1-45% and 0.1-100%. Repeatability tests of the methods were performed using two test datasets with the same fat fractions generated from different parameters, for example changing $T2^*$ and noise values. This should lead to slightly different estimations for the same value in contrast to an ideal method that would estimate the same given PDFF independently of any other parameter of the signal. This approach was used as otherwise simulations would lead invariably to the same results. In order to assess the repeatability, for each method and SNR we calculated the repeatability coefficient R_c and Bland-Altman (BA) analysis (35). Literature presents repeatability values for Multi-interference to be compared with the simulations. All other tests were performed using only the first dataset of each repeated pair. Agreement between a given method and simulated fat fractions (True PDFF) was estimated using Lin's concordance correlation coefficient ρ_c (36), BA analysis adjusted for comparing to a reference (37), and regression error characteristic (REC) curves with respective areas over the curves (AOC) (38). A Kolmogorov-Smirnov two-sample test was used to assess the significance of difference between the REC curves for Multi-interference and ADALIFE under the null hypothesis that the error generated by the models follow the same distribution. Adjustments for outliers were performed for the BA when needed considering only the data within five standard deviations (SD) of the mean of the differences. All the data analysis were performed using `StatsModels` and `SciPy` Python modules.

4 RESULTS

In this section we present the regression results for all methods in half-range and for ADALIFE in full-range, repeatability and agreement results for Multi-interference and ADALIFE in half range (0.01-45% PDFF) and for ADALIFE in full range (0.01-100% PDFF). For the sake of simplicity and as all statistics except for the Concordance Correlation Coefficient are given in PDFF units, from here on fat fractions will be stated as decimals.

4.1 Linear Regression

Figure 5 shows plots of True PDFF *versus* estimation in half range for Dual-echo, Triple-echo, Multi-interference, and ADALIFE at SNR 200 and 25. Red dashed line is the identity, with intercept zero and slope one. Regression lines are not plotted so the plots do not become too cluttered as in some of them the identity and regression lines would practically overlap. However, their intercepts and slopes are displayed in Table 1. These values are close to the ones reported *in vivo* in (39), with a maximum difference of 0.1, considering that confidence intervals were not given in the original paper. Considering slope and intercept, ADALIFE was the one that approximated the most to identity line, followed by Multi-interference, Dual echo and Triple echo. The dispersion of the results is different for each method: although it was not measured, Multi-interference visually presents a greater dispersion around high PDFF values, contrary to other methods that are more disperse around lower values. The increase in noise seems to affect all methods especially at lower PDFFs. This effect could not be verified in literature due to lack of relates. Plots for full-range estimation using ADALIFE are in Figure 6, intercept and slope values are -0.0008 and 1.0015, respectively, for SNR 200, and -0.0002 and 1.0002, respectively, for SNR 25. These values are similar to the ones in half-range. The plots qualitatively demonstrate the ability to correctly estimate fat fractions in full-range, with slightly wider dispersion at the ends of the PDFF range than in the center and a few outliers. This result will be further explored using Bland-Altman plots.

4.2 Repeatability

Table 2 presents the repeatability coefficient (R_c) calculated as 1.96 SD of the differences and the number of outliers excluded for each method and SNR. As both methods presented zero mean considering four decimal places, 95% limits can be directly obtained as $\pm R_c$ and 95% confidence intervals are in the order of 10^{-4} . For the calculation of repeatability, a few outliers had to be removed from the ADALIFE results in order to adjust the tails for a normal distribution and the Bland-Altman analysis make sense,

Figure 5: Plot of true PDFF *versus* estimation in half-range for various methods at SNR 200 and 25

Source: author's own.

Figure 6: Plot of true PDFF *versus* ADALIFE estimation in full-range at SNR 200 and 25

Source: author's own.

Table 1: Regression results for Dual echo, Triple echo, Multi-interference, and ADALIFE for half-range estimation.

