T_1 -based sensing of mammographic density using single-sided portable NMR

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Word count: Abstract 155
Main body 3828

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of record](#). Please cite this article as [doi:10.1002/mrm.27098](https://doi.org/10.1002/mrm.27098).

Abstract

Purpose: A single-sided NMR instrument was used to investigate the ability of the T_1 relaxation constant to distinguish between regions of low and high mammographic density in human breast tissue.

Methods: Measurements were performed on 5 breast slices obtained from 3 women undergoing breast reduction surgery or prophylactic mastectomy.

Results: T_1 values measured in regions of high mammographic density in both the full breast slices, $T_1 = (170 \pm 30)$ ms, and excised regions, $T_1 = (160 \pm 30)$ ms, were found to be significantly different ($p < 0.001$) to those measured in regions of low mammographic density, where $T_1 = (120 \pm 10)$ ms was observed both in full slices and excised regions. There was no statistically significant difference between the T_1 values measured in the full breast slices and those measured in the excised regions.

Conclusion: The findings suggest that portable NMR may provide a low-cost means of assessing mammographic density *in vivo*.

Keywords

breast cancer risk; mammographic density; mammography; portable single-sided NMR; longitudinal spin-relaxation time constant (T_1)

Introduction

Mammographic density (MD), also known as breast density, refers to the degree of radio-opacity of the breast as observed on an X-ray mammogram. MD is determined by the amount of the (radiodense) fibroglandular tissue (FGT), as opposed to the (radiolucent) adipose, or fat, tissue in the breast. In addition to having important implications for the efficacy of mammographic breast cancer risk screening (1), MD is an independent risk factor for breast cancer, with women in the highest MD quartile having 4-6 times the risk of developing breast cancer than those in the lowest 10%, after normalisation for body mass index and age (2,3). While the mammogram is still the current standard for assessing MD, it suffers from several limitations. Breast compression leads to tissue overlap and consequently projectional imaging artefacts, while the use of ionising radiation imposes limits on patient age (not recommended for young women) and mammogram frequency (normally no more than once every two years). Mammography is also not recommended for women recovering from surgery and women with a number of inherited syndromes known to be associated with radiosensitivity and/or cancer risk (4,5).

Consequently, there has been a recent push for the development of volumetric techniques that would enable the assessment of MD-analogous quantities without relying on ionising radiation. This includes, for example, transillumination (6), bioimpedance (7) and ultrasound (8) techniques, as well as magnetic resonance imaging (MRI) approaches (9-11). T_1 -weighted MR images can provide contrast between water-rich FGT and adipose components of breast tissue; this contrast can be further enhanced by fat suppression. The ratio of FGT to adipose tissue can be determined using image-analysis techniques, similar to the semi-automated or fully automated clustering or segmentation algorithms that can be used to determine MD from the mammogram (12-14). MRI-based techniques have shown good agreement with MD measured from the corresponding mammograms (11,15-19).

While clinical MRI provides a volumetric and spatially resolved means of interrogating breast tissue morphology, its cost is significantly higher than that of a mammogram; this limits the suitability of conventional MRI for routine breast screening. The NMR-MOUSE (20,21) is a single-sided portable MR system (22) that is based on permanent magnets. It is commercially available and very inexpensive (currently ~EUR55,000) compared to the cost of a standard clinical MRI scanner. It is also cryogen-free and therefore incurs negligibly low maintenance and running costs. Several researchers have investigated the potential utility of

portable NMR for the imaging of biological tissues (23-27). The imaging of silicone breast implants (28) is another biomedical (albeit not tissue imaging *per se*) application of portable NMR that is noteworthy in the context of the present study. We are currently investigating the capacity of this portable-NMR system to distinguish between high- and low-mammographic density breast tissue (HMD and LMD, respectively). Our initial focus was on the T_1 relaxation time constant, a quantitative physical property of the breast tissue that is sensitive to tissue composition and microenvironment. T_1 is dependent on the magnetic field but is, in principle, independent of the pulse sequence or the specific RF coil configuration. As such, it represents a more objective quantitative indicator of tissue composition than the T_1 -weighted MR signal intensity commonly used in the clinical literature (11,15-19). In this work, we demonstrate the ability of the T_1 relaxation time constant measured using the NMR-MOUSE to distinguish between HMD and LMD breast tissue. We discuss what further research and methodological development may be required in order for this approach to be applied *in vivo*.

