Low-Field NMR Relaxation Times Distributions and Their Magnetic Field Dependence as a Possible Biomarker in Cartilage

O.V. Petrov[1], E. Rössler[1], C. Mattea[1], M.T. Nieminen[2,3,4], P. Lehenkari[2], S. Karhula[2,3], S. Saarakkala[2,3], and S.Stapf[1]

[1]Dept. of Technical Physics II, TU Ilmenau, 98684 Ilmenau, Germany
[2]Research Unit of Medical Imaging, Physics and Technology, University of Oulu, P.O. 5000, 90014 Oulu, Finland
[3]Medical Research Center, University of Oulu and Oulu University Hospital, P.O. 50, 90029 Oulu, Finland
[4]Department of Diagnostic Radiology, Oulu University Hospital, P.P. 50, 90029 Oulu, Finland

Abstract— **The dependence of the proton NMR relaxation times on field strength and on location within the tissue has been determined for a number of bovine and human articular cartilage samples. While the strong variation of T_2 across the triple-layered cartilage structure as well as its orientation dependence are well known from clinical and laboratory high-field studies, T_1 shows similar behavior only in low magnetic fields. At 0.27 T, the ratio of longest to shortest T_1 has been found to cover a ratio of about 3-5 in healthy tissue. At the same time, the average T_1 was found to be strongly field dependent in the range down to 0.25 mT, but no spatially resolved data are available under these conditions. By correlating the spatially resolved T_1 distribution obtained at field strengths of 0.27 T with mathematical decompositions of the signal recovery function into multiexponential components, an attempt is made to quantify the width of $P(T_1)$ for variable field strengths, and to identify the field value where this distribution is widest, being optimally situated as a biomarker for laboratory studies or preclinical low-field investigations where spatial resolution is absent or insufficient to resolve the cartilage layer structure.**

Keywords— **relaxometry, low field NMR, cartilage, osteoarthritis**

I. Introduction

Clinical MRI investigations of cartilage tissue in joints and spine has become a standard procedure for a number of health issues; however, most clinical studies rely on topological information, such as distances between bone surfaces, and peripheral tissue such as ligaments and tendons. Despite limited resolution of the only 2-3 mm thick cartilage itself, and its rather short T_2, a wealth of information has been derived from clinical and ex-vivo studies, in particular concerning one of the most common diseases, osteoarthritis (OA). Among others, the values of T_2 and $T_{1\rho}$ and their orientational dependence, the analysis of the diffusion coefficient and its anisotropy, and the change of these parameters under mechanical load were investigated, suggesting their feasibility as biomarkers for OA. A recent book provides a summary of the state-of-the-art of MRI studies on cartilage [1]. The vast majority of these studies were carried out at either typical clinical field strength of 1.5-3T, or on high-field scanners.

In recent years, a new generation of low-field solutions, either whole-body or extremity scanners, have entered the market; they combine the reduction in cost with larger flexibility, for instance by allowing to tilt the patient together with the detection system in order to compare the state in joints with and without pressure [2]. While low magnetic field strengths inevitably lead to a loss of SNR, and consequentially of spatial resolution, measurements at lower fields often experience larger contrast and potentially hold extra information not available at typical clinical field strengths. In an early work, the superiority of T_1 vs. T_2 contrast in cartilage imaging at 0.15 T was already pointed out [3]; dedicated devices for extremities have been presented [4], and routines for osteoarthritis prediction at 0.18 T were discussed [5]. Different aspects of low-field and high-field cartilage imaging are reviewed in [6,7].

At low magnetic fields, the most promising parameter for improved contrast is T_1, but related studies have been rather limited to this date. In [8] it was shown that the variation of ^{1}H T_1 over the cross-section of mammalian cartilage can amount to a factor of 3-5 at a field of 0.27 T, similar if not larger than the variation in T_2 at any field strength, and larger than at high field [9,10]. T_1 is more robust to measure and is independent of orientation; like T_2, it allows, when measured at low fields, for the distinction of the three zones of cartilage (superficial, transition, radial). This is achieved with low-field scanners of high spatial resolution, like the NMR-MOUSE (Magritek, Aachen, Germany) providing resolution mainly along one dimension [11], which however is suitable for materials with layered structure such as cartilage. Measurements at much lower fields have recently been proposed [12], but they are subject to hardware limitations that lead to reduced spatial resolution insufficient to separate the details within cartilage tissue. This makes volume-averaged studies on field-cycling relaxometers the currently only available tool for investigating frequency dependences in tissue [13], and one parameter accessible only at low fields, the intensity

H. Eskola et al. (eds.), *EMBEC & NBC 2017*,
IFMBE Proceedings 65,
DOI: 10.1007/978-981-10-5122-7_238

of the cross-relaxation of ^{1}H with ^{14}N nuclei, was indeed shown to correlate with OA [14].