SNR	Dual echo		Triple echo		Multi-interference		ADALIFE	
	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope
200	-0.0273	0.9312	0.0249	0.8810	0.0033	1.0421	0.0000	0.9976
100	-0.0273	0.9311	0.0247	0.8823	0.0030	1.0421	0.0002	0.9960
50	-0.0278	0.9329	0.0241	0.8843	0.0033	1.0404	0.0002	0.9964
25	-0.0284	0.9354	0.0247	0.8827	0.0022	1.0452	0.0007	0.9933

Source: Author's own.

averaging 0.08% of the datasets. Their incidence did not seem to be related to the SNR but to the size of the dataset (e.g., $n = 500$ would present no outliers), although no statistics were performed to confirm this relationship. We also verified that as SNR decreases, the repeatability coefficient becomes worse. ADALIFE had a higher repeatability coefficient than Multi-interference at every signal-to-noise ratio (maximum difference = 0.0152, minimum difference = 0.0081), though Multi-interference showed a more stable repeatability to the decrease in SNR. The coefficient for ADALIFE in full range was generally higher than in half range, but closely related (maximum difference = 0.0036PDFF).

4.3 Agreement

Agreement between a selected model and true fat fraction values was estimated using the concordance correlation coefficient ρ_c , Bland-Altman, and REC curves plots. Fig 7 shows the BA plots in (a), (b), (d), and (e), and REC curves in (c) and (f) for Multi-interference and ADALIFE at SNR 200 and 25, for half-range estimation. Similar plots for full-range estimation are shown in Fig. 8 except that REC curves compare ADALIFE performance over different SNR. Values for ρ_c , AOC, and BA analysis are presented in Table 3 for Multi-interference and 4 for ADALIFE. Outliers were removed from ADALIFE results for calculation of BA analysis, averaging 0.05% of the datasets.

Comparing half-range results, concordance correlation coefficient of ADALIFE was higher at every SNR except at 25. Area over the curve was lower for ADALIFE and the mean and 95% limits of agreement did not need to include dependency on True PDFF level. These limits at 0.0625 PDFF, a binary classification threshold in literature (40) considering SNR 200 are [-0.1460, 0.0871] for Multi-interference and [-0.0045, 0.0060] for ADALIFE. 95% confidence intervals for Multi-interference are in the order of 10^{-3} in slope and 95% limits and 10^{-4} in intercept. In ADALIFE they are in the order of 10^{-4} for mean and 95% limits of agreement. REC curves presented in Figs. 7 (c) and (f) show a slow climb at start for Multi-interference which is due to bias in slope as verified in (a) and (d), in contrast to the steep ascent for ADALIFE due to the concentration of most differences being around zero. The Kolmogorov-Smirnov test for differences between the REC curves confirmed that they are significantly different with $p < 0.001$ at any SNR. Area over the curve estimates expected error for a given method, and ADALIFE obtained values six to two times smaller depending on the SNR. A noticeable feature is that expected error and limits of agreement increase more for ADALIFE than for Multi-interference as SNR decreases.

ADALIFE's full-range results are comparable to those in half range presenting higher ρ_c , lower AOC (except for SNR 200), lower mean and similar limits of agreement. The model was able to estimate fat fractions between 0.001 and 1 in the worst case of

Figure 7: Bland-Altman plots and REC curves for half-range estimation with Multi-interference and ADALIFE

Bland-Altman plots (a), (b), (d), (e), and REC curves (c), (f), for Multi-interference and ADALIFE at SNR 200 and 25. Notice the difference in scales. Data points omitted on the plot due to scaling (out of 5000): (a) 1, (b) 8, (d) 3, (e) 9

Source: author's own.

SNR 25 with maximum expected error of 0.0062 and 95% limits of agreement of $[-0.0162, 0.0166]$, which are still lower values than the ones for Multi-interference operating in half-range only. 95% confidence intervals are in the order of 10^{-4} for mean and limits of agreement. We identified a break in the continuity of the estimation around 0.56 PDFF which resulted in errors of up to ± 0.0175 . At the same time, noise seems to have a much stronger effect at the ends of the range of operation rather than in the middle. These features are noticeable in Figs. 8 (a) and (b). The REC curves plotted in (c) show visually the difference in area according to different SNR values.

Table 2: Repeatability results for Multi-interference and ADALIFE in half-range and full-range estimation

Method	SNR	R_c	Outliers
Multi-interference (half-range only)	200	0.0219	0
	100	0.0219	0
	50	0.0250	0
	25	0.0346	0
ADALIFE (half-range, full-range)	200	0.0067, 0.0088	4, 9
	100	0.0085, 0.0101	2, 2
	50	0.0134, 0.0133	5, 2
	25	0.0265, 0.0229	4, 5

Source: Author's own.

