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Review article

What are normal relaxation times of tissues at 3 T?

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ABSTRACT

The T_1 and T_2 relaxation times are the basic parameters behind magnetic resonance imaging. The accurate knowledge of the T_1 and T_2 values of tissues allows to perform quantitative imaging and to develop and optimize magnetic resonance sequences. A vast extent of methods and sequences has been developed to calculate the T_1 and T_2 relaxation times of different tissues in diverse centers. Surprisingly, a wide range of values has been reported for similar tissues (e.g. T_1 of white matter from 699 to 1735 ms and T_2 of fat from 41 to 371 ms), and the true values that represent each specific tissue are still unclear, which have deterred their common use in clinical diagnostic imaging. This article presents a comprehensive review of the reported relaxation times in the literature in vivo at 3 T for a large span of tissues. It gives a detailed analysis of the different methods and sequences used to calculate the relaxation times, and it explains the reasons of the spread of reported relaxation times values in the literature.

1. Introduction

The T_1 and T_2 relaxation times are the basic parameters behind magnetic resonance imaging (MRI). Consequently, an enormous research effort has gone into developing and validating measurement methods, and into collecting values of relaxation times for a wide range of tissues (e.g. musculoskeletal, abdominal, pelvic tissue and brain) at different magnetic fields [1]. Thus accurate knowledge of the tissue relaxation times is the corner stone for the development and optimization of MR sequences [2].

Additionally, the tissue relaxation times offer the possibility of computing pure T_1 and T_2 relaxation maps where the contrast is due solely to T_1 or T_2, respectively. These relaxation maps allow to perform quantitative imaging such as contrast agent uptake and to evaluate iron overload, and blood perfusion and volume, which is unlikely in conventional qualitative T_1 and T_2 weighted imaging. In T_1 and T_2 weighted images, the observed image contrast not only is related to differences in T_1 or T_2 relaxation times, but also is due to the influence of a myriad extraneous and intrinsic factors, for example, the radio frequency (RF) field, the coil receive sensitivity, proton density, and gain effects [3–5]. Since the relaxation times do not depend on these factors, they provide a more reliable marker of tissue state [4], a valuable property to the assessment of tissue pathology [6]. Further, if tissues possess specific relaxation times values, they could be segmented and classified according to these values.

However, the broad extent of reported values often contradicts one another, possibly because of inconsistent and different measurement methods, use of distinct sequences and differences in hardware [7]. For example, reported T_1 values for white matter range from 699 to 1735 ms at 3 T. Furthermore, even the reported values measured with the so-called Inversion Recovery (IR) gold standard disagree. This puts in question the accuracy of the most fundamental measurements in quantitative MRI.

In this article, we review the different methodologies used to compute the T_1 and T_2 relaxation times. We restrict our review to studies working at 3 T (relaxation times vary according to the magnetic field), reporting values in in vivo for healthy volunteers or healthy tissues (relaxation times change with respect to pathology) and using in-house/open software to compute the relaxation times (studies using the proprietary software of the scanner cannot be reproduced because the process is a black box for the user). These restrictions provide a sort of framework to compare the reported relaxation times. We considered only studies from year 2000 to date, since the last rather general review of the methods to compute T_1 relaxation times was from 1999 [8]. However, the previous review does not describe methods to compute T_2 relaxation times and does not have a compilation of reported T_1 values.

In some cases the relaxation times were not the main focus of the studies, but a method was used to compute the T_1 or T_2 relaxation times (e.g. studies focus on the correction on B_1 field inhomogeneities [9]), but the studies fulfill the above restrictions.

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2. T_1 relaxation time

2.1. Theory

The T_1 relaxation time (longitudinal magnetization) in the absence of any RF field or other factors (e.g. magnetization transfer) is defined by the Bloch equation:

$$\frac{\delta M_z(t)}{d\delta} = \frac{M_o + M_z(t)}{T_1} \tag{1}$$

This describes an exponential approach of the longitudinal magnetization (M_z) from some starting value to the equilibrium value (M_o) that is caused by the fluctuating magnetic field arising largely from the motion of molecules in the neighborhood of the magnetic moments (spin–lattice) [10]. After applying a flip angle pulse (θ) the solution becomes:

$$M_z(t) = M_o + \left(M_z\left(0^+\right) - M_o\right)e^{-t/T_1};\quad M_z\left(0^+\right) = M_z(0^-)\,cos(\theta) \tag{2}$$

Where, $M_z(0^+)$ and $M_z(0^-)$ are the values of M_z just before (time 0^-) and after (time 0^+) application of the pulse. For repeated application of the pulse at TR (Repetition time), the net magnetization is:

$$M_z(TR) = M_z(0^-) \tag{3}$$

and the steady solution to Eq. (3) for $M_z(0^-)$ is:

$$M_z(0^-) = M_o\frac{1-e^{-TR/T_1}}{1-cos(\theta)e^{-TR/T_1}} \tag{4}$$

The signal is proportional to the transverse magnetization (M_{xy}):

$$M_{xy}(t) = M_o\frac{1-e^{-TR/T_1}}{1-cos(\theta)e^{-TR/T_1}}\,sin(\theta) \tag{5}$$

2.2. Methods

There are different approaches and sequences for measuring T_1: partial saturation recovery, spoiled gradient echo, inversion recovery and specialist methods [11].

2.3. Partial saturation recovery

Partial saturation recovery operates with a TR sufficiently short that full T_1 relaxation is not achieved. The basic sequence starts with a 90° pulse and waits for a short TR period, and then repeated 90° pulses are applied. The state of partial saturation (constant magnetization) is achieved at the end of the pulse sequence when TR << T_1. The experiment is repeated for several different TRs in order to measure T_1. In partial saturation recovery, the signal is governed by Eq. (6) (solution of Eq. (5)).

$$M_{TR} = M_o\left(1-e^{-TR/T_1}\right)e^{-TE/T_2} \tag{6}$$

The factor e^{-TE/T_2} is approximately one, if the sequence echo time (TE) is much smaller than the expected T_2 value of the imaged tissue. Then, Eq. (6) changes to Eq. (7).

$$M_{xy}(t) = M_o\left(1-e^{-TR/T_1}\right) \tag{7}$$

If data are only acquired for two different TRs (a two point method), a look-up table of the expected ratio of the signals can be used to estimate T_1 [10]. Otherwise, for several TRs Eq. (7) must be fitted to the resulting measured signals [11].

Fennessy et al. [12] applied a 2D fast spin echo (FSE) sequence at multiple TR values to measure the T_1 relaxation of normal prostate tissue (1434±295 ms). The TR values range from 50 to 6000 ms. The received signal was assumed to follow Eq. (6) and fitted to it. In order to diminish the acquisition time, an optimized subset of three TRs (500, 1500 and 1600 ms) from the six TRs was chosen to compute the T_1 values of the prostate (1400±278 ms). No significant difference between the reported T_1 values of the three-TR and the six-TR calculations was found.

2.4. Spoiled gradient echo

Spoiled gradient echo (SPGR) consists in the active destruction of transverse magnetization by applying gradients at the end of the sequence. Assuming a longitudinal steady-state and perfect spoiling, the signal is given by Eq. (5), and effects of T_2^* are neglected due to small TE. As in partial saturation recovery, the T_1 value can be obtained using two variable flip angles (VFAs) and looking for the ratio of signal in a look-up table. For acquisition of more than two VFAs, the signal intensities must be fitted to Eq. (5).

Fennessy et al. [12] measured the T_1 values of prostate using a 3D SPGR sequence with special spectral fat suppression at different flip angles. The imperfections of the flip angles were corrected by firstly fitting the received signal to Eq. (5) for muscle's regions of interest (ROIs). In this fit, the flip angle was set as a variable and a constant muscle's T_1 value was assumed (1420 ms [13]). Secondly, the found flip angle (corrected) from the previous fit was also assumed to be the same for prostate tissue. Finally, a new fit to Eq. (5) was performed to find the T_1 of prostate (1530±498 ms).

2.5. Inversion recovery

The inversion recovery method (IR) is considered to be the method of choice for determining T_1 relaxation times, because of the larger dynamic range of the magnetic resonance signal. The universal IR sequence is one with 2 repeated pulses of flip angle (FA) = θ_1 and θ_2 separated by an inversion time (TI): [θ_1, TI, θ_2, (TR-TI)] repeated n times (number of phase encodings) [11].

