Fat fraction mapping using bSSFP Signal Profile Asymmetries for Robust multi-Compartment Quantification (SPARCQ)

Giulia MC Rossi¹, Tom Hilbert¹,²,³, Adele LC Mackowiak¹, Katarzyna Pierzchała⁴, Tobias Kober¹,²,³, Jessica AM Bastiaansen¹

¹Department of Diagnostic and Interventional Radiology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
²Advanced Clinical Imaging Technology, Siemens Healthcare AG, Lausanne, Switzerland
³LTS5, École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland
⁴Laboratory of Functional and Metabolic Imaging, Swiss Federal Institute of Technology, Lausanne, Switzerland

To whom correspondence should be addressed: Jessica AM Bastiaansen, Department of Radiology, University Hospital Lausanne (CHUV), Rue de Bugnon 46, BH 08.74, 1011 Lausanne, Switzerland, Phone: +41-21-3147516, Email: jbastiaansen.mri@gmail.com, twitter: @jessica_b_

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ABSTRACT (250/250 words)

Purpose: To develop a novel quantitative method for detection of different tissue compartments based on bSSFP signal profile asymmetries (SPARCQ) and to provide a validation and proof-of-concept for voxel-wise water-fat separation and fat fraction mapping.

Methods: The SPARCQ framework uses phase-cycled bSSFP acquisitions to obtain bSSFP signal profiles. For each voxel, the profile is decomposed into a weighted sum of simulated profiles with specific off-resonance and relaxation time ratios. From the obtained set of weights, voxel-wise estimations of the fractions of the different components and their equilibrium magnetization are extracted. For the entire image volume, component-specific quantitative maps as well as banding-artifact-free images are generated. A SPARCQ proof-of-concept was provided for water-fat separation and fat fraction mapping. Noise robustness was assessed using simulations. A dedicated water-fat phantom was used to validate fat fractions estimated with SPARCQ against gold-standard ¹H MRS. Quantitative maps were obtained in knees of six healthy volunteers, and SPARCQ repeatability was evaluated in scan rescan experiments.

Results: Simulations showed that fat fraction estimations are accurate and robust for signal-to-noise ratios above 20. Phantom experiments showed good agreement between SPARCQ and gold-standard (GS) fat fractions ($f_F^{\text{SPARCQ}} = 1.02*f_F^{\text{GS}} + 0.00235$). In volunteers, quantitative maps and banding-artifact-free water-fat-separated images obtained with SPARCQ demonstrated the expected contrast between fatty and non-fatty tissues. The coefficient of repeatability of SPARCQ fat fraction was 0.0512.
**Conclusion:** The SPARCQ framework was proposed as a novel quantitative mapping technique for detecting different tissue compartments, and its potential was demonstrated for quantitative water-fat separation.

**Keywords (3 to 10 keywords):** Water-fat separation, phase-cycling, bSSFP, quantitative MRI, 3T MRI, fat fraction
INTRODUCTION

Balanced Steady-State Free Precession (bSSFP) sequences provide high signal-to-noise ratio (SNR) and image contrast in relatively short scan times. However, two main challenges are currently limiting the clinical applicability of bSSFP acquisitions. First, tissue compartments that contain fat often appear bright due to the mixed T₁/T₂ signal weighting in bSSFP and may hinder the visualization of anatomical structures. Second, the bSSFP signal is sensitive to variations in the resonance frequency, either due to magnetic field inhomogeneities or chemical shift. This sensitivity is severe for frequencies around 1/TR and may cause signal nulling in the images known as banding artifacts. The sensitivity of the bSSFP signal to both the T₁/T₂ ratio and the resonance frequency is well reflected in bSSFP signal profiles, i.e. the steady-state transverse magnetization over a range of frequencies. bSSFP signal profiles were shown to have different shapes depending on the underlying tissue composition. Furthermore, it was reported that asymmetries in these bSSFP signal profiles indicate the presence of multiple tissue components (e.g. different types of tissue) within voxels. Such asymmetries were so far observed in gray matter, white matter and muscle. These observations suggest the potential of bSSFP acquisitions to separate and quantify tissue components.

For instance, water and fat are characterized by different resonance frequencies with a chemical shift difference of Δσ=3.5ppm and have different relaxation time ratios, pointing to a possible suitability of bSSFP sequences for water-fat separation and fat fraction mapping. The separation of fat from the water signal, or even the quantification of water and fat fractions within tissue compartments, would solve the problem of the brightness of the fat signal in bSSFP acquisitions and may benefit a multitude of clinical applications. For example, hepatic steatosis is characterized by abnormal accumulation of lipids within hepatocytes, and fatty infiltration in myocardium has been...
shown to be associated with heart failure\textsuperscript{10}. Patients with heart failure but preserved left ventricular ejection fraction\textsuperscript{11} represent about 50\% of heart failure cases\textsuperscript{12,13}. Fat quantification in bone marrow is increasingly used as a tool for evaluating the relationship between osteoporosis and bone marrow adiposity\textsuperscript{14,15} as well as for characterizing cellularity for radiation dosimetry in cancer patients\textsuperscript{16}. The clinical gold standard for fat quantification is biopsy, which is prone to sampling errors, impacts patient comfort, and is highly invasive which limits its usage in obtaining prognostic information\textsuperscript{10}. Therefore, a noninvasive MRI technique for quantification of fat fraction would improve patient comfort by avoiding invasive biopsies. Fat quantification can be achieved by quantitative proton density fat fraction methods such as single-voxel MRS, chemical-shift-based water-fat imaging or multi-echo Dixon MRI\textsuperscript{17–21}. Recent MRI techniques that quantify a combination of parameters including fat have shown promising results\textsuperscript{22–24}, but are reportedly sensitive to magnetic field inhomogeneities.