The decomposition of the signal decay into two or more components or even the determination of the relaxation distribution function by means of Inverse Laplace Transform (ILT) have become feasible also for field-cycling relaxometry studies, supported by the increased availability of appropriate inversion algorithms [15,16]. Due to its generally rather narrow relaxation time distribution, biological tissue has not yet been studied by ILT. However, cartilage appears to be a more suitable system since its T_1 range is larger than that of other tissue, and sufficiently broad to suggest deviations in the decay curves from exponentiality may become observable at low field. Considering the rather narrow T_1 distribution observed in many high-field studies [9,10] and the mentioned broad range at 0.27 T [8], it can be speculated whether the T_1 contrast across cartilage tissue, and hence the with of the T_1 distribution in the spatially unresolved signal, is growing even further towards very low fields.

In this contribution, the range of relaxation times values across articular cartilage is discussed in the context of experimentally accessible parameters with different NMR hardware, and a first attempt is made at quantifying the T_1 distribution width at different magnetic field strengths in order to identify optimal experimental parameters for a new biomarker for degenerative diseases such as osteoarthritis.

II. Materials and Methods

A total of 20 osteochondral plug samples of 6-mm diameter were extracted from human tibial plateaus from patients undergoing total knee arthroplasty, and were stored frozen at -20°C in tubes filled with phosphate buffer solution [17]. The experiments were approved by the Ethical Committee of the Northern Ostrobothnia Hospital District, Oulu, Finland (191/2000). Each sample was allowed to equilibrate for 24 h at +6°C before being exposed to room temperature, and was then placed in a tightly fitting cylindrical container that was mounted on top of an NMR-MOUSE single-sided scanner (Magritek, Aachen, Germany) operating at a ^{1}H Larmor frequency of 11.7 MHz, and the relaxation times T_2 and T_1 of the tissue were determined with a one-dimensional resolution of 50 µm. The same experiment was repeated under vertical pressure of 0.6 MPa immediately afterwards. Samples were then taken out of the cell and the cartilage was separated from the bone and calcified tissue. The cartilage samples were subsequently measured in a SpinMaster 2000 Fast Field Cycling relaxometer (Stelar, Mede, Italy), and the T_1 dispersion was obtained in the frequency range 10 kHz … 20 MHz following a single 90° pulse and integrating the FID.

A second set of field cycling experiments was carried out with bovine knee articular cartilage samples which were taken from fresh stifle joints of femur bones by cutting them into pieces tightly fitting in the sample container. Samples were stored in PBS and were treated the same way as human samples. For these samples, the signal decays were analyzed allowing for multi-exponential decays.

III. Results and Discussions

The relaxation time T_1 as a function of depth, with zero indicating the top cartilage surface, of a human articular cartilage sample obtained at 0.27 T with the NMR-MOUSE is shown in Figure 1. This particular sample features a rather large, but not unusual variation of T_1, varying between about 130 ms and 550 ms, the maximum being located in the transitional zone. For bovine articular cartilage, the variation across zones has been shown to be similar to that of T_2 [8], though the range of values is larger for T_1.

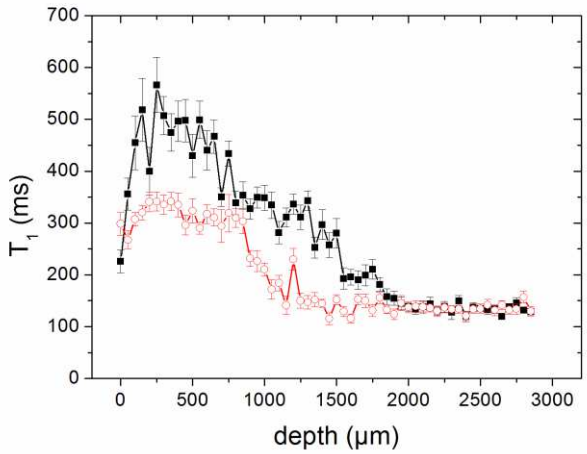

Fig. 1 T_1 distribution in a human knee articular cartilage sample obtained at 0.27 T and 293 K. Filled squares represent measurements without mechanical load, open circles for uniaxial load of 0.6 MPa.