Note: Repeatability was assessed using two estimations of the same values. As R_c is 1.96 SD, the closest to zero the better. Both methods presented zero mean as estimated to four decimal places, which makes BA 95% agreement limits simply $\pm R_c$.

Table 3: Summary of agreement results for Multi-interference (half-range)

SNR	ρ_c	AOC	Intercept	Slope	Lower 95%	Upper 95%
200	0.9928	0.0125	-0.0041	-0.0360	-0.0227	0.0146
100	0.9927	0.0126	-0.0041	-0.0361	-0.0234	0.0152
50	0.9921	0.0132	-0.0033	-0.0389	-0.0244	0.0178
25	0.9901	0.0149	-0.0037	-0.0371	-0.0310	0.0236

Source: Author's own.

Note: Due to the nonuniform differences in relation to the values of True PDFF, in order to obtain the estimated error value at a given fat fraction PDFF one must calculate intercept + slope*PDFF. For 95% limits of agreement, the calculation is the same with lower or upper limits replacing intercept. No outliers had to be removed for these calculations. ρ_c is best when close to 1, AOC when close to 0.

Figure 8: Bland-Altman plots and REC curves for full-range estimation with ADALIFE

Bland-Altman plots (a), (b), at SNR 200 and 25 and REC curves (c) at SNR 200, 100, 50, and 25 ADALIFE. Notice the difference in scales. Data points omitted on the plot due to scaling (out of 5000): (a) 43, (b) 12

Source: author's own.

Table 4: Summary of agreement results for ADALIFE

SNR	ρ_c	AOC	Mean	Lower 95%	Upper 95%	Outliers
Half-range estimation						
200	0.9994	0.0021	0.0007	-0.0045	0.0060	1
100	0.9968	0.0027	0.0006	-0.0059	0.0073	3
50	0.9955	0.0040	0.0007	-0.0091	0.0106	1
25	0.9829	0.0076	0.0008	-0.0180	0.0197	3
Full-range estimation						
200	0.9998	0.0024	0.0001	-0.0065	0.0068	6
100	0.9998	0.0027	0.0001	-0.0070	0.0074	3
50	0.9998	0.0037	0.0000	-0.0096	0.0097	3
25	0.9991	0.0062	0.0001	-0.0162	0.0166	2

Source: Author's own.

Note: The Kolmogorov-Smirnov test for differences between the Multi-interference and ADALIFE REC curves (half-range) confirmed that they differ with $p < 0.001$ at any SNR. Outliers do not apply to ρ_c and AOC.

5 DISCUSSION

This study questioned the inability of magnitude MR images to provide enough information for full-range PDFF estimation, demonstrating with a new method it is otherwise possible. We simulated signals with parameters based on *in vivo* studies and PDFFs ranging from 0.001 to 0.40 for an initial regression analysis comprising various methods and verified that simulations can provide results similar to the ones in literature. From the first analysis, ADALIFE indicated not only to be a better method within the known range of 0-0.4 PDFF but also that it is able to estimate in the full range. We then performed a second run of experiments this time including only Multi-interference and ADALIFE for half-range and only ADALIFE for full range values, testing for repeatability and agreement now using in thorough analysis. The maximum values for half-range differ in the two experiments (0.4 and 0.45 PDFF) because they were performed at different times, though both are clinically relevant and the difference should not be significant, although it was not formally assessed. As demonstrated before, errors arise for Multi-interference estimation under 0.5, hence the choice of 0.45 PDFF as a limit.

5.1 Verifying if simulations are appropriate

Our first concern was if simulations would adequately reproduce *in vivo* results. The least squares regression of the classical methods' estimation against True PDFF and corresponding plots matched literature results for Dual echo, Triple echo and Multi-interference. Although Triple echo resulted in intercepts and slopes further than Dual echo from the identity line opposing to literature, the distribution is the same presented by authors with positive intercept and negative slope crossing the identity line at some point. This divergence could be a result of the broader range of parameters used in the simulations when compared to reference *in vivo* experiments. Comparing our Multi-interference simulation results to the original publications (25, 39), the observed repeatability, intercept and slope results differ in less than 0.02 PDFF, which is within the confidence intervals provided in those studies. We confirmed that the simulations are appropriate to reproduce the MR imaging signals and methods of estimation.