The aim of this work was to develop a novel quantitative method that exploits bSSFP Signal Profile Asymmetries for Robust multi-Compartment Quantification (SPARCQ), and to provide a validation and proof-of-concept for voxel-wise water-fat separation and fat fraction mapping.
METHODS

Theory

A bSSFP acquisition is typically composed of a radiofrequency (RF) phase-cycling scheme, defining the evolution of the RF pulse phase in subsequent TRs. For a given RF-phase cycling scheme, banding artifacts might appear on the obtained bSSFP image due to local variations in resonance frequency.

Phase-cycled bSSFP consists of acquiring multiple bSSFP images with different RF phase-cycling schemes. Due to the presence of off-resonance frequencies, a change in phase-cycling schemes may cause the banding artifacts to appear in different spatial locations, and the combination of multiple bSSFP datasets (typically 2-4) can lead to a significant reduction of the artifact. However, since the combination of multiple images can modify the genuine on-resonant bSSFP contrast, these strategies are poorly suitable for quantitative imaging.

Using a phase-cycled bSSFP acquisition with smaller RF pulse phase increments allows to obtain a densely sampled bSSFP signal profile in each voxel by concatenating the complex transverse magnetization signal over the multiple acquisitions. Besides banding artifact removal, it was demonstrated that such profiles could also be used for parameter estimation, thus opening doors for quantitative applications.

SPARCQ acquisition

In order to sample the bSSFP signal profile in each voxel and detect signal asymmetries, the prototype SPARCQ acquisition (Fig. 1A) consists of multiple (N = 37) phase-cycled bSSFP acquisitions, with constant RF pulse phase increments \( \phi_i \) equidistantly distributed according to:
\[ \phi_j = \frac{2\pi}{N-1} (j-1), \quad j=1, 2, \ldots, N \]  
(Eq. 1)

For each phase cycle, k-space was acquired using a fully sampled Cartesian trajectory, with TR/TE=3.4/1.7ms, RF excitation angle \( \alpha = 35^\circ \), matrix size of 112x84, field of view of 168x224mm, an isotropic resolution of (2mm)^3 and receiver bandwidth of 930Hz/px. Total scan time was 20 minutes and 35 seconds. Magnitude and phase images of the transverse magnetization in steady-state were directly reconstructed on the scanner.

**SPARCQ reconstruction**

The SPARCQ reconstruction can be divided into five steps:

1. A complex-valued two-dimensional dictionary of simulated bSSFP signal profiles is constructed using Bloch simulations, the two dimensions being the off-resonance frequency \( df \) and the relaxation time ratio \( \Lambda (T_1/T_2) \) (Fig. 1C).
2. Complex images are computed from the acquired magnitude and phase images and a complex bSSFP profile is derived for each voxel (Fig. 1B).
3. An optimization algorithm is used to express each acquired signal profile as a weighted sum of the simulated signals in the dictionary. A weight matrix is obtained that contains information on the voxel content (Fig. 1D).
4. Distributions of \( \Lambda \) and \( df \) are obtained by projecting the weight matrix along these two dimensions (Fig. 1E).
5. Quantitative parameters (i.e. equilibrium magnetization \( M_0 \), fractions of the components of interest) are voxel-wise extracted from the obtained distributions (Fig. 1F). \( M_0 \)-weighted water-fat-separated images are obtained for each component (Fig. 1F).

All the five steps were implemented in Matlab 8.5 (MathWorks, Natick MA) and are described in more detail in the following paragraphs.
Step 1 – Construction of the dictionary

A dictionary was constructed containing a stack of complex bSSFP signal profiles that were numerically simulated. Bloch simulations were performed using a TR, TE and RF excitation angle α that match with the MRI sequence parameters. The T2 was fixed to 80ms and the T1 was varied to obtain a range of relaxation time ratios Λ from 1 to 26 in steps of 5 in the case of water and fat. Off-resonance frequencies df were chosen to cover the entire frequency range from 0 to 1/TR in 36 steps. A bSSFP signal profile was simulated for each combination of parameters (summarized in Table 1), by simulating N=37 phase-cycled bSSFP acquisitions with RF pulse phase increments φj according to (Eq. 1). For each RF pulse phase increment φi, the steady-state transverse magnetization Mxy is defined as the complex number:

\[ M_{xy}(\phi_j) = M_{ss,x} + i M_{ss,y} \quad \text{(Eq. 2)} \]

with \( M_{ss} \) being the steady-state bSSFP signal. The bSSFP signal profile (i.e. the dictionary entry for the given combination of parameters) was obtained by concatenating the complex steady-state transverse magnetizations for the N different RF pulse phases \([M_{xy}(\phi_1) \ M_{xy}(\phi_2) \ldots M_{xy}(\phi_N)]\), thus establishing a two-dimensional dictionary where each entry is an array of length N.