Figure 1 also demonstrates the effect of uniaxial load onto the sample: water becomes expelled outside the measurement volume, cartilage is compressed [18], and the maximum T_1 is decreased while the minimum remains about the same, thus reducing the dynamic range $T_{1,max}/T_{1,min}$. It should be noted that this sample has been described by an advanced stage of osteoarthritis [18], and that healthy tissue is mostly found to show much smaller changes in shape and T_1 upon loading.

The obtained values of $T_{1,max}/T_{1,min}$ were cross-correlated with a number of other parameters obtained from NMR measurements carried out at 0.27 T and at variable field ([18],

a report on a more detailed study is currently under review), and the strongest correlation was found with the frequency dependence of the average relaxation time at Larmor frequencies between 1 and 20 MHz. This dependence is frequently expressed as an apparent power-law relation, $T_1 \sim \nu^{\alpha}$. The correlation between $T_{1,max}/T_{1,min}$ (at 0.27 T) and the power-law exponent α is shown in Figure 2 for a set of 20 human cartilage samples. Despite the phenomenological observation of this behavior, an explanation of the dispersion is not yet available, while the frequency dependence in this field range is much more pronounced for cartilage than for other biological tissue. However, it can be explained in general terms by the interaction of water with its environment, i.e. predominantly collagen fibers and proteoglycans, and the molecular reorientation along the respective surfaces, where the relevant timescales of motion correspond to the reciprocal frequencies where dispersion occurs, i.e. on the order 10^{-8} to 10^{-6} s. Appropriate models were developed for inorganic porous media and are currently being discussed for biological systems, but are beyond the scope of this contribution.

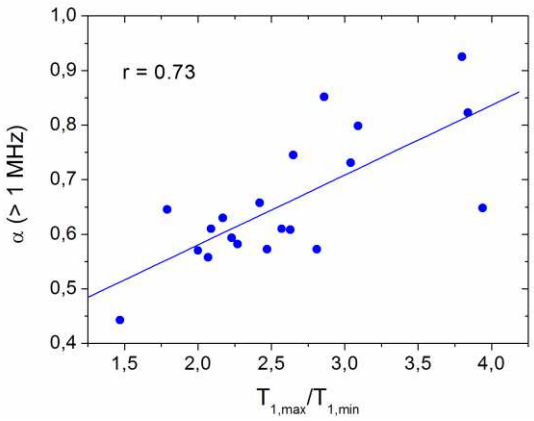

Fig. 2 Correlation between the ratio of maximum and minimum T_1 in human articular knee cartilage without load at 0.27 T and293 K, and exponent α of $T_1 \sim \nu^{\alpha}$ obtained from relaxation dispersion measurements between 1 MHz and 20 MHz ^{1}H resonance frequency (0.025 T to 0.45 T).

It is worth noting that the equivalent parameter for the transverse relaxation times, $T_{2,max}/T_{2,min}$, does not show a statistically relevant correlation with any other observed parameter (in particular, ρ=0.14 when compared to α, whereas any correlation coefficient below 0.45 is not significant for a sample set of 20 and p=0.05). The dispersion exponent α, on the other hand, shows correlation with the degree of osteoarthritis [18] and is thus possibly related to the concentration of GAGs or of water, both being indicators for OA.

The attempt to obtain $T_{1,max}/T_{1,min}$ from spatially unresolved data, i.e. purely from signal decays of the full tissue, is a mathematical problem that depends necessarily on the signal-to-noise ratio and the resolution of time points acquired during the experiment. Under perfect conditions, the two components of a biexponential decay can be resolved even when quite similar, say 10 or 20% different. The problem is much more challenging for a continuous distribution which is prevalent in cartilage. Typical estimates suggest that distributions with a width of a factor of less than 2-3 cannot be distinguished safely from a monoexponential behavior. ILT, for instance, generates a distribution that can be too broad or too narrow, depending on the choice of the normalization parameter, and can be forced towards a delta function; its use is therefore never unambiguous and the result frequently requires prior knowledge of the distribution function. For the case of cartilage, however, the smooth shape of this function can be estimated reasonably well.