Methods

Patient Cohort and Tissue Samples

Slices of breast tissue were obtained from women undergoing prophylactic mastectomy for breast cancer prevention or breast reduction surgery. In total, 5 breast slices from 3 different women were used in this study; a summary is shown in Table 1. The study was approved by the Peter MacCallum Human Research Ethics Committee (#08/21), Metro South Hospital and Health Services, Queensland (HREC/16/QPAH/107) and Mater Research (RG-16-028-AM02, MR-2016-32), and administratively approved by QUT (#1600000261). The study was conducted in accordance with the Australian National Statement on Ethical Conduct in Human Research (2007). Women were excluded from this study if they had suspicious ductal carcinoma in-situ (DCIS) or microcalcifications on radiological investigations.

Slices of breast tissue were resected using sterile technique by pathologists immediately after the completion of surgery. These methods had been detailed in our previous work (29-32). In brief, excised tissues were transported on ice to the respective pathology suites and assessed for abnormalities after routine cranio-caudal slicing using sterile procedures. Slices that were surplus to pathologists' needs were used for this study. The slice from patient 2 was stored long-term at -80°C after accrual and transported on dry ice. The slices from patients 1 and 3 were transported for mammography fresh (on ice) immediately after accrual.

Slice Mammography

The slices were transported to the Radiology Suite at Princess Alexandra Hospital for a slice mammogram (Mo target / Mo filter; tube voltage 28 kV; exposure 40 mAs). For patients 1 and 3, mammograms were recorded from the fresh slices. For patient 2, mammogram was recorded from the slice which was kept frozen during the measurement. HMD and LMD regions of each slice were determined from the mammogram by the clinical radiologist. All slices were then stored frozen at -80°C and transferred to a -20°C freezer prior to NMR measurements. A photograph and a mammogram of a representative slice (Patient 1, Slice 2 in Table 1) are shown in Figure 1.

NMR-MOUSE setup

NMR measurements were carried out using a PM5 NMR-MOUSE® (Magritek, New Zealand), a single-sided NMR scanner using a permanent magnet with a horizontal field of the strength $B_0 = 0.47$ T and a vertical permanent field gradient $g = 22.5$ T/m. A surface coil is used to excite and detect the NMR signal. The sensor and sample positioning are illustrated in Figure 2. The field gradient enables the selection of a horizontal sensing slice that is ~ 50 μm thick with a sensing area $\sim 15 \times 15$ mm. The sensing slice is located at a certain height above the top surface of the magnet (see also Figure 7d in ref. (22)). A translation stage lowers or raises the sensor in order to position the sensing slice at a desired depth (z direction in Fig. 2); this enables depth profiling of the sample. The maximum penetration depth of the PM5 system used was 5 mm.

T_1 Measurements

Prior to data acquisition, breast slices were defrosted and subsequently stored at $+4^\circ\text{C}$ when not being measured. One HMD and one LMD region in each slice was identified visually by inspection of the corresponding mammogram. The sample was kept at room temperature during the measurements. A saturation recovery sequence was used to obtain the full T_1 recovery curve; the pulse sequence consisted of a train of 90° pulses used to zero the longitudinal magnetisation, followed by a variable saturation-recovery period (T_{SR}), a CPMG detection block, and a fixed recovery time (TR). The saturation recovery curve was sampled at 24 T_{SR} values equidistantly spaced between 50 and 1200 ms. A CPMG sequence (TE = 60 μs with 30 echoes, TR = 5000 ms) was used for signal detection with NS = 16 averages. The total measurement time for each saturation recovery curve was 40 minutes.

For each HMD and LMD region, three T_1 data sets were obtained. First, the T_1 for HMD and LMD regions were measured in the full slice, with the region of interest visually identified from the marked mammogram placed above the centre of the NMR-MOUSE sensing coil. The HMD and LMD regions were then excised from the full slice (excised regions were ~ 1.5 cm $\times$ 1.5 cm in area and had the thickness of the full slice), and the T_1 measurements were repeated. Finally, the excised samples were subjected to H_2O - D_2O replacement by being soaked in 0.01 M phosphate buffered saline (PBS) solution made with 99% D_2O at $+4^\circ\text{C}$ overnight (for 16 to 18 hours); after the H_2O - D_2O replacement the T_1 measurements were

repeated again. Four of the five breast slices (slices 1, 2, 3 and 5 in Table 1) had a thickness sufficient for T_1 measurements to be made at two different depths within the HMD and LMD regions (see Table 1). Slice number 4 was relatively thin, and the T_1 measurements in this slice were made at one depth only. This resulted in a total of 9 T_1 measurements for each of the six data sets summarised in Table 2. Collection of these six data sets took place over three days, with the samples alternating between room temperature (when being measured) and +4°C (when stored) during this time. Two control samples, one HMD and one LMD region (excised from Patient 1, Slice 1), were used to check that tissue degradation during this experimental cycle did not result in changes in the measured T_1 values. The T_1 values measured in the breast tissue samples were stable throughout the three days of the measurement cycle.