Step 2 - Extraction of the complex bSSFP profile

Complex images were obtained from the acquired magnitude and phase images. For each voxel, the complex bSSFP signal profile was then obtained by taking the complex values in each voxel as function of phase cycle (Fig. 1A-B).
**Step 3 – Weights optimization algorithm**

Hardware-related phase contributions (i.e. offsets between phase of the acquired bSSFP signal profiles and phase of the best fit signal) may affect the accuracy of the fit and, therefore, a preliminary phase-correction step is performed. For this step, it is assumed that only one component (i.e. only one combination of \( \Lambda \) and \( df \)) is present in the voxel, and a single compartment fitting is performed to determine the dictionary entry with the smallest distance to the acquired data. Following the fingerprinting approach\(^3\), the best fitting signal is defined as the signal in the dictionary for which the dot product between its normalized magnitude profile (i.e. the magnitude of the bSSFP signal profile as a function of the phase cycle, divided by its Euclidean norm) and the normalized magnitude profile of the acquired signal is maximal. The phase profile of the best fitting signal (i.e. the phase of the simulated bSSFP signal profile as a function of the phase cycle) is selected and the median difference with the phase profile of the acquired signal is computed. The obtained value represents a phase shift between the dictionary entry (simulated bSSFP signal profile) and the acquired bSSFP profile and is used to correct the phase of the acquired signal.

The next step is to express the acquired complex bSSFP signal profile in each voxel as a weighted sum of the complex bSSFP signal profiles in the dictionary. This allows to account for a multi-compartment composition within the voxel and to gather information on how much each dictionary entry contributes to the measured signal. To do so, a two-dimensional empty weight matrix having the same size of the dictionary is defined, where each cell in the weight matrix (Fig. 1C) represents the weighting of the corresponding entry in the dictionary (Fig. 1D). Ideally, the weight matrix should be optimized to minimize the distance between the acquired signal and the weighted sum of the dictionary signals.
Because non-negative optimization algorithms are typically not capable of handling complex numbers, the complex problem was translated into a real-valued problem by expressing both the acquired and dictionary signals as a concatenation of their real and imaginary parts, doubling the length of each signal to 2N. To further simplify the fitting, the dictionary and the weight matrix are reshaped: the two-dimensional and three-dimensional matrices are unfolded to give rise to a 2Nxk matrix for the dictionary and a kx1 vector for the weights. By naming $s_{\text{acq}}$ the 2Nx1 acquired signal, $D$ the 2Nxk reshaped dictionary and $w$ the kx1 reshaped weight matrix, the optimization problem can be mathematically described as follows:

$$\hat{w} = \arg\min_w \left( \|D \cdot w - s_{\text{acq}}\|_2^2 + \lambda \|\Delta w\|_2^2 \right) \text{ subject to } w \geq 0$$

(Eq. 3)

The squared norm ($L^2$ norm) was chosen as a distance metric and the constraint $w \geq 0$ was added to avoid negative weights that would hinder finding a biologically plausible solution. Therefore, the first term corresponds to a classical non-negative least-squares (NNLS) problem. Since the problem is ill-posed and is prone to overfitting, a second order Laplacian regularization term was added to favor smoothness between neighboring weights. The solution of the NNLS problem is the kx1 array of weights, which can be used to compute the 2Nx1 best fit signal given by the weighted sum of all the signals in the dictionary ($D \cdot w$). The final weight matrix is obtained by representing the array of weights into its original 2D shape, with relaxation time ratio and off-resonance frequencies as dimensions.

**Step 4 - Estimation of $\Lambda$ and df spectra**

The weight matrix contains information on the voxel content in terms of relaxation time ratios and the off-resonance frequencies. To visualize this information,
Step 5 – Quantitative parameter mapping and qualitative image reconstruction

The composition of a given voxel can be extracted from the obtained spectrum (i.e. distributions of weights). For a 2-component system, the fraction of one tissue component with a specific frequency range (e.g. fat) can be computed as the integral of the projected df spectrum over the frequency range assigned to it divided by the sum of the integrals over the frequency range assigned to the first and second component (Fig. 1F).