5.2 Comparing ADALIFE and Multi-interference

Despite the nonlinear trajectory around the mean that can be observed for ADALIFE estimation in Fig. 7 (b), the errors followed a *quasi* normal distribution, except for the very few outliers mentioned before, which is confirmed by the fact that ADALIFE has the tightest distribution around the identity line. This trajectory can be associated to the nonlinear solution found by the neural network which averages close to zero. It is also present

at other SNR values although overwhelmed by noise-derived results. Multi-interference presented a skewed and leptokurtic normal distribution of errors due to the bias in slope. Therefore, we recurred to linear regression in the BA analysis around which the residuals are normally distributed. Thus, limits of agreement are dependent on the fat fraction for Multi-interference and fixed for ADALIFE. Overall, these limits were narrower for our method, and more importantly, narrower at 0.0625 PDFF, a suggested threshold for classification of fatty liver according to a comprehensive study involving 2349 participants (40). REC curves show the deviation that must be admitted in order to obtain a certain accuracy and were better for ADALIFE at any SNR and statistically different than the ones for the state-of-the-art method. Results showed that as SNR decreases, limits of agreement and AOC worsens at a higher pace for ADALIFE than for Multi-interference, indicating that the latter might be more robust to noise. However, these values are much smaller for our method in absolute values. ADALIFE demonstrated to be in better agreement with simulated True PDFF than Multi-interference.

5.3 Full-range estimation

From the first regression plot presented, it can be seen the ability of ADALIFE to estimate fat fractions over the full dynamic range. Bland-Altman plots provide a closer look in which one can see a discontinuity at 0.55 PDFF. As we mentioned before, at that fraction the major fat peaks become dominant what makes of it a problematic point also for other traditional methods such as Dixon (10) and triple-echo (12), where they start to confound water and fat. In our case it is a characteristic of the solution curve found by the MLP and should not be a problem as long as the associated deviation is acceptable. In fact, it is almost invisible in the regression plots. Repeatability, all the metrics for agreement and expected error in full range were similar to the ones obtained in half range and consequently better than by Multi-interference. ADALIFE successfully estimated fat fraction values in full range, thus breaking the paradigm that magnitude signals do not provide enough information for water-fat separation at both low and high fat ends of the PDFF spectrum.

The key explored in ADALIFE is that the dephasing between fat peaks becomes significant in the resulting signal at longer echo times and by looking how it changes the signal geometrically. For instance, by analyzing only the first three echoes in all signals from Fig. 3, one cannot easily distinguish low and high fat fractions, especially when there is added noise. While a nonlinear least squares approach tries to estimate the parameters of a reduced model of the signal in order to estimate PDFF, the proposed method models fat fraction as a direct function of changes in the signal. In fact, by consulting the matrix of weights generated by the training procedure, we noticed that the most important connections as depicted in Fig 4b are the ones between two consecutive points,

corroborating with observations in Fig. 3. We tried other combination of features such as only consecutive points, only distances, only angles, adding areas, and adding heights. The optimal combination was the one presented here. We also tried these features with other regression methods, starting with a simple decision tree (which worked loosely but was an indicator that the idea was plausible) k-nn for regression, and different combinations of hidden layers and parameters for the MLP model. In literature we found a single previous work that proposed full-range PDFF estimation using two sets of magnitude MRI obtained with different flip angles (13), a technique with limited implementation as it requires a nontraditional acquisition. What we propose here relies on a standard protocol available at any clinical site and post processing that can be easily implemented off-line with open-source software, such as the one developed by our team to analyze liver MR images and test estimation methods, Livertool (41). The presented results will be validated using *in vivo* imaging in a future work.