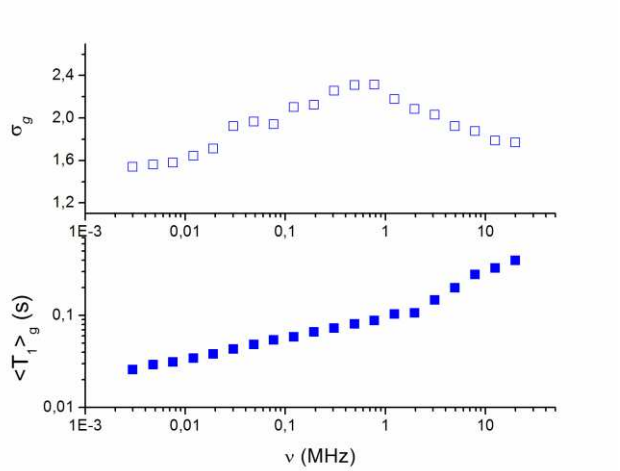

Fig. 3 Geometric mean relaxation time (bottom) and normalized standard deviation obtained from the second moment obtained from a logarithmic moments analysis (top) for bovine articular cartilage as a function of Larmor frequency at T=310 K.

As a robust parameter, the normalized second moment of the distribution as derived from an analysis involving logarithmic moments of the time-domain data [19] is suggested (manuscript in preparation). While it does not directly provide the range of T_1 in the data, it is much less affected by assumptions within the ILT process, and its results and their dependence on statistical fluctuations of experimental data are known. In Figure 3, the trend of the standard deviation, being the square root of this second moment, as a function of Larmor frequency is shown for bovine articular cartilage samples, along with the plot of the geometric mean relaxation times of the same data. Results for three different samples were averaged.

The trend for $T_1(\nu)$ confirms earlier findings [8,17,19,20], i.e. a weak frequency dependence up to about 1 MHz and a

more pronounced variation above 1 MHz as discussed along with Figure 2. Note that all earlier studies have assumed monoexponential decay functions; the apparent exponents remain similar for the geometric mean data. The variation of the width of the T_1 distributions becomes evident from the top of Figure 3, being the first time that such an observation is reported. This width assumes a maximum at about (0.65 ± 0.15) MHz, corresponding to a magnetic field strength of (15 ± 3) mT. It is assumed that the distribution of T_1 across the cartilage tissue is largest at this field strength, and it thus appears reasonable to predict that physiological variations such as tissue degeneration will affect the measured values most in this frequency range. On the other hand, the decrease of the distribution width towards both high and low fields is in agreement with observations made for T_1 at high fields [9,10] and for $T_{1\rho}$ [17,21] which is expected to behave similar to T_1 when replacing the value of the B_1 field by B_0.

IV. Conclusions

The variation of T_1 across the cartilage tissue, as obtained by MRI studies at 0.27 T and above, follows a known pattern and was observed earlier to be affected by mechanical load and by the degree of osteoarthritis [18]. At even lower fields or in experiments at variable field, technology with sufficient spatial resolution is not yet available but a correlation of the range of the T_1 distribution at 0.27 T width with the frequency dispersion is found in this study: For the first time, this width has been determined for bovine cartilage samples over the entire frequency range between 10 kHz and 20 MHz, and a maximum width has been identified around 15 mT. Further studies will concentrate on the properties of human articular cartilage and the possibility to exploit the width of $P(T_1)$ with and without load for an assessment of the stage of osteoarthritis in humans, and to provide strategies for suitable experiments carried out at this characteristic field strength *in vivo*.