In the case of water-fat separation, the fat fractions ($f_F$) and water fractions ($f_W$) are defined as:

$$f_F = \frac{F}{F + W}$$

$$f_W = 1 - f_F$$

where $F$ and $W$ are the integrals of the off-resonance df spectrum over the frequency ranges assigned to fat and to water, respectively.

In order to take into account possible frequency shifts on the water and fat resonances due to local magnetic field inhomogeneity, the position of the water peak, i.e. the peak closer to 0 or to $1/TR$, is first determined. This value is used to correct the off-resonance effect by shifting the whole spectrum of the same amount on the off-resonance frequency axis. As a result, the water peak is centered around the on-resonant frequency for water. Then, the position of the fat peak, defined as the peak with the largest amplitude between 0 and $1/TR$, is determined. The first zero crossing between 0 and the detected fat peak is used as lower limit of integration, whereas the
last zero crossing between the detected fat peak and 1/TR is used as upper limit of integration.

In addition, an estimation of the thermal equilibrium magnetization $M_0$ for the given voxel can be obtained. $M_0$ could be estimated as a weighted sum of the $M_0$ of each dictionary entry since the weight matrix gives an estimation of the contribution of each signal in the dictionary to the acquired signal. In the present case, the signals in the dictionary were simulated for $M_0=1$. Therefore, $M_0$ for the given voxel can be simply estimated with the sum of all weights in the weight matrix.

By applying the above-described framework over the whole volume, quantitative maps of the fat fraction $f_F$, water fraction $f_W$ and equilibrium magnetization $M_0$ can be obtained (Fig. 1F).

The framework also allows to extract qualitative images of individual components that may be more easily to interpret in a clinical environment (Fig. 1F). To do this, $M_0$-weighted images for each component can be obtained by voxel-wise multiplication of the corresponding fraction maps, in the current case water or fat fraction maps, with the $M_0$ map.

**Validation of SPARCQ**

SPARCQ was applied to voxel-wise water-fat separation and fat fraction mapping. The validation was carried out by means of numerical simulations and phantom experiments at 3T and 9.4T. A scan-rescan repeatability study on human knees was performed in six healthy volunteers. All simulations, data analysis and visualization were performed in Matlab 8.5 (MathWorks, Natick MA).
Numerical simulations

Numerical simulations were performed to evaluate the accuracy of SPARCQ for fat fraction quantification and to test its robustness in presence of noise.

First, $^1$H NMR spectra were simulated that consisted of a single water peak resonating at 0Hz and two fat peaks at -485Hz and -434Hz. Each peak was modeled as a Lorentzian function with a full width half maximum (FWHM) of 20Hz according to

$$L(x) = \frac{A}{1 + x^2} \quad \text{with} \quad x = \frac{2(P - P_0)}{\text{FWHM}}$$

with $A$ the peak area, $P$ the frequency ranging from -600Hz to 200Hz with steps of 1Hz, and $P_0$ the center frequency. Table 2 provides a summary of parameters used to simulate each peak. The three peak areas were adjusted for different fat fractions ranging from 0 to 1 in steps of 0.05. Then, the three Lorentzian line shapes were summed to obtain a set of simulated $^1$H NMR water-fat spectra for different fat fractions.

Second, Bloch simulations were used to obtain bSSFP signal profiles for each frequency in the simulated $^1$H NMR spectra. To do so, simulations were performed for off-resonance frequencies ranging from -600Hz to 200Hz (in steps of 1Hz), with all other parameters being fixed ($\text{TR}=3.40\text{ms}, \text{TE}=1.7\text{ms}, \alpha=35^\circ$, $\Lambda=6\ [T_1=480\text{ms}, T_2=80\text{ms}]$). To obtain a final complex bSSFP profile for each $^1$H NMR spectrum, the simulated bSSFP profiles were weighted by the amplitude corresponding to the off-resonance frequency in the simulated $^1$H NMR water-fat spectrum and then summed.

Third, randomly generated white Gaussian noise (SNR levels ranging from 5 to 100 in steps of 2.5) was added to the imaginary and real part of each bSSFP profile.

SPARCQ was used to estimate the fat fraction in each of the generated bSSFP signal profiles. The experiment was repeated 100 times, using a different seed for the
randomly generated noise in each iteration. Mean and standard deviation of the estimation error over the 100 repetitions were calculated.

**Phantom experiments at 3T and 9.4T**

Phantom experiments were performed to evaluate the accuracy of the proposed framework to quantify fat content, and for voxel-wise water-fat separation and fat fraction mapping.

First, a dedicated fat-water phantom was created according to a validated protocol. It is composed of six 50mL Falcon tubes with different partial volumes of peanut oil (0%, 20%, 40%, 60%, 80%, 100%) immersed in a box containing 3%wt agar solution (Figure 4C). Peanut oil was chosen as fat compartment because it has similar resonance frequencies compared to triglycerides in human adipose tissue.