Data analysis was performed using a *Mathematica* (Wolfram Inc, Illinois) code written in-house. The apparent T_1 values were determined using a two-parameter monoexponential least-squares fit (LSF) of the form $S = S_0(1 - e^{-TR/T_1})$, which was performed on each saturation recovery curve. The suitability of the monoexponential model was verified using the Runs test performed on the residuals of monoexponential least-squares fits (see Table 2). The statistical significance of the differences between HMD and LMD T_1 values, and changes in the T_1 values following H₂O-D₂O replacement, were evaluated using the Student's T-test with a significance level of $p = 0.001$.

Results

The T_1 values of the two control samples were measured on the three consecutive days of the measurement cycle. The T_1 values (mean $\pm$ 95% CI from the monoexponential LSF) in the HMD region were $T_1 = (131 \pm 6)$ ms, (127 ± 8) ms, and (131 ± 8) ms in days 1, 2 and 3, respectively. The corresponding values in the LMD region were $T_1 = (121 \pm 7)$ ms, (123 ± 6) ms, and (120 ± 7) ms. These results demonstrate that there was no statistically significant change in T_1 as a result of sample degradation over the course of the measurement cycle.

Representative recovery curves and fits for the excised HMD and LMD regions are shown in Figure 3. Figure 4 shows the distributions of the T_1 values obtained from the monoexponential LSF of the saturation-recovery data. The means and standard deviations of the T_1 for each group of data are summarised in Table 2. The Wald-Wolfowitz runs test was performed on the residuals of each fit to determine the applicability of fitting the saturation recovery data with a two-parameter monoexponential curve (as opposed to, for example, a bi-exponential or a three-parameter monoexponential fit). The fit function can be considered appropriate when the number of runs in the fit residuals is within ~ 1 standard deviation of the expected number of runs for a completely random (“white-noise”) data set of the same size. The probability of finding the number of runs to be one standard deviation (σ) less than the expected mean (μ) is $P(\mu - \sigma) \approx 0.1587$. The mean of the runs statistic for each group of data was between 0.16 and 0.5 for all data sets (Table 2), indicating that the two-parameter, monoexponential fit was appropriate for treating the saturation recovery data.

The mean T_1 time constants in the HMD regions were longer than those in the LMD regions both when measured in the full slice and when excised regions were measured (Figure 4; Table 2). In both scenarios, the difference between HMD and LMD regions was statistically significant, as seen from Table 3.

The excised regions of the samples exhibited shorter T_1 values upon H_2O - D_2O replacement (Table 2; Figure 4). The respective change in the T_1 values was statistically significant for both the HMD and LMD regions (see Table 3). Furthermore, following the H_2O - D_2O replacement, there was no statistically significant difference between the T_1 values measured in the HMD and LMD regions (Table 2). Additionally, the spread of measured T_1 values was reduced in the excised samples following H_2O - D_2O replacement (Table 2; Figure 4).

Discussion

The principal chemical components of breast tissue contributing to the NMR proton signal are water (associated either with the extracellular matrix or cells) and fat. In the first approximation, the measured monoexponential T_1 time constant can be represented as the weighted average of the T_1 time constants of water, T_1^w , and that of fat, T_1^f :

$$\frac{1}{T_1} = \rho_w \frac{1}{T_1^w} + \rho_f \frac{1}{T_1^f} \quad (1)$$

where ρ_w is the fraction of water protons in the breast tissue, ρ_f is the fraction of fat protons, and $\rho_w + \rho_f = 1$. Because $T_1^w > T_1^f$, the longer T_1 values seen in the HMD regions, compared to the LMD regions, indicates that the ratio of water to fat (ρ_w / ρ_f) is larger in HMD regions than in LMD regions. This finding is consistent with the known composition of FGT, which largely comprises HMD regions of the breast.