Acknowledgment

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 668119 (project "IDentIFY"). ER gratefully acknowledges Carl Zeiss Stiftung for the scholarship to pursue his PhD research. MTN is indebted to Jane and Aatos Erkko Foundation, Finland for financial support.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Xia Y, Momot K (editors), Biophysics and Biochemistry of Cartilage by NMR and MRI, London: Royal Soc. Chem., 2016.
2. Dahabreh IJ, Hadar N, Chung M (2011) Emerging Magnetic Resonance Imaging technologies for musculoskeletal imaging under loading stress: Scope of the literature. Ann. Internal Med. 155: 616-624
3. Adams ME, Li DKB, McConkey JP et al. (1991) Evaluation of cartilage lesions by magnetic resonance imaging at 0.15 T – comparison with anatomy and concordance with arthroscopy, J. Rheumatology 18:1573-1580
4. Yoshioka H, Ito S, Handa S et al. (2006) Low-field compact magnetic resonance imaging system for the hand and wrist in rheumatoid arthritis, J. Magn. Reson. Imaging 23:370-376
5. Qazi AA, Folkesson J, Pettersen PC et al. (2007) Separation of healthy and early osteoarthritis by automatic quantification of cartilage homogeneity, Osteoarthritis Cartilage 15: 199-1206
6. Link TM, Stahl R, Woertler K (2007) Cartilage imaging: motivation, techniques, current and future significance, Europ. Radiol. 17:1135-1146
7. Ostendorf B, Edelmann E, Kellner H, Scherer A (2010) Low-field magnetic resonance imaging for rheomatoid arthritis, Z. Rheumatologie 69:79-86
8. Rössler E, Mattea C, Mollova A, Stapf S (2011) Low-field one-dimensional and direction-dependent relaxation imaging of bovine articular cartilage. J. Magn. Reson. 213:112–118
9. Berberat JE, Nissi MJ, Jurvelin JS, Nieminen MT (2009) Assessment of Interstitial Water Content of Articular Cartilage with T1 Relaxation, Magn Reson Imaging 27:727-32
10. Xia Y, Wang N, Lee J, Badar F (2011) Strain dependent T1 relaxation profiles in articular cartilage by MRI at microscopic resolutions, Magn. Reson. Med. 65: 1733-1737
11. Blümich B, Perlo J, Casanova F. (2008) Mobile single-sided NMR. Prog Nucl Magn Reson Spectrosc 52:197–269
12. Lurie DJ, Aime S, Baronic S et al. (2010) Fast field-cycling MRI, C R Phys 11:136–148
13. Kimmich R, Anoardo E. (2004) Field-cycling NMR relaxometry, Prog Nucl Magn Reson Spectrosc 44:257–320
14. Broche LM, Ashcroft GP, Lurie DJ (2012) Detection of osteoarthritis in knee and hip joints by fast field-cycling NMR. Magn. Reson. Med. 68:358–362
15. Borgia GC, Brown RJS, Fantazzini P (1998) Uniform-penalty inversion of multiexponential decay data. J. Magn. Reson. 132: 65-77
16. Venkataramanan L, Song YQ, Hürlimann MD (2002) Solvin Fredholm Integrals of the First Kind With Tensor Product Structure in 2 and 2.5 Dimensions. IEEE Trans Sign Proc 50:1017-1026
17. Rautiainen J, Nissi MJ, Salo EN et al. (2015) Multiparametric MRI Assessment of Articular Cartilage Degradation: Correlation with quantitative histology and mechanical properties. Magn. Reson. Med.74: 249-259
18. Rössler E, Mattea C, Stapf S et al. (2017) Load-dependent NMR low-field profiling and relaxation dispersion study of osteoarthritic articular cartilage, Microporous Mesoporous Mater, in press
19. Zorn R (2002) Logarithmic moments of relaxation time distributions. J. Chem. Phys. 116: 3204-3209
20. Rössler E, Mattea C, Stapf S (2015) NMRD investigations of enzymatically degraded bovine articular cartilage, Magn. Reson. Med. 73, 2005-2014
21. Wang N, Xia Y (2012) Depth and orientational dependencies of MRI T-2 and T-1 rho sensitivities towards trypsin degradation and Gd-DTPA(2-) presence in articular cartilage at microscopic resolution, Magn. Reson. Imaging 20: 361-370

Enter the information of the corresponding author:

Author: Siegfried Stapf
Institute: TU Ilmenau, Dept. Technical Physics II
Street: PO Box 100565
City: 98684 Ilmenau
Country: Germany
Email: siegfried.stapf@tu-ilmenau.de