To quantify the final fat and water content in each Falcon tube, unlocalized 1H MRS was performed in a 9.4T MRI scanner (Magnex Scientific, Oxford, UK) with a Direct Drive spectrometer (Agilent, Palo Alto, CA, USA). The peak areas of all visible resonances were calculated by line shape fitting and integration in jMRUI4.0. Because peanut oil contains several resonance frequencies close to water that are not resolved at lower magnetic field strengths, resonance peaks between 3.5ppm and 6.0ppm were assigned to water and resonance peaks between 0ppm and 3ppm to fat. Gold-standard fat fractions were then calculated for each Falcon tube.

Additionally, whole-phantom acquisitions were performed on a clinical 3T scanner (MAGNETOM Prisma-fit, Siemens Healthcare, Erlangen, Germany) using a commercially available 18-channel body coil and the prototype phase-cycled bSSFP sequence as described in the previous section. The SPARCQ framework was then used to quantify fat fractions in manually drawn regions of interest (ROIs).
corresponding to the six vials. For comparability with unlocalized spectroscopy data, ROIs were chosen to span over five consecutive slices. To focus on accuracy of SPARCQ and not on its sensitivity to $B_0$ inhomogeneities, the five slices per vial were chosen in regions where the effect of $B_0$ inhomogeneities in the agar surrounding the vials was observed to be as small as possible. Fat fractions obtained at 3T were compared with the gold-standard fat fractions determined via unlocalized spectroscopy at 9.4T.

**Volunteer experiments**

A scan-rescan repeatability study on human knees was performed in six healthy volunteers. Volunteer experiments were performed on a clinical 3T scanner (MAGNETOM Prisma, Siemens Healthcare, Erlangen, Germany) using a commercially available 15-channel Tx/Rx knee coil (Quality Electrodynamics, Mayfield, OH, USA). The volunteers gave written and informed consent. The study was carried out according to the institutional rules.

The acquisition protocol consisted of a scan-rescan acquisition with repositioning using the proposed prototype sequence. For reference, a Dixon acquisition was performed with a standard turbo spin echo (TSE) Dixon sequence with $TR/TE=3470/100\text{ms}$, RF excitation angle $\alpha=150^\circ$, matrix size $128x80$, field of view $160x256\text{mm}$, an isotropic resolution of $(2\text{mm})^3$, receiver bandwidth $601\text{Hz/px}$ and turbo factor 18. In-phase, out-of-phase, water and fat images were reconstructed on the scanner.

Quantitative maps were obtained with SPARCQ. Spectra and estimated parameters in areas close to air-tissue interfaces (e.g. patella) were checked to evaluate the efficacy of SPARCQ in regions of strong $B_0$ inhomogeneity. A Bland-
Altman analysis was performed on the scan-rescan datasets on the mean fat fractions obtained with SPARCQ in five elliptical ROIs in five different tissues (vastus medialis, biceps femoralis, semimembranous muscles, bone marrow and subcutaneous fat). Water-fat-separated images were obtained with SPARCQ and compared with water-fat-separated images obtained with Dixon.
RESULTS

Numerical simulations

bSSFP signal profiles (Fig. 2B, only magnitude is shown) obtained from simulated $^1$H MR spectra (Fig. 2A) show a clear difference in shape when the fat fraction is changed from 0 to 1, whereas signals that have mixed water and fat show large asymmetries. The off-resonance frequency spectra (Fig. 2D) derived from the weight matrix (Fig. 2C) correlate well with the simulated $^1$H MR spectra. It should be noted that whilst the simulated $^1$H MR spectra cover a large frequency range, the spectra derived from SPARCQ are limited to the range 0-1/TR. Therefore, a wrapping of the $^1$H MR spectra can be observed. The fat resonance frequencies around -440Hz in the simulated $^1$H MR spectra are found at around 150Hz in the off-resonance frequency spectra derived from the fitting. This is reasonable, since unwrapping the phase advance accumulated in a TR of 3.4 ms for a frequency of -440Hz leads to a phase advance of 178°, corresponding to a frequency of 148Hz. In addition, it should be considered that the resolution of the dictionary and the regularization factor can influence the shape of the peaks.

Comparing the fat fractions estimated with SPARCQ (Fig. 3B) in presence of different noise levels to nominal fat fractions (Fig. 3A), allowed to evaluate the accuracy and noise robustness of the algorithm. The mean fitting error and its standard deviation over the 100 repetitions (Fig. 3C and Fig. 3D) showed that strong noise (SNR<20) leads to reduced accuracy (Fig. 3C) and precision (Fig. 3D), which is confirmed by both the higher mean and the higher standard deviation of the error over repetitions. In noisy signals (SNR<10), small fat fractions (~0.2) seem to be more accurately estimated than higher ones (~0.8). In this region, fat fractions tend to be underestimated. For higher SNR (>20) estimations gain in both accuracy and precision. Nonetheless, small underestimations (for $f_f>0.7$) or overestimations (for
0.15<\(f_F<0.7\) were observed. Low fat fractions \((f_F<0.15)\) tend to be very accurately estimated (error <1%).

