15th International Symposium on Computer Methods in Biomechanics and Biomedical Engineering
and
3rd Conference on Imaging and Visualization
CMBBE 2018
P. R. Fernandes and J. M. Tavares (Editors)

T1 UNCERTAINTY ESTIMATION OF BONE MARROW IN LUMBAR VERTEBRAE USING MAGNETIC RESONANCE IMAGING

Mohan L. Jayatilake*, **Teresa Gonçalves**†

*Department of Radiography/Radiotherapy, Faculty of Allied Health Science
University of Peradeniya, Sri Lanka
jayatiml@pdn.ac.lk

†Departament of Informatics, School of Science and Technologies
University of Évora, Portugal
tcg@uevora.pt

Keywords: Magnetic Resonance Imaging, Longitudinal Relaxation Time, Acute Myeloid Leukaemia.

Abstract: *The precise determination and analysis of T1 is crucial for diagnosis, prognosis, and monitoring therapeutic response in a variety of diseases such as Acute Myeloid Leukaemia either by comparing the native T1 values in longitudinal studies or by quantifying the physiological parameters in MRI. Therefore, in this study we optimize the accuracy of T1 using the derived uncertainty evaluation expression with the fixed two-flip angles and assess the error of T1 measurement in bone marrow of five Acute Myeloid Leukaemia (AML) patients. MR image data was collected and MATLAB software was used in the image processing and data analysis. For quantitative MRI data analysis, Regions of Interest (ROI) on multiple image slices were drawn encompassing vertebral bodies of L3, L4 and L5. Both the T1 and the uncertainty of T1 were evaluated using the T1 maps obtained. Then the accurate bone marrow mean value of T1 out of five subjects was estimated as 760.3 (ms) at 3T. However, the reported T1 value of healthy subjects is significantly higher (946.0 ms) than the present finding. This suggests that the T1 for bone marrow can be considered as a potential prognostic biomarker for AML patients.*

1. INTRODUCTION

The longitudinal relaxation time constant (T1), is one of the basic fundamental parameters in understanding Magnetic Resonance Imaging (MRI) [1]. An accurate and precise determination and analysis of T1 is crucial for diagnosis, prognosis, and monitoring therapeutic response in a variety of diseases either by comparing the native T1 values in longitudinal studies or by quantifying the physiological parameters in MRI [1, 2]. In the dynamic contrast enhanced (DCE)-MRI data quantification, native T1 value is a critical parameter, in order to convert the MRI signal intensity to the contrast concentration-time curve. The signal intensity variation pre- and post- contrast injection is dependent on the native longitudinal relaxation rate of R10 ($R10 = 1/T1$); any error in the R10 measurement propagates comparably into the pharmacokinetic parameters derived in DCE-MRI. Further, the T1 value is expected to significantly

change with pathology. In order to make precise comparisons of T1 values found in healthy and diseased tissue and perform longitudinal or inter-subject comparisons, T1 measurements should be of high accuracy. Hence, it is important to optimize the accuracy of T1 measurement by minimizing the effect of its uncertainty.

For fast 3D mapping of T1 relaxation time in vivo, the Spoiled Gradient Echo (SPGR) imaging with two fixed flip angles is a widely used and this technique has a greater noise efficiency when compared to other T1 measurement methods [3, 4]. Within the bone marrow, increased microvascular density is observed in Acute Myeloid Leukaemia (AML) [3, 4]. Although it is increasingly recognized that AML is a biologically heterogeneous disease, relatively few prognostic markers have been identified and the results of these laboratory studies are typically not available prior to the initiation of therapy in most patients [3].

Consequently, there is a critical need to identify rapidly evaluable biomarkers associated with the most important therapeutic endpoint in AML, a complete remission (CR). Early identification of patients who are unlikely to respond to conventional chemotherapy would permit the rapid development of personalized therapeutic approaches for this high risk population while avoiding exposure to toxic and ineffective therapies. MRI can facilitate an estimation of bone marrow cellularity for prognosis of AML and assessment of response to therapy [3, 4]. Quantitative determination and analysis of relaxation times enable development of novel imaging protocols and may be useful in characterization and long term follow up of pathological conditions. T1 measurements in musculoskeletal tissue have been utilized in several previous studies as a prognostic indicator [3, 4, 5].