During H₂O-D₂O replacement, the water (H₂O) volume fraction contributing to the proton signal is decreased ($\rho_w \rightarrow 0$) and the fat contribution is increased ($\rho_f \rightarrow 1$). Because of this and $T_1^w > T_1^f$, the shortening of the measured T_1 values observed in the excised regions upon H₂O-D₂O replacement is expected. The following conclusions can be made from the observed changes in the T_1 's upon H₂O-D₂O replacement: (a) the H₂O-D₂O replacement of 16 - 18 hours was sufficient to replace nearly all the tissue water, i.e. arrive at $\rho_w \sim 0$, $\rho_f \sim 1$, and the T_1 values measured in the excised samples after H₂O-D₂O replacement correspond to the fat contribution only, i.e. $T_1 \sim T_1^f$; (b) the fact that the T_1 change upon H₂O-D₂O replacement is greater in the HMD regions than in the LMD regions indicates that the longer T_1 time constants in the HMD tissue are the result of a higher water-to-fat ratio (ρ_w / ρ_f) in the HMD regions compared to the LMD; and (c) the spread of T_1 values measured in the HMD regions (and to a lesser extent in the LMD) is the result of compositional variability of the tissue, i.e. variations in the values of ρ_w and ρ_f within a given type of tissue.

Small differences between the T_1 values measured in a given region within the full slice and in an excised sample are evident from Fig. 2. Such differences can be expected due to

topographical variations of ρ_w / ρ_f within both HMD and LMD regions, which are apparent from Fig. 1(b). While HMD and LMD regions would ideally contain only FGT and adipose tissue, respectively, in reality the “HMD” region contains some adipose tissue and the “LMD” region contains some FGT, and the density of these components within the respective regions is non-uniform. When the region is measured as part of the full slice, it is inevitable that some “foreign” tissue is contained within the sensing volume besides the target tissue. A properly targeted excision of the sample can be expected to minimise this cross-contamination, resulting in a slight change of ρ_w / ρ_f within the sensing volume and consequently a slightly different T_1 value.

Interestingly, the separation between the HMD and LMD T_1 constants became *smaller* upon the excision of the regions from the full breast slice. This is the result of a decrease in the apparent HMD T_1 constant from (170 ± 30) ms to (160 ± 30) ms (Table 2). While not statistically significant (Table 3), this change is noteworthy. It could be attributed to a change in the ρ_w / ρ_f ratio in the sensing volume due to imperfect targeting of the excised sample, or the fact that the mammogram is a 2D projection of tissue composition and HMD regions identified from the mammogram can still contain some adipose tissue. Nevertheless, the results demonstrate the ability of the NMR-MOUSE to distinguish between known HMD and LMD regions in the full breast slice just as effectively in the excised regions; we consider this an indication of the potential of portable NMR to characterise mammographic density *in vivo*.

In our view, the portable-NMR approach to quantification of MD holds significant promise in terms of both clinical and biomedical research applications. While the current study is preliminary in nature and subject to several limitations, these limitations can be addressed through further research. One of the main limitations of this initial study is the binary identification of the breast tissue within the NMR sensing volume as simply “High Density” or “Low Density”. Mammographic density is a continuous quantity, and the importance of its graduated quantification is well-recognised in clinical breast imaging and cancer risk screening (11,33). Our future work will therefore include the investigation of the correlation between the apparent T_1 value and the continuously quantified MD obtained from a mammogram. Physical considerations suggest that such a correlation should exist. The values of T_1^w and T_1^f in Eq. (1) appear to be well-separated, which implies that the apparent T_1 measured by NMR-MOUSE should be correlated with the relative amounts of FGT and

adipose tissue within the sensing volume (a lower T_1 value should correspond to a higher adipose tissue content and therefore lower MD). Further studies could build upon the analysis presented here by characterising the breast tissue in terms of relative proportions of FGT and adipose tissue; digital X-ray mammograms and histology can be used as the “gold standard” for evaluation of the accuracy of NMR-MOUSE analysis. Similar methodology based the T_2 values measured using NMR-MOUSE or similar low-field, permanent magnet single-sided spectrometers has been successfully applied to the measurement of fat and water content in food products and model food systems (34,35) and Atlantic salmon *in vivo* (36). Other NMR parameters (e.g. the diffusion coefficient) could also be used either alongside, or instead of, T_1 values, for quantifying the relative ratios of FGT and adipose tissue in the breast.