**Phantom experiments at 3T and 9.4T**

Unlocalized 1H spectra acquired at 9.4T in the different Falcon tubes showed the exact content in terms of molecular composition and resonance frequencies (Fig. 4A). Due to the strong magnetic field (9.4T), all the resonances of fat are well resolved (Fig. 4A). Besides the Falcon tube containing 80% of peanut oil by volume (V80), all phantom components formed neat agar emulsions without any phase separation of water and oil. Using a frequency-based water and fat assignment, gold-standard fat fractions of 0%, 20%, 39%, 58%, 91% were found for Falcon tubes V0, V20, V40, V60, V100, respectively (Fig. 4B). Results from V80 were excluded because of the water-oil phase separation.

Fat-fraction quantification with SPARCQ at 3T in the dedicated fat phantom (Fig. 4C) showed a good agreement with gold-standard fat fractions, with a regression line 
\[ f_F(\text{SPARCQ}) = 1.02* f_F(\text{GS}) + 0.00235 \]
which testifies to good linearity and accuracy of estimations. (Fig. 4D). The higher standard deviation of fat fractions estimated in V60 is likely due to inhomogeneous distribution of water and oil, or local phase separations within the vial.

**Volunteer experiments**

All quantitative maps (Fig. 5A) and water-fat-separated images (Fig. 5B) obtained with SPARCQ demonstrated the expected contrast between fatty (bone marrow, subcutaneous fat) and non-fatty (muscles) tissues, with the exception of peripheral
regions close to the air-tissue interface (e.g. patella), where an inverted contrast was observed.

Off-resonance frequency spectra obtained from the weight matrices in fatty regions (Fig. 6A) and non-fatty regions (Fig. 6B) far from the air-tissue interface showed the expected frequency components: a narrow on-resonant peak corresponding to water, and a broader off-resonant peak corresponding to fat. Conversely, in a region close to an air tissue interface (Fig. 6C) showed a misclassification of water and fat, due to the local $B_0$ inhomogeneity and the rigid assignment of water being the peak which is closer to the resonance frequency in the current implemented algorithm.

Fat fractions in ROIs in different tissues (Fig. 7B) showed good agreement between all the subjects, with muscles showing a low fat content (3.2±0.9% vastus medialis, 7.3±2.8% biceps femoralis, 5.8±1.5% semimembranous muscles) and bone marrow and subcutaneous fat confirming their high fat content (81.7±2.4% bone marrow, 94.3±0.9% subcutaneous fat).

The Bland-Altman analysis on the fat fraction maps in the scan-rescan experiment (Fig. 7A) revealed very low bias $b=0.0074$ and a good coefficient of repeatability $CR=0.0512$.

Despite the difference in contrast in water-fat-separated images obtained with SPARCQ ($M_0$ weighting) and with Dixon (T2 weighting) (Fig. 5B), SPARCQ fat and Dixon fat images were in good agreement based on a visual assessment. In water images, hyperintensities were observed in the same structures filled with liquid.
DISCUSSION

This work presents a novel quantitative framework for detecting different tissue compartments based on bSSFP signal profile asymmetries (SPARCQ). SPARCQ estimates voxel-wise off-resonance frequency and relaxation time ratio spectra from acquired phase-cycled bSSFP signal profiles. The obtained spectra reveal the presence of multiple components and allows to quantify their individual contribution to the overall signal intensity within the same voxel. SPARCQ provides an estimation of the equilibrium magnetization $M_0$, enabling the generation of distinct $M_0$-weighted images for each component.

The SPARCQ framework was validated and a proof-of-concept was demonstrated for fat fraction mapping. SPARCQ simulations showed robustness to noise for SNR>20 when 37 phase-cycles were acquired. Since the bSSFP sequence is one of the most SNR/time-efficient sequences in MR, this robustness can be traded for acquisition speed in the future. The SNR behavior of SSFP depends only on pulse sequence efficiency, voxel dimensions and relaxation parameters. Thus, if tissues with specific relaxation parameters were to be imaged with SPARCQ, acquisition parameters can be adapted accordingly to achieve a good trade-off between image resolution and estimation accuracy.

The fat fractions estimated with SPARCQ were successfully validated against gold-standard fat fractions in phantoms, whereas volunteer experiments demonstrated the repeatability of SPARCQ. The framework provided in vivo quantitative maps with the expected contrast between fatty and non-fatty regions. The $M_0$-weighted water-fat-separated images obtained with SPARCQ compared well with those obtained with Dixon. Nonetheless, SPARCQ results showed that in some tissue regions close to air-tissue interfaces (e.g. in the patella) fat was misclassified. This was caused by the rigid
peak selection strategy applied to the frequency spectra, which assumes that the peak closest to on-resonance is water, which may fail in the presence of strong $B_0$ inhomogeneities. Making use of additional SPARCQ characteristics, such as the peak width in the frequency spectrum or the information in the $T_1/T_2$ spectrum, may aid in $B_0$ independent peak assignment and provide simultaneously an estimation of local off-resonance, which will be subject of future investigations. For example, fat can typically be identified as a broader peak in the frequency spectrum within each voxel (Fig. 6).