The abnormalities of femoral marrow in T1 weighted images in relation to development of Leukaemia were investigated and positive findings were obtained [5, 6]. It was revealed that the T1 relaxation time changes of the bone marrow in patients with AML reflected changes in disease activity and it has been suggested that serial measurements of T1 values may provide clinically useful information with the possibility for identification of residual disease in regions inaccessible for biopsy [7]. A similar study has evaluated T1 relaxation time measurements of vertebral bone marrow in paediatric Acute Lymphoblastic Leukaemia patients and a significant correlation between T1 relaxation time and the malignant blast cells in the vertebral bone marrow was found [7, 8].

Therefore, in this study, the potential for a prognostic biomarker using MRI will be explored by evaluating precise value of T1 in bone marrow of AML patients. The precision of T1 is optimized using the derived error expression with the fixed two-flip angles. Further, this study aims to assess the uncertainty in T1 measurement in bone marrow of human subject with AML. The results will be helpful to improve the understanding of how advanced imaging technologies can be utilized to distinguish AML patients non-invasively.

2. THEORY

The SPGR imaging with variable flip angles will be used to evaluate the T1 relaxation times in vivo within vertebral bodies of L2, L3, and L4. T1 will be calculated using the theoretical expression for SPGR signal intensity (S) at steady state which is given in equation 1 [9].

$$S(TR, TE, \alpha) = \frac{M_0 \cdot \sin(\alpha) \cdot (1 - E_1) \cdot E_2}{1 - E_1 \cdot \cos(\alpha)} \tag{1}$$

M_0 is the product of the proton density and system gain (equivalent to the signal measured when $TR >> T1$ and $TE << T2*$ at a flip angle of 90°), α is the true flip angle, $E1 = e - TR/T1$ and $E2 = e - TR/T2*$. Based on the ratio of signal intensities (S) for two flip angles, ϕ and ψ, the $T1$ will be obtained using equation 2 [8, 10].

$$T1 = TR/\ln \frac{\rho \cdot \sin(\phi) \cdot \cos(\psi) - \cos(\phi) \cdot \sin(\psi)}{\rho \cdot \sin(\phi) - \cos(\psi)} \tag{2}$$

Here ρ is defined as the ratio of signal intensities (S) for the two flip angles (ϕ and ψ) and is given by equation 3.

$$\rho = \frac{S(TR, TE, \psi)}{S(TR, TE, \phi)} \tag{3}$$

Using the theory of propagation of errors and combining 1, 2 and 3, we can write the uncertainty in T1 as

$$U(T1) = \frac{2 \cdot T1^4 \cdot E_\psi^2 \cdot E_\phi^2 \cdot (E_\psi^2 \sin^2(\phi) + E_\phi^2 \sin^2(\psi)}{2 \cdot SNR^2 \cdot TR^2 \cdot E_1^2 \cdot E_2^2 (E_1 - 1) \cdot \sin^2(\phi) \cdot \sin^2(\psi) \cdot (\cos(\psi) - \cos(\phi))^2} \tag{4}$$

We define the signal-to-noise ratio as $SNR = M_0\sqrt{N}/\rho$, where M_0 is the signal corresponding to an acquisition performed with a 90° flip angle in the long TR limit, N is the number of measurements and ρ is the noise in the measured signals [2, 10, 11]. Moreover, $E_\psi = E_1 \cdot \cos(\psi) - 1$ and $E_\phi = E_1 \cdot \cos(\phi) - 1$.

3. MATERIALS AND METHODS

3.1 Data Acquisition and Image Analysis

Five newly diagnosed AML patients consented to a research DCE-MRI study before undergoing standard induction chemotherapy. All the MRI scans were performed with a 3T Siemens Tim Trio system using the body coil and the spine matrix phased array coil as the transmitter and receiver, respectively. Following pilot and anatomic MRI, a 3D-SPGR pulse sequence was used to acquire coronal MRI data with variable flip angles (5° and 10°), $TE/TR = 1.4/6.0$ ms, 34 cm FOV and 288x288 matrix size. Each image volume set included 22 slices with 5mm slice thickness, covering the anterior-to-posterior spatial range of lumbar vertebrae to iliac crest where bone marrow (BM) biopsy was performed to confirm diagnosis and remission status. The MR image data was collected in the Digital Imaging and Communications in Medicine (DICOM) format and MATLAB Simulink 2011 software was used in the image processing and data analysis.