The value of M_z just before θ_2 determines the signal:

$$M_z(\theta_2) = M_o\frac{1-(1-cos\theta_1)e^{-TI/T_1} - cos\theta_1 e^{-TR/T_1}}{1-cos\theta_1\,cos\theta_2 e^{TR/T_1}} \tag{8}$$

If the FAs are set to 90°(θ_1) and 180°(θ_2), Eq. (8) becomes:

$$M_z(\theta_2) = M_o\left(1-2e^{-TI/T_1} - e^{-TR/T_1}\right) \tag{9}$$

However, if the TR is sufficiently long (>5 T_1 of the tissue with the longest T_1), a sufficient longitudinal relaxation of the protons is assured before the next excitation [14] and the magnetization signal is governed by:

$$M_z(\theta_2) = M_o\left(1-2e^{-TI/T_1}\right) \tag{10}$$

On the other hand, by adjusting the TI while keeping θ_1, θ_2 and TR fixed after setting arbitrary flip angles (θ_1, θ_2), the signal takes the following form:

$$M_z(\theta_2) = A + Be^{-TI/T_1} \tag{11}$$

where A and B constants depend on θ_1, θ_2 and TR.

Different authors have implemented this methodology to compute the T_1 values of different tissues.

Rakow-Penner et al. [7] computed the T_1 relaxation time of adipose and fibroglandular tissues using an FSE-IR and an FSE-IR IDEAL (Iterative Decomposition of Water and Fat) sequences in six volunteers with identical sequence parameters. The FSE-IR IDEAL sequence advantages are that it produces three different images: 1) mixed water–fat image, 2) fat image (without water component in fat) and 3) water image (without lipid component in glandular tissue) using three different echo times; and accounts for partial volume effects because of the fat–water decomposition. Eq. (12) was fitted to obtain T_1, where M_i corresponds to the received signal at the four different TIs_i.

$$M_i = M_o\left(1-2(1+\epsilon)e^{\frac{-TI_i}{T_1}}\right) \tag{12}$$

The error term ϵ accounts for imperfect magnetization inversion by the 180° pulse. M resulted from an average of three regions of interest (ROIs) drawn in the fat and fibroglandular region for each TI value per volunteer. The FSE-IR IDEAL is robust to B_o inhomogeneities, since a map of the field strength is calculated as part of the reconstruction. The difference in reported values of the FSE-IR IDEAL (fat =366±78 ms, fibroglandular =1445±93 ms) and FSE-TI (fat =450±26 ms, fibroglandular =1324±168 ms) methods are due to the fat–water IDEAL separation. The fat image provides only the T_1 values of fat, and the water image provides only those of the water component of fibroglandular tissue.

Bojorquez et al. [15] also computed the T_1 values of different tissues at the level of the pelvis (fat, muscle, prostate) by fitting the signal intensity to Eq. (12). The acquisition was performed in three volunteers using an IR-TSE (Turbo Spin Echo) sequence with nine TI values, optimally spaced. The purpose of the study was to segment and classify the different tissues according to the relaxation times.

To cope with the long acquisition time of the IR method, De Bazelaire et al. [16] implemented a Single Shot FSE-IR using six TI values to compute the T_1 relaxation times of fat, bone marrow, pancreas, liver, paravertebral muscle, spleen, prostate, uterus myometrium, uterus endometrium, uterus cervix, medulla, and cortex of the kidney in four volunteers. The received signal was fitted to Eq. (13).

$$M_z = \sqrt{\left(M_o-2M_oe^{\frac{-TI}{T_1}}+M_oe^{\frac{-T_{sat}}{T_1}}\right)^2+C^2} \tag{13}$$

In Eq. (13), C represents a noise constant, T_{sat} is the saturation time (4500 ms in this case) and it is not equal to TR, because the refocusing pulses of the SSFSE-sequence continue to saturate during its duration [16].

Edden et al. [2] implemented an inversion recovery-prepared multi-shot spin-echo (IRMSSE) sequence with ten TI values to compute the T_1 relaxation times of adipose fat and fibroglandular tissue in the breast of six volunteers. The T_1 values were calculated to optimize breast MRI sequence parameters. The T_1 values were computed by a non-linear fitting of the received signal to the magnitude values in a voxel-by-voxel basis with a slight modification of Eq. (9). Edden et al. did not assume a perfect inversion pulse and fitted for this variable. The reported values of adipose fat (423±12 ms) and fibroglandular (1680±180 ms) are roughly 15% higher than those reported in [7].

On the other hand, Preibisch and Deichmann [17] used a single-slice single-shot IR-EPI (echo planar imaging) with fifteen TI values to measure the T_1 relaxation times of white matter. The T_1 value was calculated by fitting the received signal to Eq. (12). The reported T_1 value of white matter was measured in six volunteers. In a posterior study, Preibisch and Deichmann [18] implemented the same sequence as in [17] to measure the T_1 value of white matter in 4 volunteers. In both studies, the values obtained with the IR-EPI sequence were used as a reference to compare the values obtained with the proposed new methodology.

Stikov et al. [19] implemented an inversion recovery spin-echo sequence (IRSE) to compute the T_1 relaxation times of white matter using four TI values in 10 volunteers. The T_1 values were computed by fitting the received signal to Eq. 10. The objective of Stikov et al. was to explain the variations of T_1 values obtained with different methodologies and to propose ways to mitigate them.

Shin et al. [20] reported values for white matter, gray matter, and cerebrospinal fluid (CSF) using a single-slice Inversion Recovery Echo Planar Imaging sequence (IR-EPI) with 10 different TIs to measure T_1 in brain tissues. The IR-EPI's T_1 values were used as a reference to compare the T_1 values obtained with a new methodology proposed in their study.

Lu et al. [21] also measured the T_1 relaxation times of white matter, gray matter, and CSF of 10 volunteers using an IR sequence (ten TIs). The relaxation times were calculated on a voxel-by-voxel basis with the goal of defining image parameters for routine brain MRI pulse sequences at 3 T.

Chen et al. [22] also calculated in a voxel-by-voxel basis the T_1 relaxation times of white matter, gray matter, and CSF. Chen et al. used an FSE-IR sequence (five TIs). The acquisitions were performed in a single axial section in ten volunteers. The received signal was fitted using a non-linear least square algorithm. The objective of the study was to measure the T_1 relaxation times to optimize neuro-imaging protocols.

Dieringer et al. [23] used a two-dimensional IR sequence to measure the T_1 relaxation times of white matter and gray matter in six volunteers. The values were obtained by fitting the received signal to a three-parameter model (Eq. (12)). The IR's T_1 values served as reference values to test the proposed new methodology in the study.

The universal IR sequence can serve as the base of other pulse sequences to measure the T_1 relaxation time. Wright et al. [4] implemented a 3D Magnetization Prepared Rapid Gradient Echo sequence (MPRAGE) to measure the T_1 relaxation times of white and gray matter with the objective of optimizing the sequence parameters to obtain a better signal to noise ratio (SNR).

Barral et al. [24] used an SE-IR sequence to compute the T_1 relaxation times of the hypodermis (sub-cutaneous fat) and muscle. The T_1 values were calculated by fitting the received signal to Eq. (11) with a developed algorithm denominated 'Reduced-Dimension Nonlinear Least Squares', which turns the multiparameter minimization into a one-dimensional search [24]. The T_1 value of hypodermis and muscle was determined as the mode of the T_1 histogram of ROIs and the root mean square deviation about the mode.

2.6. Specialist methods

Specialist methods do not use the conventional approaches described above to measure the T_1 relation times, and are not always available in commercial scanners. In this section, we describe the Look–Locker and VFA T_1 specialist methods.

2.6.1. The Look–Locker

The Look–Locker (LL) special sequence is based on the inversion recovery method, but it uses multiple low flip angle pulses to obtain data in a single TR. First, an RF pulse with a flip angle sets the longitudinal magnetization $M(0)$ to a defined starting value (e.g, $\alpha=90^\circ$ sets $M(0)=0$); then a train of interrogating pulses (N) with small flip angles (α) is used to create a set of gradient echoes. The time (τ) between interrogating pulses and precession angles is chosen to be constant. After the acquisition of each gradient echo, the remaining transversal magnetization is destroyed by a spoiler gradient [25].