Using the SPARCQ framework for water-fat quantification may facilitate fat suppression in bSSFP acquisitions and may benefit various clinical applications, such as the assessment of liver steatosis\textsuperscript{9} or the prognosis of heart failure\textsuperscript{10,11}. SPARCQ may represent a noninvasive alternative to biopsy, allowing regular monitoring of the evolution of fat fractions in tissues. Because a non-interrupted sequence is required to maintain the bSSFP steady state, SPARCQ may be combined with a motion-resolved reconstruction to enable liver and cardiac imaging\textsuperscript{35}.

The voxel-wise extraction of $\Lambda$ and $df$ spectra suggests the potential of the SPARCQ framework for multi-compartment applications in which voxels are composed of different off-resonance frequencies and/or different relaxation time ratios. The proposed approach may therefore contribute to the current research on myelin mapping, which has a different chemical shift\textsuperscript{36,37}, or in the field of $T_1$ and $T_2$ mapping, especially since joint $T_1$ and $T_2$ parameter estimation has been demonstrated with phase-cycled bSSFP before\textsuperscript{8,30}. SPARCQ may enable banding-artifact-free frequency-specific quantitative maps with high SNR, with the potential to reconstruct synthetic MR images\textsuperscript{29}.
The current work was intended to be a proof-of-concept of SPARCQ, therefore the acquisition time was not minimized and a full sampling of the bSSFP profile was performed. The acquisition time (~33s/phase cycle) could be optimized by a reduction of phase cycles, parallel imaging\textsuperscript{38} or compressed sensing with regularization along phase cycles\textsuperscript{29,39–41}. The choice of TR is fundamental in preventing signals from different components to overlap when wrapping into the 1-1/TR range. Additionally, the regularization parameters and the resolution of the dictionary were manually tuned. A precise selection of those parameters may allow to obtain higher discriminability of multiple peaks in conjunction with more realistic peak shapes as compared to \textsuperscript{1}H MR spectra.

Compared with other dictionary-based approaches\textsuperscript{22–24}, approximating the signal profile as a weighted sum of multiple dictionary entries rather than the best match with a single dictionary entry that is composed of a water and a fat signal with a given fraction, T1/T2, and off-resonance frequency provides various benefits. 1) It minimizes the dimensionality of the dictionary, a 2-dimensional dictionary can be used instead of a 4-dimensional one, speeding up the processing and reducing the memory footprint of the algorithm. 2) It relies on simple signal models, where profiles are simulated for a single combination of resonance frequency and relaxation time ratio, without needing prior knowledge of the number of spectral components of water and fat. 3) It allows to obtain a more realistic representation of \textit{in vivo} situations where distributions of values are expected.

Nevertheless, the SPARCQ reconstruction is relatively slow. Improving the algorithm by exploiting joint sparsity constraints\textsuperscript{42} may help to accelerate the reconstruction and increase the robustness of the algorithm. The current framework uses a range of T1/T2 ratios to generate the dictionary by fixing the T2 and varying
T1. While this assumption was acceptable for the purpose of separating frequency components, for a correct estimation of joint T1 and T2, the T2 should also be allowed to vary. Although it is known that effects of magnetization transfer, exchange between compartments and diffusion may affect accuracy on T1/T2 estimations\textsuperscript{43,44}, they were not included in the current SPARCQ framework.

Off-resonance was encoded by the acquisition of phase-cycled bSSFP signal profiles which provided single-voxel frequency spectra, albeit of limited bandwidth, allowing for a robust detection and quantification of water and fat compartments. The current SPARCQ implementation used asymmetries in bSSFP signal readouts, but the technique could potentially be extended to other non-spoiled steady-state acquisitions such as fast-interrupted steady-state (FISS) sequences\textsuperscript{36,37}. 
CONCLUSION

The SPARCQ framework was validated as a novel quantitative method for detection of different tissue compartments within the same voxel. A proof-of-concept was provided for voxel-wise water-fat separation and fat fraction mapping. SPARCQ showed noise robustness, accuracy and repeatability corroborated by simulations, phantom and volunteer experiments.

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TABLES

| TR [ms] | TE [ms] | α [°] | M₀ [a.u.] | Λ [-] | df [Hz] | N [-] |
|---------|---------|-------|-----------|-------|---------|-------|
| 3.40    | 1.70    | 35    | 1         | 1:5:26| 0: \frac{1}{35·TR·10^{-3}}: \frac{1}{TR·10^{-3}} | 37 |

Table 1. Parameters used to construct the dictionary. A dictionary of simulated bSSFP signal profiles were constructed based on Bloch simulations. Parameter ranges are reported as minimum:stepsize:maximum.

| P₀ [Hz] | A     | FWHM [Hz] |
|---------|-------|-----------|
| Peak water | 0     | 1 - iF    | 20    |
| Peak fat 1 | - 434 | 0.8 iF    | 20    |
| Peak fat 2 | - 485 | 0.2 iF    | 20    |