3.2 Measurement of T1

For quantitative data analysis, ROIs on multiple image slices were drawn encompassing vertebral bodies of L3, L4 and L5. The T1 pixel values were computed with equation 1 and equation 2 using all pixel values within the multi-slice ROIs. The mean T1 value of each anatomic location was then calculated. Subsequently, for each patient, an overall bone marrow mean value of T1 was calculated by averaging the mean values of the three locations. Then the T1 maps within ROIs of L3, L4, and L5 were overlaid on the anatomical images.

3.3 Measurement of uncertainty of T1

The signal-to-noise ratio was set in order to maintain the constant noise efficiency when comparing acquisitions with $TE = 1.4$ ms and $TR = 6.0$ ms. The parameter value of $T2*$ was set to 50 ms. The precise values of SNR and $T2*$ chosen are irrelevant for purposes of measuring uncertainty of T1, because these parameters simply scale the T1 measurement uncertainty. The T1 pixel values within both anatomic location and the multi-slice ROIs were determined using equation 4. Then, the box plot for measured T1 pixel values and optimized T1 pixel values within L3, L4 and L5 were plotted.

4. RESULTS

The magnitude of the T1 pixel values was analysed within the measured, simulated uncertainty and the corrected coronal view of each of the five subjects under study.

Figure 1 shows the coronal view of T1 pixel values (measured and uncertainty values) over lumbar vertebrae L3, L4 and L5. The measured T1 values within the soft tissues and bone marrow varies from 500 ms to 1000 ms, but the uncertainty or error of T1 pixel values varies from 60 ms to 130 ms. The mean uncertainty of T1 shows significantly high at the third column number and the row number of five (at L5); however, uncertainty of T1 is not significantly higher in other lumbar vertebrae regions.

Table 1 illustrates the measured, uncertainty and corrected mean T1 values of overall bone marrow of each individual subject. The measured T1 value varies from 835 ms to 864 ms. However, the corrected mean T1 value varies from 750 ms to 792 ms, so it is clearly observed that there is a significant difference between measured and corrected T1 pixel values of lumbar vertebrae.

Subject	Measured	Uncertainty	Corrected
S1	834.6	66.6	768.0
S2	841.7	91.8	749.9
S3	854.2	81.0	773.2
S4	834.6	69.6	765.0
S5	863.6	71.6	792.0

Table 1. Measured, uncertainty and corrected mean T1 values of overall bone marrow of five subjects. The units of T1 values are in ms.