The signal after the n^{th} sampling pulse is given by [26]:

$$S_n = \beta\left(1-DRe^{n\tau/T_1^*}\right) \tag{14}$$

where

$$\beta = \frac{M_o\left(1-e^{-\tau/T_1}\right)}{(1-cos(\alpha e^{\theta/T_1}))sin\alpha} \quad (15)$$

$$DR = -\frac{cos\alpha\left(1-\left[cos\alpha e^{-\tau/T_1}\right]^{N-1}\right)}{1+cos\alpha\left[cos\alpha e^{-\tau/T_1}\right]^{N-1}}+1 \quad (16)$$

$$T_1^* = \frac{\tau}{\tau/T_1 - In(cos\alpha)} \quad (17)$$

Stikov et al. [19] implemented an LL sequence using a non-selective composite inversion pulse to compute the T_1 relaxation times of white matter in the brain of 10 volunteers.

Gold et al. [13] also used the LL sequence to measure the T_1 relaxation times of muscle, cartilage, synovial fluid, bone marrow, and subcutaneous fat with flip angles of 10° in five volunteers. The relaxation time of a given tissue was calculated by performing a monoexponential fit of the voxel intensities of selected ROIs at the different sampling times. The objective of the study was to define the T_1 relaxation times to optimize musculoskeletal MRI methods at 3 T.

Shin et al. [20] presented a method that measures the T_1 relaxation time between negative and positive steady states using an Inversion Recovery Look–Locker Steady State Echo Planar Imaging sequence (IR LL-EPI SS). The difference of this sequence with conventional LL is that it does not require the time duration for a full or partial recovery of the magnetization, which reduces the total image acquisition time. Shin et al. reported values for white matter, gray matter, and CSF.

Von Knobelsdorff-Brenkenhoff et al. [27] utilized an SSFP-based Modified Look–Locker Inversion Recovery (MOLLI) technique to measure the T_1 relaxation time of the myocardium in 59 volunteers. The T_1 relaxation time was calculated by using a non-linear least square curve fitting method of the received signal to Eq. (11). However, given that the SSFP readout used in MOLLI perturbs the T_1 recovery curve, the obtained T_1^* value from Eq. (11) must be corrected to recover the real T_1 [28]. The goal of the study was to find the reference T_1 values of the myocardium.

On the other hand, Piechnik et al. [29] developed a Shortened Modified Look–Locker Inversion Recovery (ShMoLLI) method to compute the T_1 values of the myocardium within a 9-heartbeat breath-hold. In this method, full recovery of the longitudinal magnetization between sequential inversion pulses is not achieved, and conditional interpretation of samples is used to compute the accurate T_1 relaxation times. The reported values of the myocardium were not significantly different from those obtained in the same study with a MOLLI sequence.

2.6.2. VFA T_1

One common method to measure T_1 is VFA imaging, also known as Driven Equilibrium Single-Pulse Observation of T_1 (DESPOT1), which uses several short TR radiofrequency SPGR acquisitions with varying flip angles (θ) [9].

In VFA T_1 mapping, the measured SPGR signal intensity (S_{SPGR}) from Eq. (5) is used to compute a T_1 value in a linear form (Eq. (18)) [9].

$$\frac{S_{SPGR}}{sin\theta} = \frac{S_{SPGR}}{tan\theta}e^{\frac{-TR}{T_1}} + M_o\left(1-e^{\frac{-TR}{T_1}}\right) \quad (18)$$

If different flip angles (θ_n) are applied, Eq. (18) generates different points ($S_{SPGR}/\sin\theta$, $S_{SPGR}/\tan\theta$) and it is linearized. Then, its slope ($e^{\frac{-TR}{T_1}}$) can be estimated by linear regression and the T_1 relaxation time can be extracted from Eq. (19) [9,19].

$$T_1 = -\frac{TR}{In\left(e^{\frac{-TR}{T_1}}\right)} \quad (19)$$

Since VFA T1 mapping is sensible to flip angle inaccuracies (B_1 field variations) and these inaccuracies are severe at 3 T, a B_1-map is usually calculated to solve this problem.

Castro et al. [30] implemented a dual 3D VFA SPGR Fast Field Echo (FFE) sequence with FAs selected (5°, 15°) to achieve maximum accuracy in the range of T_1 values of the imaged tissues. The B_1-map was computed using the dual-*TR* method, in which two images are acquired with different *TR*, but the same *TE* and prescribed FAs. The B_1-map values are computed from the ratio of the signal of the two TR_s acquisitions for every voxel [31]. The data acquisition was done on nineteen volunteers. The T_1 values were reported for white matter and gray matter. The study presented a template-based B_1 heterogeneity correction methodology. Castro et al. [30] also calculated the T_1 values of white matter and gray matter using Deoni's method [32]. The reported values agree with those reported by Deoni [32].

Sung et al. [9] also applied the VFA method to measure the T_1 relaxation time of fat in the left and right breast of 25 volunteers. The B_1-map was calculated using a double angle method [33]. The reported value of fat agrees with that reported in [7] using the FSE-IR IDEAL method. The study goal was to quantify the T_1 values variations with and without B_1 heterogeneity correction method.

Stikov et al. [19] used the VFA T1 mapping method to measure the T_1 relaxation time of white matter in the brain in 10 volunteers. The data were acquired with an SPGR sequence at four flip angles (3°, 10°, 20°, 30°). The received signals were fit to Eq. (18) to solve for the T_1 value. The reported T_1 value for white matter was taken over the pooled histogram of all the volunteers.

Cheng and Wright [34] implemented a 3D fast SPGR sequence to measure the relaxation times of white matter and gray matter in two volunteers. The study presented an optimized VFA method that improves the accuracy and precision of the calculated T_1 values. This is done by taking into account the influence of imperfect B_1 field, noise bias, and selection of flip angles.

Clique et al. [35] obtained T_1 relaxation times of the myocardium with an optimized 3D fast SPGR steady-state pulse sequence. The sequence integrated B_1 correction. The acquisition was made on seven volunteers. The study objective was to optimize myocardial T_1 mapping by proposing a VFA approach with B_1 correction.

Fleysher et al. [36] developed a method called TriTone (Appendix A) based on the acquisition of three 3D SPGR EPI images to compute unbiased and precise T_1 values. Contrary to the two-SPGR method of T_1 estimation, the method requires a third SPGR acquisition to compensate for the B_1 deviations, making it robust to flip angles' imprecisions. The TriTone method was used to measure the T_1 relaxation time of white matter and gray matter in one volunteer.

Samson et al. [37] computed the T_1 of cervical cord, white matter, and gray matter using a multi-echo three dimensional fast low-angle shot (3D FLASH) in thirteen volunteers. The goal of the study was to measure not only T_1 values, but also apparent proton density, magnetization transfer ratio, and apparent transverse relaxation rate R_2^*.

In the same way, Preibisch and Deichmann [17] computed the T_1 values of white matter using a 3D spoiled FLASH sequence. Preibisch and Deichmann [17] investigated the effects of RF spoiling in the accuracy of the calculated T_1 values.

In a posterior study, Preibisch and Deichmann [18] investigated the improvement in SNR and T_1 accuracy achieved by using 3D double echo FLASH-EPI hybrid sequences with different *TR*. The T_1 relaxation values were calculated in 4 volunteers by using the same

methodology described in [17]. The reported T_1 values for white matter and gray matter were similar to those obtained by 3D spoiled FLASH sequence (as described in [17]), but the hybrid sequences produce better SNRs.

Liberman et al. [38] developed a new method based on the typical VFA-SPGR sequence. The method uses uniform weighting of all the FAs, and a new weighting coefficient is added to Eq. (18) to make it weakly dependent on the FAs (θ). It takes into account the inaccuracies of the prescribed FAs, and it estimates the actual FAs using linear approximation and the half-angle substitution. The method also uses data-driven local B_1 inhomogeneity correction, the N3 algorithm [39]. Liberman et al. measured the T_1 relaxation times in eight volunteers. Several ROIs were defined to measure the mean T_1 values in the different brain areas.