Table 2. Parameters used to simulate 1H MR water fat spectra. Parameters used to generate the 1H NMR spectra are reported.
FIGURES

A: Data acquisition

B: Extraction of bSSFP signal profile

C: Dictionary construction

D: Weights optimization algorithm

E: Estimation of $\Lambda$ and $df$ spectra

F: Parametric mapping and image reconstruction

Figure 1. Overview of the SPARCQ framework. A: A phase-cycled bSSFP acquisition is performed. B: For each voxel, a complex bSSFP signal profile is obtained. C: A dictionary of simulated bSSFP signal profiles is constructed. D: The acquired complex bSSFP signal profile (B) is fitted to the dictionary (C) and a weight matrix is obtained, where each weight gives the contribution of the corresponding dictionary entry to the acquired signal. E: $\Lambda$ and $df$ spectra are obtained by projecting the weight matrix along its dimensions. F: For a 2-component system, the fraction of one component is computed as the integral over the frequency range assigned to this component ($C_1$, red background) divided by the sum of the integrals over the frequency range assigned to the first ($C_1$, red background) and second component ($C_2$, blue background). The equilibrium magnetization ($M_0$) is estimated by summing all the weights in the weight matrix. Applying the same procedure to the whole imaging
volume allows to obtain quantitative maps. $M_0$-weighted images for each component separately are obtained by multiplying the fraction maps by the $M_0$ map.
Figure 2. Simulation experiment. A: Simulated $^1$H MR spectra in the frequency range -200 to 600 Hz for fat fractions going from 0 to 1 in steps of 0.25. B: Simulated bSSFP profiles (magnitude). C: Matrices of weights. D: Off-resonance frequency spectra in the range 0 to 1/TR. The locations of water and fat peaks (C,D) are wrapped within a 1/TR frequency range.
Figure 3. Noise robustness of SPARCQ. 

A: Nominal fat fractions that were used to simulate bSSFP signal profiles. 

B: Fat fractions estimated with SPARCQ depending on the SNR for one repetition. 

C: Mean error on the fat fraction estimation (estimated-nominal) depending on the SNR for 100 repetitions. 

D: Standard deviation of the fat fraction estimation error depending on the SNR for 100 repetitions.
Figure 4. Accuracy of SPARCQ. A: $^1$H MR spectra obtained from unlocalized spectroscopy at 9.4T for three out of six tubes. B: Nominal (N) and gold-standard (GS) fat fractions in each of the six tubes are reported. GS fat fractions were obtained by integration of the $^1$H MR spectra acquired at 9.4T, resonances above 3.5 ppm were assigned to water, below 3.5 ppm to fat. C: Configuration of the phantom for the experiment at 3T. D: Fat fractions estimated with SPARCQ in each vial (mean±std over 5 consecutive slices in a ROI corresponding to the vial) versus gold-standard fat fractions at 9.4T. The unit line (black line) and the regression line (dashed red line) are also reported. * V80 was excluded because of the water-oil phase separation.
Figure 5. Quantitative maps and water-fat-separated images. Example images of one volunteer. A: Quantitative maps obtained with SPARCQ in an axial, sagittal and coronal view. B: M0-weighted water-fat-separated images obtained with SPARCQ and T2-weighted water-fat-separated images obtained with TSE Dixon (TR/TE =
3470/100 ms, resolution (2mm)³, receiver bandwidth 601 Hz/px, turbo factor 18; in-phase, out-of-phase, water and fat images were reconstructed on the scanner).

Figure 6. Example of fitting results in three voxels belonging to different tissues. Acquired bSSFP signal profile (left), optimized matrix of weights (middle) and off-resonance frequency spectrum (right) for a voxel belonging to fatty (bone marrow, A), non-fatty (muscle, B) tissue and a voxel close to the air-tissue interface (patella, C). The df spectrum (right) is obtained by projecting the matrix of weights (middle) onto the df axis (SOW: sum of weights). The selected ranges of tissue-specific frequencies are marked blue (fat) and red (water). In bone marrow (A), multiple frequency components are detected (on-resonant water, off-resonant fat). In muscle (B), a single frequency component (on-resonant water) is detected. Close to the air-tissue interface (C), the fat peak is wrongly assigned to water.
Figure 7. Scan-rescan repeatability of the fat fractions estimated with SPARCQ. A: Bland-Altman analysis of scan-rescan repeatability in 6 volunteers (1 volunteer = 1 color) for 5 regions of interest (1 marker type = 1 region). Limits of agreement: LOA = 0.0074 ± 1.96*0.0574. Coefficient of repeatability: CR = 0.0512.

B: Fat fractions in different tissues (mean±std over the 6 subjects) for scan and rescan.

BM: bone marrow, VM: vastus medialis, BF: biceps femoralis, SM: semimembranous muscle, SCF: subcutaneous fat.