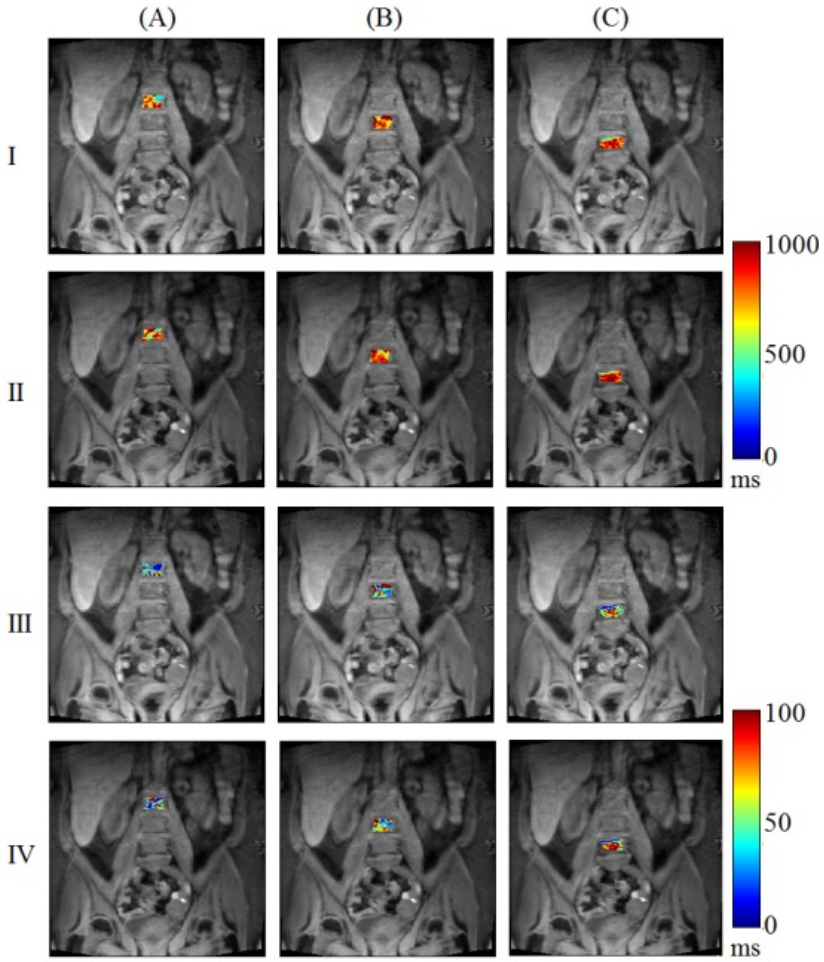

Figure 1. A subject with suspected Acute Myeloid Leukaemia. The coronal view of measured (I and II) and uncertainty (III and IV) T1 pixel values over the lumbar vertebrae of L3 (A), L4 (B) and L5 (C) are overlaid on anatomical sites of slice numbers of 14 and 15. The simulated uncertainty T1 pixel values was computed at variable flip angles of 5° and 10°, with $TE = 1.4$ ms and $TR = 6.0$ ms.

The box plot shown in Figure 2 illustrates the measured and corrected pixel T1 value distribution in overall bone marrow of each individual subject (S1, S2, S3, S4 and S5). The horizontal line (in red) on each box indicates the mean value of T1 within overall lumbar vertebrae. It is easily observed that measured and corrected values are significantly different.