Chavez and Stanisz [40] proposed a new methodology to perform simultaneous B_1 and T_1 mapping developed from the 3D VFA SPGR sequence. It relies on the dependence of the flip angle and T_1 of the SPGR signal (Eq. (5)), and it exploits the linearity of the signal versus flip angle to compute the T_1 maps (Eq. (19)). Chavez and Stanisz used this method to measure the T_1 relaxation times of white matter and gray matter in four volunteers.

Dieringer et al. [23] implemented a 2D VFA FLASH (SPGR) sequence to measure the T_1 relaxation times of white matter and gray matter and to examine the feasibility of rapid 2D T_1 quantification. The measures were performed in six volunteers. The implementation corrects the deformed slices profiles (a familiar problem in 2D acquisition) due to common non-ideal radio-frequency slice excitation pulses by using mathematical integration of simulated slices profiles for different flip angles. B_1-maps were used to account for B_1 non-uniformities [41]. The received signal was assumed to be governed by Eq. (18).

3. T_2 relaxation time

3.1. Theory

The T_2 relaxation time (transverse magnetization) in the absence of any RF field derives from the Bloch equation:

$$\frac{\delta M_{xy}(t)}{d\delta} = -\frac{M_{xy}(t)}{T_2} \tag{20}$$

The traverse magnetization is generated by the application of a RF pulse in the presence of longitudinal magnetization. It is related to the dephasing of the net magnetization (M_0) following the removal of the RF pulse (B_1) usually of 90°. The dephasing is due principally to the energy transfer between spins (spin–spin interactions) and time-independent inhomogeneities of the external magnetic field (B_0) [11,42]. By forming a spin echo (after a 180° RF), some sources of decay are reversed and the amplitude of the spin echo is governed by an exponential decay:

$$M_{xy}(TR, TE) = M_0\left(1-e^{-TR/T_1}\right)e^{-TE/T_2} \tag{21}$$

If a TR >> 5 T_1 is used, then Eq. (21) changes to its simplest form:

$$M_{xy}(TE) = M_0 e^{-TE/T_2} \tag{22}$$

3.2. Methods

The Carr–Purcell Meiboom–Gill (CPMG) sequence is considered as the gold standard to measure the T_2 relaxation time. The Carr–Purcell sequence is a multiple spin-echo sequence with signal decay measured at different echo times. In the modified CPMG sequence, the phase (direction) of the 180° refocusing pulse is alternated to prevent accumulative errors in pulse angles and to produce a more accurate T_2 value [43].

Lu et al. [21] measured the T_2 relaxation times of white matter and gray matter of 10 volunteers using a CPMG sequence with six TEs. The relaxation times were calculated on a voxel-by-voxel basis in a single-oblique axial slice with the goal of defining image parameters for routine brain MRI pulse sequences.

Nevertheless, alternative sequences can be used to measure the T_2 relaxation times. Rakow-Penner et al. [7] used a two Hahn echo scan protocol to accurately measure the T_2 relaxation times of fat and fibroglandular tissue in the breast. The protocol consisted in the acquisition of two T_2-weighted images at TEs of 20 and 100 ms in six volunteers. The T_2 values were found by solving Eq. (22) with the two known measurements of the transverse magnetization (M_{xy}) at the two different echo times (TE). A constant net magnetization (M_o) between the two measurements was considered. The reported values of fat and fibroglandular tissue do not show a significant difference between the tissues.

Edden et al. [2] also measured the T_2 relaxation times of fat and fibroglandular tissue in the breast in six volunteers, but they implemented a 16-echo spin echo sequence with echo times from 10 to 160 ms in 10 ms steps. The received signal was fitted to the following three-parameter model:

$$M_{TE_i} = M_o\left(e^{\frac{-TE_i}{T_2}}\right) + C \tag{23}$$

The single difference with respect to Eq. (22) is an added y-Offset (C) variable to compensate for noise. The reported T_2 values of adipose fat and fibroglandular tissue are significantly different between the tissues. The T_2 values for fibroglandular tissue correlate well with those reported in [7], but the T_2 values of adipose tissue are substantially longer (285 ms) than those reported in the same study.

Bojorquez et al. [15] also computed the T_2 values of different tissues at the level of the pelvis (fat, muscle and prostate) by fitting the signal intensity to Eq. (23). The acquisition was performed in 3 volunteers with a 32-echo spin echo sequence. The objective of the study was to classify and segment fat, muscle, and prostate according to their relaxation times.

On the other hand, Gold et al. [13] used a spiral preparation sequence to measure the T_2 relaxation times of muscle, cartilage, synovial fluid, bone marrow, and subcutaneous fat in five volunteers to optimize musculoskeletal sequence parameters. Images were acquired with six different TEs.

De Roquefeuil et al. [44] measured the T_2 relaxation time of the myocardium using an ECG-triggered FSE Black Blood breath-held sequence in six volunteers. The received signal was fitted to Eq. (21) to obtain the relaxation time. But, since the longitudinal magnetization relaxation is not fully recovered because the condition TR>>5 T_1 is not fulfilled in ECG-triggered FSE sequences [44], images used in the T_2 fitting procedure have different effect if TR_{eff} and each magnitude contributing to the T_2 were corrected by the factor α_n (Eq. (24)) to obtain the real T_2 relaxation time. For this correction, an assumed value of T_1 of 1500 ms for the myocardium was considered.

$$\alpha_n = \left[1-exp\left(\frac{TR_{eff_n}}{T_1}\right)\right]^{-1} \tag{24}$$

Von Knobelsdorff-Brenkenhoff et al. [27] also measured the T_2 relaxation times of the myocardium in 59 volunteers. They used a T_2-prepared single-shot SSFP sequence, and the T_2 values were obtained by fitting the received signal in a voxel-wise to Eq. (22). The objective of the study was to find the reference T_2 relaxation time for the myocardium.

Similarly, Van Heeswijk et al. [45] also measured the T_2 relaxation time of the myocardium, but Van Heeswijk et al. utilized a T_2 prepared GRE sequence and an optimized model equation to fit the received signal. The optimized model equation includes the standard exponential decay and an empirical variable that accounts for T_1 relaxation.

De Bazelaire et al. [16] used a single shot multi-excitation SE sequence to measure the T_2 relaxation times of fat, bone marrow, pancreas, liver, paravertebral muscle, spleen, prostate, uterus myometrium, uterus endometrium, uterus cervix, medulla, and cortex of the kidney in four volunteers. The received signal was fitted to Eq. (25).

$$M_{xy} = \sqrt{\left(M_o e^{\frac{-TE}{T_2}}\right)^2 + C^2} \tag{25}$$

Pai et al. [46] evaluated the sequence dependent differences in T_2 quantification of cartilage, muscle, fat, and bone marrow in the knee joint in axial plane. The T_2 quantification was performed using the following sequences: a spiral acquisition with a T_2 preparation sequence, a multi-echo multi-slice spin echo sequence (MESE), a single-echo spin echo sequence, a fast spin echo sequence with three different ETLs (4, 8, 16), a T_2 quantification sequence based on a 3D SPGR sequence, and a 3D SPGR acquisition in an elliptic–centric trajectory in segmented k-space.

Even though the most accurate technique to measure T_2 relaxation times is derived from the CPMG sequence, other methods without using spin echoes have been developed to obtain the T_2 values. Wang et al. [47] developed a method denominated 'Dual-τ' T_2 measurement, which computes the T_2 values from the ratio of MRI signals acquired with short- and long-duration adiabatic pulses. The method was implemented to measure the T_2 relaxation times of muscle and bone marrow in one volunteer. Two acquisitions of a coronal 3D FFE sequence were acquired. The reported muscle value correlates well with the value obtained with the reference 32-echo CPMG sequence, which was applied on the same volunteer (identical sequence parameters as for Dual-τ method). However, the reported bone marrow value was longer than the one reported with the reference CPMG sequence.