The small sample size is another limitation of the present study. We are currently undertaking an extension study composed of a larger cohort of prophylactic mastectomy patients. The 5 mm penetration depth of the PM5 NMR-MOUSE model represents another limitation: while this depth is sufficient for excised slices of breast tissue, it will likely be insufficient for MD measurements *in vivo*. This can be addressed through the use of currently available models with larger penetration depths (e.g. NMR-MOUSE PM25, penetration depth 25 mm) and, in the long term, the design of custom instrumentation with still larger penetration depths. Finally, we are evaluating the potential of other NMR modalities (T_2 , diffusion) for MD quantification.

In practical terms, we envisage that for measurements *in vivo* portable NMR instrumentation would be used to obtain depth profiles of T_1 (or an alternative proxy MD quantifier) at several “key” locations in the breast (e.g. the upper-lateral quadrant or the area above the nipple). This would provide a depth profile of MD at each location. While this would not provide the full 3D map of the breast in the way conventional MRI does, it has the potential to provide a condensed MD “fingerprint” of the breast. Importantly, such a fingerprint would provide volume-selective information about the spatial distribution of MD, as opposed to a single scalar breast density score such as BIRADS. This approach appears encouraging in light of other existing applications of portable NMR *in vivo* (23,26).

An example of application where the benefits of portable-NMR-based MD measurements are particularly readily apparent is the monitoring of whether MD reduction occurs during anti-estrogen Tamoxifen treatment for breast cancer prevention or breast cancer therapy (37). MD is currently the only known biomarker capable of predicting risk reduction resulting from

Tamoxifen therapy. Approximately 2/3 of all breast cancers express estrogen receptors, and most of these are treated with hormonal therapy, which is unsuccessful in approximately 1/3 of those treated. Accumulating data show that MD drops by >10% if the treatment is working, and doesn't drop when it isn't working, so the ability to rapidly, cheaply and conveniently measure MD in conjunction with these therapies would be advantageous. Portable NMR systems provide an attractive platform for MD monitoring in this context because repeated measurements of MD are not feasible with X-ray mammography due to X-ray exposure, while cost represents a major impediment to the use of conventional MRI for this purpose.

A further argument in favour of using portable NMR for MD assessment is that, besides being inexpensive, this technology is mobile. It could therefore be used to provide routine MD screenings to women in remote and regional areas, who may not have facile access to traditional mammography or clinical MRI.

Finally, the results presented here raise a case for investigating the ability of T_1 maps to quantify mammographic density clinically. Sensitivity of T_1 -weighted images to MD is already well-recognised in breast imaging (38,39). Acquisition of the full T_1 recovery curve is not routine in clinical settings due to imaging time constraints. However, unlike the signal intensity in T_1 -weighted images, which is dependent the pulse sequence and hardware configuration, T_1 maps are an intrinsic property of the tissue and can be compared across different clinical scanners of similar field strength. For example, T_1 maps have been shown to be less sensitive to the choice of segmentation algorithms than T_1 -weighted images when distinguishing between white and grey matter and cerebrospinal fluid in the brain (40). The results of the present study suggest that the potential of T_1 maps of the breast to provide a spatially resolved and quantitative means of comprehensively assessing mammographic density *in vivo* merits further investigation. Conversely, the overlap between quantitative measurement capabilities of clinical MRI and portable NMR suggests that the potential of spatially-selective quantitative T_1 measurements using portable-NMR instrumentation for MD quantification merits also further investigation and development.

Conclusions

We have demonstrated the ability of T_1 spin-relaxation time constants measured using a low-field, single-sided portable NMR instrument (NMR-MOUSE) to distinguish between regions of high and low mammographic density in human breast tissue. The apparent T_1 value was shorter in the LMD tissue than in HMD tissue, consistent with a higher proportion of fibroglandular tissue and lower proportion of adipose tissue in HMD regions, compared to LMD. This was confirmed by H_2O - D_2O replacement of water in the excised HMD and LMD regions. We are currently undertaking work on a larger sample group and investigating other modalities to verify the potential of NMR-MOUSE to provide a low-cost, portable means of assessing mammographic density *in vivo*.