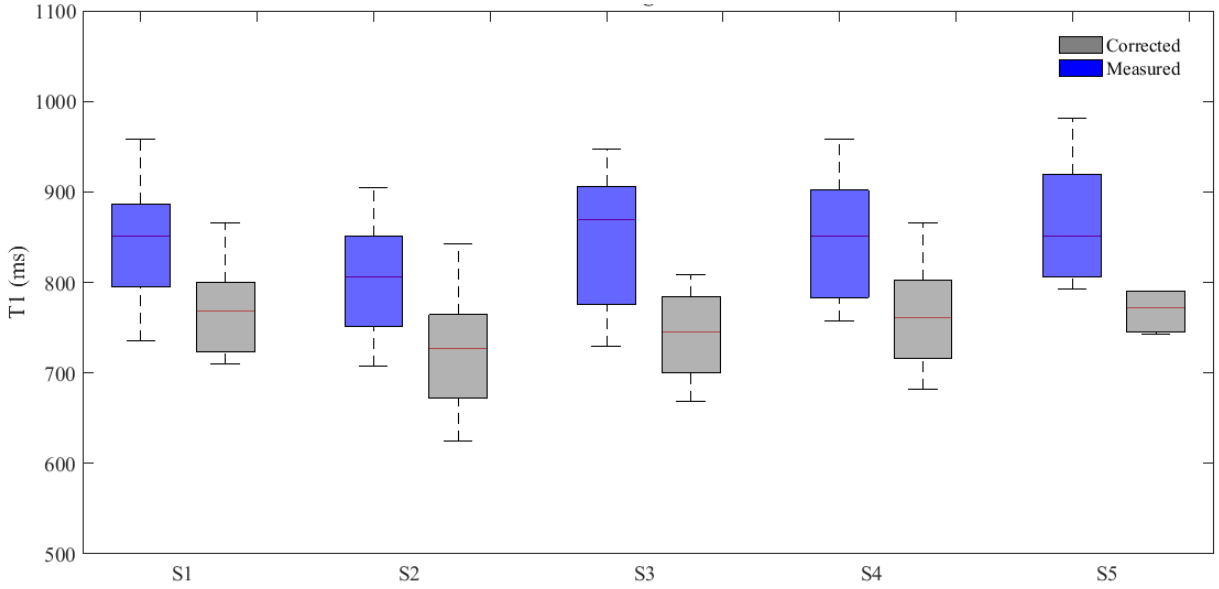

Figure 2. Box plots of the T1 for measured and corrected pixel value within overall bone marrow of individual five subjects, S1, S2, S3, S4 and S5. Horizontal line indicates the median, box the interquartile range (IQR) of T1 of corrected and measured, whiskers extended to upper adjacent value (large value = 75th percentile $+1.5\times$IQR) and lower adjacent value (smallest value = 25th percentile $-1.55\times$IQR).

Table 2 displays the mean values over the five subject for each of the L3, L4 and L5 lumbar vertebrae. The measured mean T1 values vary from 753 ms to 892 ms whereas corrected T1 values vary between 724 ms and 810 ms. Further, uncertainty of T1 vary between 28 ms and 122 ms. This significant higher magnitude of T1 uncertainty is observed in L5.

Vertebrae	**Measured**	**Uncertainty**	**Corrected**
L3	752.6	28.3	724.3
L4	891.8	81.5	810.3
L5	884.8	122.4	759.7

Table 2. Measured, uncertainty and corrected mean T1 values of overall bone marrow of L3, L4 and L5 lumbar vertebrae of five subjects. The units of T1 values are in ms.

The box plot shown in Figure 3 illustrates the measured and corrected pixel T1 value distribution in overall bone marrow of all five subjects. The overall bone marrow mean T1 value is 840.6 ms at 3T but the corrected one is 760.3 ms. It is then, clearly observed that there is a significant difference between measured and corrected T1 pixel values.

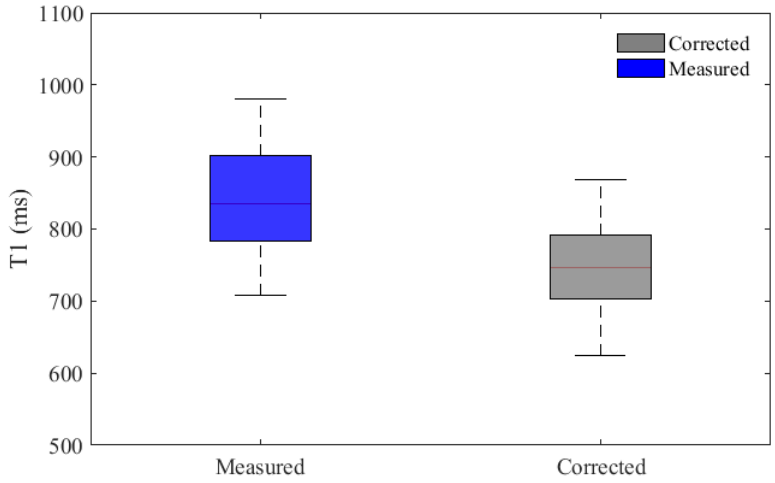

Figure 3. Box plots of the T1 for measured and corrected pixel value over the within overall bone marrow of all five subjects T1 pixel values within overall bone marrow. Horizontal line indicates the median, box the inter-quartile range (IQR), whiskers extended to upper adjacent value (large value = 75th percentile $+1.5\times$IQR) and lower adjacent value (smallest value = 25th percentile $-1.55\times$IQR).

5. DISCUSSION, CONCLUSION AND FUTURE WORK

The major goal of this study was to estimate the uncertainty of T1 relaxation time constant in bone marrow of AML patients. Even though, T1 values increase when moving from low to high magnetic field strengths, the corrected T1 at 3T for bone marrow of AML patients was estimated as 760.3 ms. However, the value of healthy subjects reported is significantly (946.0 ms) higher [1]. The findings suggest that the T1 of bone marrow is a potential prognostic biomarker for AML patients. Active enrolment of more subjects for this study is currently ongoing to validate the preliminary results. Further, knowledge of T1 relaxation time at 3T will allow intelligent design of new AML imaging protocols. For example, T1 values can be used to optimize inversion times for inversion recovery imaging.