4. Simultaneous T_1 and T_2 relaxation time measurements

Most of the described T_1 and T_2 measurement techniques require several acquisitions to quantify the relaxation times. These techniques need to vary a single parameter among each acquisition (e.g. TR, TE, TI, FA) until the full k-space (Fourier space) is filled in the same way for all acquisitions. Then, the Fourier transform is used to reconstruct the images and a fitting process is applied over the voxel's signal to obtain the T_1 or T_2 values. Two different processes have to be implemented if measurement of both T_1 and T_2 values is required (i.e. simultaneous T_1 and T_2 mapping is not possible). However, with Magnetic Resonance Fingerprinting (MRF) simultaneous measurements are possible. In fact, not only simultaneous T_1 and T_2 mapping is possible, proton density can also be computed at the same time [48]. In MRF, the sequence parameters (FA, TR and k-space trajectory) are varied in a pseudo-random fashion during the acquisition to generate fingerprints for each tissue (a unique signal which is a function of the multiple tissue properties under investigation) [5]. The fingerprints are compared to those stored in a dictionary (using pattern recognition techniques) and the dictionary entry that best matches the fingerprint is used to extract the T_1 and T_2 values. The dictionary entries are generated using the model describing the process of the acquisition sequence. The number of parameters that can be extracted depends on the complexity of the model (number of variables). The method can be virtually applied to any kind of sequence [48]. Nevertheless, MRF is a new approach and the literature is still limited.

Jiang et al. [49] utilized the MRF method to measure in one volunteer the relaxation times in the brain. The data acquisition was done with the fast imaging steady-state free precession sequence (FISP). T_1 and T_2 values were reported for white matter and gray matter.

Chen et al. [50] also implemented the MRF method to obtain the relaxation times of five abdominal tissues in 8 volunteers. The MRF method was based again on the FISP sequence. The B_1 map was computed using the Bloch–Siegert technique. T_1 and T_2 values were reported for liver, kidney medulla, kidney cortex, spleen, skeletal muscle, and fat.

5. Reported T_1 and T_2 relaxation times of different tissues

The reported T_1 and T_2 relaxation times from the different methods for the distinct tissues can be seen in Tables 1 and 2.

Table 1 was further subdivided according to specific tissues: gray matter (1a), white matter (1b), CSF (1c), fat (1d), muscle (1e), myocardium (1f), and diverse tissues (1g). A big variability of values is evident (e.g. gray matter values range from 968 to 1815 ms, muscle values range from 898 to 1509 ms).

Table 2 was also subdivided according to specific tissues: fat (2a), muscle (2b), myocardium (2c), bone marrow (2d), cartilage (2e), and diverse tissues (2f). As in the case of the reported T_1 values, there is a big dispersion of the reported T_2 values (e.g. fat values range from 41 to 371 ms, bone marrow values range from 40 to 160 ms, muscle values range from 28 to 44 ms).

6. Considerations in measuring T_1 and T_2 relaxation times

Many factors can cause systematic errors that can compromise the accuracy of the T_1 and T_2 maps. However, we will focus in the main factors to consider when computing the relaxation times, which affect most of the methods.

6.1. Noise

The majority of methodologies used to compute the relaxation times assume a model to describe the received signal. Then, the received signal is fitted to this model to obtain the relaxation times. Nevertheless, not all implemented models account for the noise present in the received signal, which gives rise to random errors that will compromise the accuracy of the calculated T_1 and T_2 relaxation times. A solution to mitigate this error consists in adding an extra parameter representing the noise in the fitting model [15,16]. However, since the extra parameter increases the complexity of the model, the fitting timing will increase accordingly. Another alternative could be to denoise the received signal before the fit, with care taken to avoid disrupting the shape of the expecting received signal (i.e. after denoising the signal, the fit model must still be able to describe the received signal). There are different denoising methods to serve this purpose such as the adaptative non-local means denoising technique [51], which can deal with the common Gaussian and Rician MR noise distributions. Anyway, it is always recommendable to calculate a metric to evaluate the fit goodness (e.g. R-squared value) and to perform a random visualization of the fit in real data (some voxels).

6.2. Partial volume effect

Partial volume effects concern all in vivo experiments [7]. It occurs when the voxel dimensions of the sequence cover several biological tissues, and the received signal from these voxels experienced a multiexponential behavior. If the model utilized to describe the received signal assumes a monoexponential behavior, the accuracy of the calculated relaxation times is compromised [10,52]. Imperfect RF pulses may also cause partial volume effects by exciting tissues outside the desired slice (cross-talk). The main strategy to decrease partial

volume effects consists of defining small voxel resolution. However, the trade-off is a decrease in the SNR of the received signal.

6.3. B_1 effects

The majority of the methods described for computing T_1 and T_2 relaxation times are susceptible to B_1 errors (i.e. FA errors), specially when implemented in fast acquisitions [11]. The main causes of the B_1 errors are: 1) Non uniformity of the transmitted radio frequency (B_1) (the actual flip angle in tissue is different from the nominal flip angle set in the scanner procedure) [9,33]; 2) Standing-wave or dielectric resonance effects (the wavelength of the RF field has the same order of magnitude as the geometric dimensions of the imaged tissue causing constructive or destructive interferences of the transmitted RF pulse, which result in regional signal loss or regional brightening) [11,53]; 3) Inaccurate and variable setting of FA in the prescan sequence [11]. To obtain accurate relaxation times, the methodologies used to compute these values must implement a procedure to mitigate the B_1 inhomogeneities (e.g. phase sensitive B_1 mapping, the AFI method or the N3 method) [33,54] or be immune to it. However, in some cases the penalty to pay is a time increment of the scan procedure.

6.4. Transverse coherences or spoiling

In the sequences used to compute the T_1 relaxation times, it is sometimes assumed that the transverse magnetization was crushed (spoiled) after the acquisition of the free induction decay (i.e. no residual transverse magnetization exists at the end of the TR), which is a good assumption for $TR >> T_2$ (as in IR and LL) [19]. Nevertheless, when the transverse magnetization is not crushed throughout the sequence, it creates spurious spin and stimulated echoes that bias the accuracy of the estimated T_1 values [10]. To verify if transverse coherences are perturbing the received signal, the readout pulses must be turned off and the signal measured. If any signal is measured, the transverse magnetization arises before the readout pulse and the amplitude or length of the crusher gradients must be modified to eliminate it [10]. In sequences with short TR (such VFA), additional gradient and RF spoiling pulses must be applied to eradicate the residual transverse magnetization, which is standard in SPGR sequences used for VFA [19].

7. Discussions

The hope that each individual tissue would have particular range of normal T_1 and T_2 relaxation times, and that reliable measurements of these times would enable an unambiguous identification of different tissues seems to fade with the large spread of T_1 and T_2 relaxation times found in the literature. This spread of values indicates that there is not a common set of reference values for the relaxation times of tissues, and that there is a huge amount of ambiguity surrounding the measurements.

For example, the optimal number of sample points to fit the received signal (if applicable) is still not well defined in the literature, but it is known that the number of samples has a dramatic effect in the standard deviation of the calculated relaxation times in the presence of noise (e.g. when the data points used for fitting the relaxation curve were reduced from seven to three, the standard deviation error doubled [55]).

There are different flavors of models to fit the received signal (e.g. IR) and noise is generally not considered in these models, which could introduce bias in the estimated relaxation times. Moreover, these models are usually fitted with different optimization techniques (e.g. non-linear square) without typically reporting the algorithm's parameters (different parameters converge to different values) and the values of the metric evaluating the good of fitness (the most important value to evaluate the quality of the model [38]), which prevent reproducibility. Further, the models usually assume a monoexponential received signal without considering partial volume effects (e.g. fat and water composition), which certainly affect the accuracy of the estimated relaxation times.

Another bias represents the fact that the fit is done in a voxel-by-voxel basis or only over the mean value of a set of ROIs, without considering that the reported values came from different arithmetic metrics calculated over ROIs (e.g. the mean [15], the median [38], the mode [24] or peaks over the histogram of relaxation times [19]). Moreover, the ROIs are often very different in size (i.e. number of voxels, area and volume) and this introduces another sort of bias [56].