5.4 Limitations of this study and future perspective

The limitations of the liver fat model we used are in the sense that there is not much information about each fat moiety $T2^*$ values at different MR fields, especially the ones less prominent in human liver. These characterization studies are rather complex as they require large groups of volunteers. For the same reason we were not able to compare ADALIFE to models for full-range PDFF estimation based on complex signal rather than magnitude, as a realistic simulation of those would require even more biological parameters that have not been fully characterized in literature. A current limitation of ADALIFE is the need of seven echoes due to the late expression of phase accumulation of fat, although we believe this task can be performed with even less information. Future works should investigate a minimum number of echoes and improved robustness to noise. Also, ADALIFE estimates PDFF as a function of the geometrical characteristics of the signal, whereas the other methods first estimate tissue parameters that can be used for other calculations, including fat fraction. Nevertheless, we believe that the same principles behind ADALIFE should allow the regression of parameters other than PDFF, given adjustments on the training set. An example of application is the regression of $T2^*$ values, which is commonly used for calculation of liver iron content. As high resolution spectroscopy advances and maps the spectrum of other tissues in the human body, the proposed method can be extended for peripheral or visceral fat estimation, or musculoskeletal applications such as fatty degeneration. These tasks usually involve tissue segmentation, for which we have already developed a solution for fatty tissues based on fuzzy logic (42).

6 CONCLUSION

ADALIFE is a relatively simple approach to the open problem of full-range fat estimation using a classic neural network model. We demonstrated how shape features of a MR signal of the liver can be used to train an artificial neural network and estimate fat fraction without additional acquisition techniques. We verified that simulations can appropriately be used to reproduce the magnitude MR imaging signals from hepatic tissue and estimation methods. ADALIFE had its performance compared to Multi-interference, a state-of-the-art method for PDFF estimation and showed better repeatability and agreement in half range of operation at every tested SNR. Finally, in full-range estimation, our method presented similar results compared to when performing in half-range, already better than Multi-interference. We conclude that magnitude MR images do carry the information needed to separate water and fat at any PDFF as long as longer echo times and the right techniques are used to explore the late dephasing of the magnetizations. Future works aim at *in-vivo* validation, improving robustness to noise, expanding applications to other fatty tissues, and considering current tendencies in machine learning that have recently found applications in the field of medical imaging analysis.

REFERENCES

- 1 YOUNOSSI, Z. M. et al. Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes. **Hepatology**, v. 64, n. 1, p. 73–84, 7 2016. ISSN 15273350. Disponível em: <<http://www.ncbi.nlm.nih.gov/pubmed/26707365><http://doi.wiley.com/10.1002/hep.28431>>.
- 2 LE, M. H. et al. Prevalence of non-Alcoholic fatty liver disease and risk factors for advanced fibrosis and mortality in the United States. **PLoS ONE**, Public Library of Science, v. 12, n. 3, p. e0173499, 2017. ISSN 19326203. Disponível em: <<http://www.ncbi.nlm.nih.gov/pubmed/28346543><http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC5367688>>.
- 3 HERNANDO, D. et al. Multisite, multivendor validation of the accuracy and reproducibility of proton-density fat-fraction quantification at 1.5T and 3T using a fat-water phantom. **Magnetic Resonance in Medicine**, Wiley-Blackwell, v. 77, n. 4, p. 1516–1524, 4 2017. ISSN 07403194. Disponível em: <<http://doi.wiley.com/10.1002/mrm.26228>>.
- 4 HAYASHI, T. et al. Multicenter, multivendor phantom study to validate proton density fat fraction and T2* values calculated using vendor-provided 6-point DIXON methods. **Clinical Imaging**, Elsevier, v. 51, p. 38–42, 9 2018. ISSN 18734499. Disponível em: <<https://www.sciencedirect.com/science/article/pii/S0899707118300135?via%3Dihub>>.
- 5 PARENTE, D. B. et al. Is MR spectroscopy really the best MR-based method for the evaluation of fatty liver in diabetic patients in clinical practice? **PloS one**, v. 9, n. 11, p. e112574, 1 2014. ISSN 1932-6203. Disponível em: <<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4245094&tool=pmcentrez&rendertype=abstract>>.
- 6 KANG, B.-k. et al. Feasibility of modified Dixon MRI techniques for hepatic fat quantification in hepatic disorders: validation with MRS and histology. **The British Journal of Radiology**, The British Institute of Radiology., p. 20170378, 10 2017. ISSN 0007-1285. Disponível em: <<http://www.birpublications.org/doi/10.1259/bjr.20170378>>.
- 7 HERNANDO, D. et al. Addressing phase errors in fat-water imaging using a mixed magnitude/complex fitting method. **Magnetic resonance in medicine**, Wiley-Blackwell, v. 67, n. 3, p. 638–44, 3 2012. ISSN 1522-2594. Disponível em: <<http://doi.wiley.com/10.1002/mrm.23044><http://www.ncbi.nlm.nih.gov/pubmed/21713978><http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3525711><http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3525711&tool=pmcentrez&rendertype=abstract>>.
- 8 KÜHN, J.-P. et al. Quantitative chemical shift-encoded MRI is an accurate method to quantify hepatic steatosis. **Journal of magnetic resonance imaging : JMRI**, Wiley-Blackwell, v. 39, n. 6, p. 1494–501, 6 2014. ISSN 1522-2586. Disponível em: <<http://doi.wiley.com/10.1002/jmri.24289><http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4276715&tool=pmcentrez&rendertype=abstract><http://www.ncbi.nlm.nih.gov/pubmed/24123655><http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4276715>>.