In conclusion, this technique can be used to optimize the T1 accuracy that maximizes the benefit of increased SNR (Signal-to-Noise Ratio) at 3T.

One possible line of future work includes the use of Machine Learning techniques aiming to get a model that is able to distinguish between AML patients and healthy subjects through the analysis of MRI images.

ACKNOWLEDGEMENTS

The research reported in this publication was supported by the Erasmus Mundus Action 2, Strand 1 LEADER project.

References

[1] G.J. Stanisz, E.E. Odrobina, J. Pun, M. Escaravage, and S.J. Graham. T1, t2 relaxation and magnetization transfer in tissue at 3t. *Magnetic Resonance in Medicine*, 54(3):507–12, 2005.

[2] H.L. Cheng and G.A. Wright. Rapid high-resolution t(1) mapping by variable flip angles: accurate and precise measurements in the presence of radiofrequency field inhomogeneity. *Magnetic Resonance in Medicine*, 55(3):566–74, 2006.

[3] G. Paone, G. Stüssi, M. Pons, L. Giovanella, and L. Ceriani. Bone marrow involvement in unknown acute myeloid leukemia detected by 18f-fdg pet/mri. *Clinical Nuclear Medicine*, 40(10):486–7, 2015.

[4] M. Jayatilake, A. Afzal, X.Li, Y.Chen, W.J. Woodward, T.J. Kovacsovics, W.H. Fleming, and W.Huang. Quantitative dce-mri as a predictor of acute leukemia response to therapy. *Proceedings of the International Society for Magnetic Resonance in Medicine*, 21., 2013.

[5] S. Takagi, O. Tanaka, H. Origasa, and Y. Miura. Prognostic significance of magnetic resonance imaging of femoral marrow in patients with myelodysplastic syndromes. *Journal of Clinical Oncology*, 17(1):277–83, 1999.

[6] M. Rozman, J.M. Mercader, J.L. Aguilar, E. Montserrat, and C. Rozman. Estimation of bone marrow cellularity by means of vertebral magnetic resonance. *Haematologica*, 82(2):166–70, 1997.

[7] K.E. Jensen, C. Thomsen, O. Henriksen, H. Hertz, H.K. Johansen, and M. Yssing. Changes in t1 relaxation processes in the bone marrow following treatment in children with acute lymphoblastic leukaemia. a magnetic resonance imaging study,. *Pediatric Radiology*, 20(6):464–8, 1990.

[8] E.K. Fram, R.J. Herfkens, G.A. Johnson, G.H. Glover, A. Shimakawa J.P. Kari and, T.G. Perkins, and N.J. Pelc. Rapid calculation of t1 using variable flip angle gradient refocused imaging. *Magnetic Resonance Imaging*, 5(3):201–8, 1987.

[9] C.L. Deoni. High-resolution t1 mapping of the brain at 3t with driven equilibrium single pulse observation of t1 with high-speed incorporation of rf field inhomogeneities (despot1-hifi). *Journal of Magnetic Resonance. Imaging*, 26(4):1106–11, 2007.

[10] M.C. Schabel and G.R. Morrell. Uncertainty in t1 mapping using the variable flip angle method with two flip angles. *Physics in Medicine & Biology*, 54(1), 2009.

[11] T.L. Chenevert, D.I. Malyarenko, D. Newitt, X.Li, M.Jayatilake, A.Tudorica, A.Fedorov, R. Kikinis, T.T. Liu, M. Muzi, M.J. Oborski, C.M. Laymon, X.Li, K.C. Jayashree Y.Thomas, J.M. Mountz, P.E. Kinahan, D.L. Rubin, F. Fennessy, W. Huang, N. Hylton, and B.D. Ross. Errors in quantitative image analysis due to platform-dependent image scaling. *Translational Oncology*, 7(1):65–71, 2014.