In addition, the accuracy of the reported relaxation times may be also limited due to few number of volunteers included in the experiments, often from 1 to 3. Additionally, there are differences in hardware (sensitivity profile and gain of the receiver coil), scanner performance (different scanners add variability to the quantification of T_1 and T_2 values [46]), sequence design, strategies for acquiring the data (filling k-space) and a lack of common scanned reference phantoms (or volunteers). All these ambiguities make it difficult to compare the measurements objectively among studies, and give rise to the issues of reproducibility and standardization.

Although the measurements could be compared according to the sequence acquisition because it was argued that the type of sequence produces particular values-trends [46], this is not always the case. In some cases, the comparison makes sense, e.g. difference of 8 ms for T_2 of fat between [15] and [46]. In others, the difference is disproportionate, e.g. difference of 284 ms for T_1 of white matter between [34] and [38]. However, the comparison is inappropriate due to the ambiguities mentioned above. In addition, the comparison could be difficult to perform in multicenter clinical scanners because many of the important features of the sequence may be hidden from the user [10].

Furthermore, it is possible that poor measurement techniques are also partially responsible for the extent of reported relaxation times [10], if the principal factors affecting the relaxation times were not considered during the study, i.e. noise, partial volume effect, B_1 effects and spoiling.

Nevertheless, when reproducibility and standardization have been achieved, the segmentation and classification of tissues were done based solely on the relaxation times (e.g. fat, muscle, and prostate at the level of the pelvis [15] and different regions of the hypothalamus [57]). This was possible because the experiments were performed under the same conditions in all the cases (identical sequence parameters, scanner, hardware, k-space fill, T_1 and T_2 calculation method, etc.). The results from these experiments show that if the ambiguities are removed from the studies, the measurements can be reproducible and standardized and that tissues really have a particular range of relaxation times that can be used to identify them. On the other hand, the results suggest that methods using or assuming predetermined T_1 and/or T_2 of tissues from other studies, to perform B_1 inhomogeneities and FA corrections (e.g. [12]) or to calculate the relaxation times (e.g. MRF), should compute these predetermined T_1 and T_2 values according to their specific resources (scanner, received and transmitter coil, sequence). In practice, we have to recognize that this level of standardization could be extremely difficult to achieve in a multicenter study. Since differences among scanners from different manufactures may impede the use of identical protocols at every center [56]. If multicenter study standardization is achieved, the obtained values can be compared in repeated studies on a given subject, between subjects and in multicenter examinations, which in turn will certainly increment the use of the relaxation times in image

Table 1
T_1 relaxation times.

Imaging Method	Specific Sequence	T_1 (ms) (mean ± STD)	Volunteers/Age number/(mean ± STD)	Reference
(a) Gray matter				
Partial Saturation	PRESS	1470 ± 50	8(28.7 ± 4.4)	Ethofer et al. [14]
Inversion Recovery	2D IR	1615 ± 149	6	Dieringer et al. [23]
Inversion Recovery	IR-EPI	1460 ± 33	3	Shin et al. [20]
Inversion Recovery	IR-EPI	1165 ± 113	10 (28 ± 5)	Lu et al. [21]
Inversion Recovery	IR-FSE	1445 ± 119	10 (31 ± 10)	Chen et al. [22]
Inversion Recovery	MPRAGE	1600 ± 110	4 (36 ± 8)	Wright et al. [4]
Specialist techniques	IR LL-EPI SS	1465 ± 148	3	Shin et al. [20]
Specialist techniques	VFA SPGR	1717 ± 61	2	Cheng and Wright [34]
Specialist techniques	VFA SPGR	1501[a]	3 (females)	Liberman et al. [38]
Specialist techniques	VFA SPGR	1349[a]	5 (males)	Liberman et al. [38]
Specialist techniques	VFA SPGR	1558 ± 88	19(39 ± 11)	Castro et al. [30]
Specialist techniques	3D VFA SPGR	1700	4(25–36)	Chavez and Stanisz [40]
Specialist techniques	FLASH (SPGR)	1815 ± 170	13 (36.4 ± 12.3)	Samson et al. [37]
Specialist techniques	3D HYBRID12.5 (FLASH-EPI)	1402 ± 53	4(28 ± 7)	Preibisch and Deichmann [18]
Specialist techniques	3D HYBRID15.2 (FLASH-EPI)	1405 ± 53	4(28 ± 7)	Preibisch and Deichmann [18]
Specialist techniques	3D HYBRID15.9 (FLASH-EPI)	1427 ± 63	4(28 ± 7)	Preibisch and Deichmann [18]
Specialist techniques	3D FLASH (SPGR)	1380 ± 59	4(28 ± 7)	Preibisch and Deichmann [18]
Specialist techniques	2D VFA FLASH(SPGR)	968 ± 85	6	Dieringer et al. [23]
Specialist techniques	TriTone (SPGR)	1550	1	Fleysher et al. [36]
MRF	FISP	1193 ± 65	1	Jiang et al. [49]
[a]median value				
(b) White matter				
Partial Saturation	PRESS	1110 ± 40	8(28.7 ± 4.4)	Ethofer et al. [14]
Inversion Recovery	IR	830[a]	10 (22 ± 1.7)	Stikov et al. [19]
Inversion Recovery	2D IR	911 ± 15	6	Dieringer et al. [23]
Inversion Recovery	IR-EPI	943 ± 57	3	Shin et al. [20]
Inversion Recovery	IR-EPI	954 ± 39[b]	6(30 ± 5)	Preibisch and Deichmann [17]
Inversion Recovery	IR-EPI	894 ± 23	4 (28 ± 7)	Preibisch and Deichmann [18]
Inversion Recovery	IR-EPI	728 ± 433	10 (28 ± 5)	Lu et al. [21]
Inversion Recovery	IR-FSE	791 ± 27	10 (31 ± 10)	Chen et al. [22]
Inversion Recovery	MPRAGE	840 ± 50	4 (36 ± 8)	Wright et al. [4]
Specialist techniques	VFA	1070[a]	10 (22 ± 1.7)	Stikov et al. [19]
Specialist techniques	LL	750[a]	10 (22 ± 1.7)	Stikov et al. [19]
Specialist techniques	VFA SPGR	1085 ± 64	2	Cheng and Wright [34]
Specialist techniques	VFA SPGR	883[c]	3 (females)	Liberman et al. [38]
Specialist techniques	VFA SPGR	801[c]	5 (males)	Liberman et al. [38]
Specialist techniques	3D VFA SPGR	1100	4(25–36)	Chavez and Stanisz [40]
Specialist techniques	VFA SPGR	1107 ± 80	19(39 ± 11)	Castro et al. [30]
Specialist techniques	FLASH (SPGR)	1735 ± 205	13 (36.4 ± 12.3)	Samson et al. [37]
Specialist techniques	3D FLASH (SPGR)	895 ± 23	4 (33 ± 3)	Preibisch and Deichmann [17]
Specialist techniques	3D HYBRID12.5 (FLASH-EPI)	933 ± 15	4(28 ± 7)	Preibisch and Deichmann [18]
Specialist techniques	3D HYBRID15.2 (FLASH-EPI)	949 ± 31	4(28 ± 7)	Preibisch and Deichmann [18]
Specialist techniques	3D HYBRID15.9 (FLASH-EPI)	959 ± 33	4(28±7)	Preibisch and Deichmann [18]
Specialist techniques	3D FLASH (SPGR)	933 ± 15	4(28±7)	Preibisch and Deichmann [18]
Specialist techniques	2D VFA FLASH(SPGR)	1433 ± 80	6	Dieringer et al. [23]
Specialist techniques	TriTone (SPGR)	950	1	Fleysher et al. [36]
Specialist techniques	IR LL-EPI SS	964 ± 116	3	Shin et al. [20]
MRF	FISP	781 ± 61	1	Jiang et al. [49]
[a]peak value over the histogram of relaxation times [b]average value of the reported mean values of the ROIs set on frontal and occipital white matter of the left and right section of the brain [c]median value				
(c) Cerebro spinal fluid				
Inversion Recovery	IR-EPI	4391 ± 545	3	Shin et al. [20]
Inversion Recovery	IR-EPI	3817 ± 424	10 (28 ± 5)	Lu et al. [21]
Inversion Recovery	IR-FSE	4163 ± 263	10 (31 ± 10)	Chen et al. [22]
Specialist techniques	IR LL-EPI SS	4522 ± 417	3	Shin et al. [20]
Specialist techniques	VFA SPGR	6873[a]	3 (females)	Liberman et al. [38]
Specialist techniques	VFA SPGR	4184[a]	5 (males)	Liberman et al. [38]
[a]median value				
(d) Fat				
Inversion Recovery	FSE-IR	450 ± 26	6 (36 ± 12.6)	Rakow-Penner et al. [7]
Inversion Recovery	FSE-IR IDEAL	366 ± 75	6 (36 ± 12.6)	Rakow-Penner et al. [7]
Inversion Recovery	TSE-IR	385 ± 34	3(32 ± 8)	Bojorquez et al. [15]
Inversion Recovery	IR-MS-SE	423 ± 12	6 (34 ± 6)	Edden et al. [2]
Inversion Recovery	SE-IR	421 ± 104[a] (slice1)	1	Barral et al. [24]
Inversion Recovery	SE-IR	392 ± 132[a] (slice2)	1	Barral et al. [24]
Inversion Recovery	SSFSE-IR	(382 ± 13)	6 (31.5)	De Bazelaire et al. [16]
Specialist techniques	VFA SPGR	346 ± 35 (right breast)	25 (50 ± 11)	Sung et al. [9]