Acknowledgements and Funding

Funding from Princess Alexandra Research Foundation (ALH Breast Cancer Project Grant) and Translational Research Institute (SPORE Grant) is acknowledged. The Translational Research Institute is supported by a grant from the Australian Government. The authors are grateful to Dr Andrew Coy and Dr Robin Dykstra (Magritek Ltd) and A/Prof Petrik Galvosas (Victoria University Wellington, New Zealand) for the loan of PM5 NMR-MOUSE and invaluable discussions. MCT and TSA thank Dr R. Mark Wellard (QUT) for useful discussions concerning experimental design. The authors thank the women who gave permission for their breast tissue to be used for this study, Ms Gillian Jagger (Princess Alexandra Hospital) for the expert coordination of tissue accrual aspects of the project, and Ms Claire Davies for assistance with the accrual of the Mater Hospital specimen.

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Figures

Figure 1. A photograph (left) and a mammogram (right) of a representative breast tissue slice (Patient 1, Slice 2 in Table 1) used in the measurements.

Figure 2. NMR-MOUSE sensor and sample positioning: (a) Side view showing the permanent magnets (N and S), the directions of the static magnetic field (B_0) and the static gradient (g), the sensing area (red circle) and the positioning of the sample (grey slice); (b) View from the top showing the permanent magnets (N and S), the direction of the static magnetic field (B_0), the sensing area (red circle) and the positioning of the sample (grey slice).

Figure 3. Example of T_1 recovery curves and monoexponential fits for HMD (open circles; red line) and LMD (open squares; blue line) regions.

Figure 4. T_1 time constants measured in high density (HMD; red circles) and low density (LMD; blue squares) regions in the full breast slice (left), when excised from the full slice (centre) and after H_2O - D_2O replacement (right). Statistically significant differences between data sets ($p < 0.001$) are denoted by * (see Table 3 for the corresponding p values).

Tables

Table 1. Summary of breast tissue samples.

Patient	Tissue slice	Approximate slice thickness	Penetration depth	Comments
Patient 1	Left Breast Slice 1	10 mm	2 and 4 mm	Breast Reduction
	Left Breast Slice 2	10 mm	2 and 4 mm	
	Right Breast Slice 3	10 mm	2 and 4 mm	
Patient 2	Medial Lateral	4 mm	2 mm	Mastectomy
Patient 3	Lateral	10 mm	2 and 4 mm	Mastectomy; with chemotherapy

Table 2. Summary of T_1 values averaged across all breast slices and the mean Runs statistic from the monoexponential fits of the saturation recovery curves for each data set.

Data Set		T_1 (ms) Mean $\pm$ SD	Mean Runs statistic ^{a)}
Full Slice	Low Density	120 $\pm$ 10	0.38
	High Density	170 $\pm$ 30	0.28
Excised Regions	Low Density	120 $\pm$ 10	0.20
	High Density	160 $\pm$ 30	0.16
Excised Regions after D ₂ O	Low Density	99 $\pm$ 5	0.31
	High Density	100 $\pm$ 4	0.32

^{a)} Fit residuals were considered random if the mean Runs statistic was between 0.1587 and 0.8413, corresponding to the number of runs being within one standard deviation of the expected mean.

Table 3. Results of the Student's T-test between different sample groups. Shaded cells indicate a statistically significant difference between two data sets ($p < 0.001$).

		Full Slice		Excised Regions		Excised Regions after D ₂ O	
		High Density	Low Density	High Density	Low Density	High Density	Low Density
Full Slice	High Density		2.78×10^{-6}	0.12			
	Low Density	2.78×10^{-6}			0.60		
Excised Regions	High Density	0.12			2.26×10^{-4}	5.69×10^{-5}	
	Low Density		0.60	2.26×10^{-4}			1.44×10^{-5}
Excised Regions after D ₂ O	High Density			5.69×10^{-5}			0.02
	Low Density				1.44×10^{-5}	0.02

Figure 1

169x174mm (300 x 300 DPI)

Auth

Figure 2

202x91mm (300 x 300 DPI)

Author Mar

Figure 3

1304x870mm (96 x 96 DPI)

Author N

Figure 4

95x31mm (300 x 300 DPI)

Author Mani

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Title:

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Date:

2018-09-01

Citation:

Tourell, M. C., Ali, T. S., Hugo, H. J., Pyke, C., Yang, S., Lloyd, T., Thompson, E. W. & Momot, K. I. (2018). T-1-based sensing of mammographic density using single-sided portable NMR. *MAGNETIC RESONANCE IN MEDICINE*, 80 (3), pp.1243-1251. <https://doi.org/10.1002/mrm.27098>.

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