-
- 9 HERNANDO, D.; LIANG, Z.-P.; KELLMAN, P. Chemical shift-based water/fat separation: A comparison of signal models. **Magnetic Resonance in Medicine**, NIH Public Access, v. 64, n. 3, p. 811–822, 9 2010. ISSN 07403194. Disponível em: <<http://www.ncbi.nlm.nih.gov/pubmed/20593375><http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC2992842><http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2992842&tool=pmcentrez&rendertype=abstract><http://doi.wiley.com/10.1002/mrm.22455>>.
- 10 DIXON, W. T. Simple proton spectroscopic imaging. **Radiology**, v. 153, n. 1, p. 189–194, 10 1984. ISSN 0033-8419. Disponível em: <<http://pubs.rsna.org/doi/10.1148/radiology.153.1.6089263>>.
- 11 REEDER, S. B. et al. Quantitative assessment of liver fat with magnetic resonance imaging and spectroscopy. **Journal of Magnetic Resonance Imaging**, Wiley Subscription Services, Inc., A Wiley Company, v. 34, n. 4, p. spcone–spcone, 10 2011. ISSN 10531807. Disponível em: <<http://doi.wiley.com/10.1002/jmri.22775><http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3177109&tool=pmcentrez&rendertype=abstract><http://www.ncbi.nlm.nih.gov/pubmed/22025886><http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3177109>>.
- 12 BYDDER, M. et al. Relaxation effects in the quantification of fat using gradient echo imaging. **Magnetic Resonance Imaging**, v. 26, n. 3, p. 347–359, 4 2008. ISSN 0730725X. Disponível em: <<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2386876&tool=pmcentrez&rendertype=abstract>>.
- 13 HUSSAIN, H. K. et al. Hepatic fat fraction: MR imaging for quantitative measurement and display—early experience. **Radiology**, v. 237, n. 3, p. 1048–55, 12 2005. ISSN 0033-8419. Disponível em: <<http://www.ncbi.nlm.nih.gov/pubmed/16237138>>.
- 14 MA, D. et al. Magnetic resonance fingerprinting. **Nature**, Nature Publishing Group, v. 495, n. 7440, p. 187–192, 3 2013. ISSN 0028-0836. Disponível em: <<http://www.nature.com/articles/nature11971>>.
- 15 MCGIVNEY, D. F. et al. SVD Compression for Magnetic Resonance Fingerprinting in the Time Domain. **IEEE Transactions on Medical Imaging**, v. 33, n. 12, p. 2311–2322, 12 2014. ISSN 0278-0062. Disponível em: <<http://ieeexplore.ieee.org/lpdocs/epic03/wrapper.htm?arnumber=6851901>>.
- 16 VIRTUE, P.; YU, S. X.; LUSTIG, M. Better than real: Complex-valued neural nets for MRI fingerprinting. In: **2017 IEEE International Conference on Image Processing (ICIP)**. IEEE, 2017. p. 3953–3957. ISBN 978-1-5090-2175-8. ISSN 15224880. Disponível em: <<http://arxiv.org/abs/1707.00070><http://ieeexplore.ieee.org/document/8297024/>>.
- 17 COHEN, O.; ZHU, B.; ROSEN, M. S. **MR fingerprinting deep reconstruction network (DRONE)**. Wiley-Blackwell, 2018. Disponível em: <<http://doi.wiley.com/10.1002/mrm.27198>>.
- 18 DAMADIAN, R.; GOLDSMITH, M.; MINKOFF, L. NMR in cancer: XVI. FONAR image of the live human body. **Physiological chemistry and physics**, v. 9, n. 1, p. 97–100, 1977. ISSN 0031-9325. Disponível em: <<http://www.ncbi.nlm.nih.gov/pubmed/909957>>.