Table 1 (*continued*)

Imaging Method	Specific Sequence	T_1 (ms) (mean ± STD)	Volunteers/Age number/(mean ± STD)	Reference
Specialist techniques	VFA SPGR	374 ± 45 (left breast)	25 (50 ± 11)	Sung et al. [9]
Specialist techniques	LL	371 ± 8	5 (range 27 to 38)	Gold et al. [13]
MRF	FISP	253 ± 42	8 (range 22 to 45)	Chen et al. [50]
[a]mode±root mean square deviation about the mode				
(e) Muscle				
Inversion Recovery	SE-IR	1509 ± 150[a] (slice1)	1	Barral et al. [24]
Inversion Recovery	SE-IR	1269 ± 149[a] (slice2)	1	Barral et al. [24]
Inversion Recovery	SSFSE-IR	898 ± 33	6 (31.5)	De Bazelaire et al. [16]
Inversion Recovery	TSE-IR	1295 ± 83	3 (32 ± 8)	Bojorquez et al. [15]
Specialist techniques	LL	1420 ± 38	5 (range 27 to 38)	Gold et al. [13]
MRF	FISP	1100 ± 59	8 (range 22 to 45)	Chen et al. [50]
[a]mode±root mean square deviation about the mode				
(f) Myocardium				
Spoiled GE	3D SPGR	1341 ± 42	7 (31 ± 12)	Clique et al. [35]
Specialist techniques	MOLLI	1157[a] (1075–1246)[b]	59 (range 20 to 80)	Von Knobelsdorff-Brenkenhoff et al. [27]
Specialist techniques	MOLLI	1159[c] (1074–1250)[b]	59 (range 20 to 80)	Von Knobelsdorff-Brenkenhoff et al. [27]
Specialist techniques	MOLLI	1181[d] (1074–1298)[b]	59 (range 20 to 80)	Von Knobelsdorff-Brenkenhoff et al. [27]
Specialist techniques	MOLLI	1169 ± 45	10	Piechnik et al. [29]
Specialist techniques	ShMOLLI	1116 ± 60	10	Piechnik et al. [29]
[a]Base of myocardium [b]95% tolerance interval [c]Middle of myocardium [d]Appex of myocardium				

Tissue	Imaging Method	Specific Sequence	T_1 (ms) (mean ± STD)	Volunteers/Age number/(mean ± STD)	Reference
(g). Diverse tissues					
Fibrogladular Tissue	Inversion Recovery	FSE-IR	1324 ± 168	6 (36 ± 12.6)	Rakow-Penner et al. [7]
Fibrogladular Tissue	Inversion Recovery	FSE-IR IDEAL	1445 ± 93	6 (36 ± 12.6)	Rakow-Penner et al. [7]
Fibrogladular Tissue	Inversion Recovery	IR-MS-SE	1680 ± 180	6 (34 ± 6)	Edden et al. [2]
Prostate	Partial Saturation	six-TR 2D FSE	1434 ± 295	11	Fennessy et al. [12]
Prostate	Partial Saturation	three-TR 2D FSE	1400 ± 278	11	Fennessy et al. [12]
Prostate	Spoiled GE	3D SPGR	1530 ± 498	11	Fennessy et al. [12]
Prostate	Inversion Recovery	SSFSE-IR	1597 ± 42	6 (31.5)	De Bazelaire et al. [16]
Prostate	Inversion Recovery	TSE-IR	1700 ± 175 ms	3(32 ± 8)	Bojorquez et al. [15]
Pancreas	Inversion Recovery	SSFSE-IR	725 ± 71	6 (31.5)	De Bazelaire et al. [16]
Liver	Inversion Recovery	SSFSE-IR	809 ± 71	6 (31.5)	De Bazelaire et al. [16]
Liver	MRF	FISP	745 ± 65	8 (range 22 to 45)	[50]
Spleen	Inversion Recovery	SSFSE-IR	1328 ± 31	6 (31.5)	De Bazelaire et al. [16]
Spleen	MRF	FISP	1232 ± 92	8 (range 22 to 45)	[50]
Uterus myometrium	Inversion Recovery	SSFSE-IR	1514 ± 156	6 (31.5)	De Bazelaire et al. [16]
Uterus endometrium	Inversion Recovery	SSFSE-IR	1453 ± 123	6 (31.5)	De Bazelaire et al. [16]
Uterus cervix	Inversion Recovery	SSFSE-IR	1616 ± 613	6 (31.5)	De Bazelaire et al. [16]
Kidney medulla	Inversion Recovery	SSFSE-IR	1545 ± 142	6 (31.5)	De Bazelaire et al. [16]
Kidney medulla	MRF	FISP	1702 ± 205	8 (range 22 to 45)	Chen et al. [50]
Kidney cortex	Inversion Recovery	SSFSE-IR	1142 ± 154	6 (31.5)	De Bazelaire et al. [16]
Kidney cortex	MRF	FISP	1314 ± 77	8 (range 22 to 45)	Chen et al. [50]
Cervical cord	Specialist techniques	FLASH (SPGR)	1848 ± 143	13 (36.4 ± 12.3)	Samson et al. [37]
Cartilage	Specialist techniques	LL	1240 ± 107	5 (range 27 to 38)	Gold et al. [13]
Bone marrow	Inversion Recovery	SSFSE-IR	586 ± 73	6 (31.5)	De Bazelaire et al. [16]
Bone marrow	Specialist techniques	LL	365 ± 9	5 (range 27 to 38)	Gold et al. [13]
Bone marrow	Specialist techniques	3D Dual-τ FFE	135 ± 13	1	Wang et al. [47]
Bone marrow	Specialist techniques	32-echo CPMG	106 ± 4	1	Wang et al. [47]
Synovial fluid	Specialist techniques	LL	3620 ± 320	5 (range 27 to 38)	Gold et al. [13]

diagnostic and improve the development of optimized MR sequences for quantitative imaging.

It is difficult to recommend a sequence or specific method to compute the relaxation times, thus the selection depends completely on the constraints and requirements of the study. For instance, if time is a constraint then a two-point method could be used to compute the T_1 (two acquisitions at different TIs or TRs) and T_2 (two acquisitions at two different TEs) relaxation times. If volumetric imaging is required, then the VFA T_1 mapping would be a good option. In general, each method has its underlying assumptions and limitations, therefore the choice of the method is defined by the problem to solve and the available resources. However, we must always try to achieve the highest precision (reproduction of measurements) and accuracy (closeness of measurements), the most important criteria in the evaluation of techniques measuring the relaxation times [1].

8. Conclusions

This paper presented a comprehensive report of reference T_1 and T_2 values measured at 3 T in various studies with different sequences obtained from healthy subjects. A large interstudy variability is evident, suggesting that universal T_1 and T_2 reference values are still unknown. The large spread of diverse values may be due to the ambiguities surrounding the measurements. However, reproducibility and

Table 2
T_2 relaxation times.

Imaging Method	Specific Sequence	T_2 (ms) (mean ± STD)	Volunteers/Age number/(mean ± STD)	Reference
(a) Fat				
SE	MESE	113	10 (27)	Pai et al. [46]
SE	MESE	121 ± 20	3 (32 ± 8)	Bojorquez et al. [15]
SE	SE	41	10 (27)	Pai et al. [46]
SE	FSE (ETL 4)	103	10 (27)	Pai et al. [46]
SE	FSE (ETL 8)	125	10 (27)	Pai et al. [46]
SE	FSE (ETL 8)	143	10 (27)	Pai et al. [46]
SE	SSFSE	68 ± 4	6 (31.5)	De Bazelaire et al. [16]
SE	Two Hahn echo	54 ± 9	6 (36 ± 12.6)	Rakow-Penner et al. [7]
SE	16-echo spin echo	154 ± 9	6 (34 ± 6)	Edden et al. [2]
SE	Hybrid-SE	371 ± 8	5 (range 27 to 38)	Gold et al. [13]
MRF	FISP	68 ± 4	8 (range 22 to 45)	Chen et al. [50]
(b) Muscle				
SE	MESE	28	10 (27)	Pai et al. [46]
SE	MESE	34	10 (27)	Pai et al. [46]
SE	MESE	40 ± 3	3 (32 ± 8)	Bojorquez et al. [15]
SE	SE	27	10 (27)	Pai et al. [46]
SE	FSE (ETL 4)	37	10 (27)	Pai et al. [46]
SE	FSE (ETL 8)	40	10 (27)	Pai et al. [46]
SE	FSE (ETL 16)	44	10 (27)	Pai et al. [46]
SE	3D SPGR	28	10 (27)	Pai et al. [46]
SE	SSFSE	29 ± 4	6 (31.5)	De Bazelaire et al. [16]
SE	Hybrid-SE	32 ± 2	5 (range 27 to 38)	Gold et al. [13]
SE	3D Dual-τ FFE	29 ± 1	1	Wang et al. [47]
SE	32-echo CPMG	29 ± 4	1	Wang et al. [47]
MRF	FISP	44 ± 9	8 (range 22 to 45)	Chen et al. [50]
(c) Myocardium				
SE	T_2prep-GRE	39 ± 5	10 (27 ± 4)	Van Heeswijk et al. [45]
SE	SSFP	44[a] (39–50)[b]	59 (range 20 to 80)	Von Knobelsdorff-Brenkenhoff et al. [27]
SE	SSFP	45[c] (40–50)[b]	59 (range 20 to 80)	Von Knobelsdorff-Brenkenhoff et al. [27]
SE	SSFP	47[d] (49–54)[b]	59 (range 20 to 80)	Von Knobelsdorff-Brenkenhoff et al. [27]
SE	ECG-triggered FSE	67 ± 5	6 (27 ± 5)	De Roquefeuil et al. [44]
[a]Base of myocardium				
[b]95% tolerance interval				
[c]Middle of myocardium				
[d]Appex of myocardium				
(d) Bone marrow				
SE	MESE	122	10 (27)	Pai et al. [46]
SE	SE	40	10 (27)	Pai et al. [46]
SE	FSE (ETL 4)	110	10 (27)	Pai et al. [46]
SE	FSE (ETL 8)	127	10 (27)	Pai et al. [46]
SE	FSE (ETL 8)	160	10 (27)	Pai et al. [46]
SE	SSFSE	49 ± 4	6 (31.5)	De Bazelaire et al. [16]
(e) Cartilage				
SE	Spiral	38	10 (27)	Pai et al. [46]
SE	MESE	34	10 (27)	Pai et al. [46]
SE	SE	28	10 (27)	Pai et al. [46]
SE	FSE (ETL 4)	28	10 (27)	Pai et al. [46]
SE	FSE (ETL 8)	41	10 (27)	Pai et al. [46]
SE	FSE (ETL 16)	45	10 (27)	Pai et al. [46]
SE	3D SPGR	32	10 (27)	Pai et al. [46]
SE	Hybrid-SE	37 ± 4	5 (range 27 to 38)	Gold et al. [13]
(f) Diverse tissues				
Prostate	SSFSE	74 ± 9	6 (31.5)	De Bazelaire et al. [16]
Prostate	MESE	80 ± 34	3 (32 ± 8)	Bojorquez et al. [15]
Pancreas	SFSE	43 ± 7	6 (31.5)	De Bazelaire et al. [16]
Liver	SSFSE	34 ± 4	6 (31.5)	De Bazelaire et al. [16]
Liver	MRF-FISP	31 ± 6	8 (range 22 to 45)	Chen et al. [50]
Spleen	SSFSE	61 ± 9	6 (31.5)	De Bazelaire et al. [16]
Spleen	MRF-FISP	60 ± 19	8 (range 22 to 45)	Chen et al. [50]
Uterus myometrium	SSFSE	79 ± 10	6 (31.5)	De Bazelaire et al. [16]
Uterus endometrium	SSFSE	59 ± 1	6 (31.5)	De Bazelaire et al. [16]
Uterus cervix	SSFSE	83 ± 7	6 (31.5)	De Bazelaire et al. [16]
Kidney medulla	SSFSE	81 ± 8	6 (31.5)	De Bazelaire et al. [16]
Kidney medulla	MRF-FISP	60 ± 21	8 (range 22 to 45)	Chen et al. [50]
Kidney cortex	SSFSE	76 ± 7	6 (31.5)	De Bazelaire et al. [16]
Kidney cortex	MRF-FISP	47 ± 10	8 (range 22 to 45)	Chen et al. [50]
Synovial fluid	Hybrid-SE	767 ± 49	5 (27–38)	Gold et al. [13]
Fibroglandular tissue	Two Hahn echo	54 ± 9	6 (36 ± 12.6)	Rakow-Penner et al. [7]

Table 2 (*continued*)

Imaging Method	Specific Sequence	T_2 (ms) (mean ± STD)	Volunteers/Age number/(mean ± STD)	Reference
Fibroglandular tissue	16-echo spin echo	71 ± 6	6 (34 ± 6)	Edden et al. [2]
Gray matter	CPMG	83±4[a]	10 (28 ± 5)	Lu et al. [21]
Gray matter	MRF-FISP	109 ± 11	1	Jiang et al. [49]
White matter	CPMG	75±3[b]	10 (28 ± 5)	Lu et al. [21]
White matter	MRF-FISP	65 ± 6	1	Jiang et al. [49]
Marrow fat	Hybrid-SE	365 ± 9	5 (range 27 to 38)	Gold et al. [13]

[a]mean of reported values of occipital and frontal gray matter.
[b]mean of reported values of occipital and frontal white matter.

standardization are achieved when these ambiguities are removed. In the future, it might be of interest to perform standardized multicenter trial to evaluate existing methods and to set reference T_1 and T_2 values once and for all. Meanwhile, we recommend to compute reference relaxation time values according to the center's MR resources.

Appendix A. TriTone Method

In the TriTone method, the observed signal M_z is a function of the sequence parameters, longitudinal (T_1) and transverse (T_2^*) relaxation times, flip angle inhomegeneity described by the actual-to-nominal flip angle ratio (B_1) and a factor proportional to the equilibrium magnetization (M_o). The observed signal is given by Eq. (26).

$$M_z = M_o \frac{1-e^{-TR/T_1}}{1-cos(\beta\alpha)e^{-TR/T_1}} sin(\beta\alpha)e^{-TE/T_2^*} \quad (26)$$

From Eq. (26), it is possible to estimate T_1 using only three SPGR images (M_{zm}, m = 1, 2, 3) obtained with either different TRs or FAs, but keeping constant the rest of the sequence parameters (FOV, bandwidth, spatial resolution). The T_1 estimation is possible because the ratio of any two images depends only on the unknown T_1 and B_1. Therefore, a pair of such ratios, M_{z1}/M_{z2} and M_{z2}/M_{z3} or, equivalently, a pair of spherical angles $\rho = arctan(M_{z3}, M_{z1})$ and $\theta = \left(\frac{M_{z2}}{\sqrt{M_{z1}^2+M_{z2}^2+M_{z3}^2}}\right)$ can be used to generate a two dimensional look-up table $T_1(\rho,\theta)$. The table is then polled for T_1 extraction [36].

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