-
- 19 LAUTERBUR, P. C. Image Formation by Induced Local Interactions: Examples Employing Nuclear Magnetic Resonance. **Nature**, Nature Publishing Group, v. 242, n. 5394, p. 190–191, 3 1973. ISSN 0028-0836. Disponível em: <http://www.nature.com/doi/10.1038/242190a0>.
- 20 MANSFIELD, P.; P. Multi-planar image formation using NMR spin echoes. **Journal of Physics C: Solid State Physics**, v. 10, n. 3, p. L55–L58, 2 1977. ISSN 0022-3719. Disponível em: <http://stacks.iop.org/0022-3719/10/i=3/a=004?key=crossref.f48893f3d8bf21cb4a102c6293b5ce83>.
- 21 LIU, C. Y. et al. Fat quantification with IDEAL gradient echo imaging: Correction of bias from T1 and noise. **Magnetic Resonance in Medicine**, Wiley-Blackwell, v. 58, n. 2, p. 354–364, 8 2007. ISSN 07403194. Disponível em: <http://doi.wiley.com/10.1002/mrm.21301>.
- 22 HAMILTON, G. et al. In vivo characterization of the liver fat 1H MR spectrum. **NMR in biomedicine**, v. 24, n. 7, p. 784–90, 8 2011. ISSN 1099-1492. Disponível em: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3860876&tool=pmcentrez&rendertype=abstract>.
- 23 GUIU, B. et al. Quantification of Liver Fat Content: Comparison of Triple-Echo Chemical Shift Gradient-Echo Imaging and in Vivo Proton MR Spectroscopy. **Radiology**, Radiological Society of North America, v. 250, n. 1, p. 95–102, 1 2009. ISSN 0033-8419. Disponível em: <http://pubs.rsna.org/doi/10.1148/radiol.2493080217>.
- 24 LONGO, R. et al. Proton MR spectroscopy in quantitative in vivo determination of fat content in human liver steatosis. **Journal of Magnetic Resonance Imaging**, Wiley-Blackwell, v. 5, n. 3, p. 281–285, 5 1995. ISSN 15222586. Disponível em: <http://doi.wiley.com/10.1002/jmri.1880050311>.
- 25 YOKOO, T. et al. Nonalcoholic fatty liver disease: diagnostic and fat-grading accuracy of low-flip-angle multiecho gradient-recalled-echo MR imaging at 1.5 T. **Radiology**, v. 251, n. 1, p. 67–76, 5 2009. ISSN 1527-1315. Disponível em: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2663579&tool=pmcentrez&rendertype=abstract>.
- 26 FLORES, G. et al. Evaluation of Fitting Parameters for Fat Fraction Estimation with MRI. In: **Anais do SIIM/SPS 2017**. Sao Bernardo do Campo: [s.n.], 2017. p. 170. Disponível em: <http://eventos.ufabc.edu.br/siimsps/anais.html>.
- 27 SZCZEPANIAK, L. S. et al. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. **American journal of physiology. Endocrinology and metabolism**, American Physiological Society, v. 288, n. 2, p. 462–8, 2 2005. ISSN 0193-1849. Disponível em: <http://www.physiology.org/doi/10.1152/ajpendo.00064.2004http://ajpendo.physiology.org/cgi/doi/10.1152/ajpendo.00064.2004http://www.ncbi.nlm.nih.gov/pubmed/15339742>.
- 28 COSTA, Y. et al. Full-range hepatic fat fraction estimation by using magnitude MRI. In: **Book of abstracts of the World Congress on Medical Physics and Biomedical Engineering 2018**. Prague: IOMP/IFMBE, 2018. p. 337–338. Disponível em: <http://www.iupesm2018.org/>.

- 29 _____. Noise effects in hepatic fat fraction estimation methods by using magnitude MRI. In: **Book of abstracts of the World Congress on Medical Physics and Biomedical Engineering 2018**. Prague: IOMP/IFMBE, 2018. p. 338–339.
- 30 GUIU, B. et al. Mapping of liver fat with triple-echo gradient echo imaging: validation against 3.0-T proton MR spectroscopy. **European radiology**, Springer-Verlag, v. 19, n. 7, p. 1786–93, 7 2009. ISSN 1432-1084. Disponível em: <http://link.springer.com/10.1007/s00330-009-1330-9><http://www.ncbi.nlm.nih.gov/pubmed/19247667>.
- 31 GUDBJARTSSON, H.; PATZ, S. The rician distribution of noisy mri data. **Magnetic Resonance in Medicine**, Wiley Subscription Services, Inc., A Wiley Company, v. 34, n. 6, p. 910–914, 12 1995. ISSN 07403194. Disponível em: <http://doi.wiley.com/10.1002/mrm.1910340618>.
- 32 YOKOO, T. et al. Quantitative R2* MRI of the liver with rician noise models for evaluation of hepatic iron overload: Simulation, phantom, and early clinical experience. **Journal of magnetic resonance imaging : JMRI**, v. 42, n. 6, p. 1544–59, 12 2015. ISSN 1522-2586. Disponível em: <http://doi.wiley.com/10.1002/jmri.24948><http://www.ncbi.nlm.nih.gov/pubmed/25996989>.
- 33 WEN, Z. et al. Noise considerations of three-point water-fat separation imaging methods. **Medical Physics**, American Association of Physicists in Medicine, v. 35, n. 8, p. 3597–3606, 8 2008. ISSN 00942405. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/18777920><http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC2673650>.
- 34 KINGMA, D. P.; BA, J. Adam: A Method for Stochastic Optimization. **Journal of neuroscience methods**, v. 148, n. 2, p. 167–76, 12 2014. ISSN 0165-0270. Disponível em: <http://arxiv.org/abs/1412.6980><http://linkinghub.elsevier.com/retrieve/pii/S0167865517300995><http://www.ncbi.nlm.nih.gov/pubmed/16023730>.
- 35 BLAND, J. M.; ALTMAN, D. G. Statistical methods for assessing agreement between two methods of clinical measurement. **The Lancet**, v. 327, n. 8476, p. 307–310, 2 1986. ISSN 01406736. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/2868172>.
- 36 LIN, L. I.-K. A Concordance Correlation Coefficient to Evaluate Reproducibility. **Biometrics**, International Biometric Society, v. 45, n. 1, p. 255, 3 1989. ISSN 0006341X. Disponível em: <https://www.jstor.org/stable/2532051?origin=crossref><http://www.jstor.org/stable/2532051?origin=crossref>.
- 37 KROUWER, J. S. **Why Bland-Altman plots should use X, not (Y + X)/2 when X is a reference method**. Wiley-Blackwell, 2008. 778–780 p. Disponível em: <http://doi.wiley.com/10.1002/sim.3086>.
- 38 BI J.; BENNETT, K. Regression Error Characteristic Curves. **Proceedings of the Twentieth International Conference on Machine Learning (ICML-2003)**, p. 43–50, 2003. ISSN 1577351894. Disponível em: <http://www.aaai.org/Papers/ICML/2003/ICML03-009.pdf>.
- 39 YOKOO, T. et al. Estimation of hepatic proton-density fat fraction by using MR imaging at 3.0 T. **Radiology**, v. 258, n. 3, p. 749–59, 3 2011. ISSN 1527-1315. Disponível em: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3042639&tool=pmcentrez&rendertype=abstract>.

- 40 SZCZEPANIAK, L. S. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. **AJP: Endocrinology and Metabolism**, American Physiological Society, v. 288, n. 2, p. E462–E468, 2 2005. ISSN 0193-1849. Disponível em: <<http://www.physiology.org/doi/10.1152/ajpendo.00064.2004><http://ajpendo.physiology.org/cgi/doi/10.1152/ajpendo.00064.2004>>.
- 41 COSTA, Y. et al. Livertool: an Open-source Tool for Liver Fat Fraction Estimation with Magnetic Resonance Images. In: **Anais do SIIM/SPS 2017**. Sao Bernardo do Campo: [s.n.], 2017. p. 162. Disponível em: <<http://eventos.ufabc.edu.br/siimsp/s/anais.html>>.
- 42 _____. Segmentation of Hepatic Tissue in MRI Using Fuzzy Logic. In: **Anais do SIIM/SPS 2017**. Sao Bernardo do Campo: [s.n.], 2017. p. 163. Disponível em: <<http://eventos.ufabc.edu.br/siimsp/s/anais.html>>.