Sensing mammographic density using single-sided portable Nuclear Magnetic Resonance

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1. Introduction

Breast cancer (BC) is caused by numerous risk factors that occur in isolation (Britt et al., 2020; Tourell et al., 2018). The most popular ones include, high post-menopausal body mass index (BMI), ageing (Tyrer et al., 2004), oral contraceptives, less breast feeding, congenital factors (family history of the disease), high mammographic density (MD), exposure to ionizing radiation, and early menstrual occurrences (early menarche) at the age of 11 years and below (Tamam et al., 2021; Bell, 2020; National Health and...
Medical Research Council, 2018, Brinton et al., 2018; Sulieman et al., 2019). Sung et al estimated that the incidence of breast cancer is 2.3 million new cancer cases representing 11.7% of all cancer incidence worldwide (Sung et al., 2021). For women aged 50–69, BC screening is suggested every one to two years. For high-risk females, an MRI of the breast is also indicated (Niell et al., 2017). Regardless of ethnicity, it was revealed that roughly 30% of patients under the age of 30 have fatty breasts, and around 25% of patients over 70 have DB. Breast density was higher in groups younger than 50 years old, while older ladies had a tendency to have reduced breast density (Salem et al., 2017; Liu et al., 2014). However, elimination of breast cancer risk is possible through awareness improvement, effective health services and reduction of the stress (Karim et al., 2019). MD is considered as the strongest indicator of breast cancer risk (Cil et al., 2010). It is defined as the level of radiodense fibro glandular deposits in breast tissues (Shang et al., 2021; Kopans, 2009). The hyper-intense region on a mammographic image is indicative of high MD, with high levels of fibro glandular tissue (FGT) (Tourell et al., 2018; Bell, 2020). Most of the women within the age bracket of 40–75 years exhibit high levels of MD. This means that they are more likely to be at risk of breast cancer than women in other age groups (Huang, 2018). It is important to accurately estimate an individual’s MD at the early stages of manifestation to facilitate risk evaluation and prognosis of BC (Collaborative Group on Hormonal Factors in Breast Cancer, 2012). Research reveals that the risk exposure of an Australian woman to BC over their entire lifetime is in every 8 or about 12.5% (AIHW, 2017). This figure is comparable to that of the United Kingdom (12.5%) and that of the United States of America (12%). On average, approximately 500,000 deaths arising from BC complications have been reported recently from the 14 million detected cases of BC; an indication of the severity of the global BC contrac tion (Ghosh et al., 2011; National Cancer Institute, 2017). Studies conducted in the recent past have shown that MD has a direct impact on the progression and spread of BC cells (Aiello et al., 2005; Eriksson et al., 2013a). The radio-dense regions on a mammogram (high MD regions) correlate to FGT (collagen stroma) zones and display a white appearance. On the contrary, radio-lucent zones (low MD regions) are rich in adipose tissues and are dark in appearance (Ghosh et al., 2011). Research suggests that collagen and proteoglycans are key determinants of MD (Ghosh et al., 2011; Huo et al., 2015). Breast density has a significant impact on the sensitivity of mammograms for the identification of BC. Mammogram sensitivity ranges from 80 to 98 percent for women with fatty breasts while the sensitivity drops to 30–65 percent for women with thick breasts (Butler, 2015). Typically, the Breast Imaging Reporting and Data System (BI-RADS) is a viable tool for classifying MD in breast tissues. For example, dense tissues are represented as BIRADS > 75% (Sickles, 2013). In such cases, the utility of mammography diminishes as a breast cancer detection tool. Based on the BI-RADS scale, women in the upper MD quartile have about 5 times higher chances of exposure to BC compared to those in the lower quartile (McCormack & Silva, 2006). It has been suggested that dense tissue concentration in the breast is influenced by single nucleotide polymorphism, estrogen fluctuations stereotypical during the menstrual cycle, and onset of menopause (White et al., 1998; Stone et al., 2006). Other than physiological factors, lifestyle factors that affect MD include alcohol abuse (which increases MD), one’s diet, engagement in physical activities (reduces MD), and lack of parity (increases MD). More so, the above indicators suggest that MD evolves over time (Brentnall et al., 2015). As such, MD-related BC risk can be modified (Woolcott et al., 2012). This can be achieved by monitoring MD iteratively to reveal individual-specific risks to BC (Eriksson et al., 2013b). Nuclear Magnetic Resonance (NMR) technique is based on the fact that in living tissues have plenty of protons mainly in water and fat molecules whose nuclei contain positively charged protons with a net spin and consequently, an intrinsic induced magnetic field around them. The MRI image contrast is determined by regions of low (hypointense – black) and high (hyper-intense/ white) signal intensities (Dale et al., 2015). The shades of grey reflect regions of intermediate signal intensity. Image contrast is attributed to three primary mechanisms: the proton density (PD) of hydrogen within a tissue, T2, and T1. For example, in T2-weighted image, tissues with considerable levels of the transverse coherent magnetization components tend to create hyper-intense regions on the image scan. In tandem, the NMR coil receives a high amplitude signal output. In contrast, tissues with low or no levels of coherent transverse magnetization at a time TE, tend to return a low amplitude signal. Diffusion (D), T1 and T2 parameters in the portable NMR can be used to improve the quantification of MD as a risk factor for breast cancer. The time constants, T1 and T2 are derived from the high and low MD domains (LMD and HMD) of digital slice mammography (Daniil & Blümich, 2013). T2 measurements, unlike T1, reveal the water-to-fat (w/f) ratio of a breast tissue (Ali et al., 2019), and the both techniques provide accurate discrimination between HMD and LMD regions in the breast tissue samples (Tourell et al., 2018). Indeed, Tourell et al. (2018) concluded that the difference between the HMD and LMD regions of both excised and full breast tissues was statistically significant, where p < 0.001. The samples were obtained from BC patients undergoing prophylactic mastectomy. In this study, the CPGM decay curves for T2 were constructed using Inverse Laplace Transformation (ILT). The T2 spectra of both the LMD and HMD regions revealed two distinct water and fat peaks, which were further revealed statistically significant differences (p < 0.005) via t-paired tests (Tourell et al., 2018). Recently, Huang et al. (2018) measured samples of breast tissues with dissimilar MDs. The investigators extracted volumetric MD image for 10 samples of breast tissues through μCT. In this study, the saturation recovery sequence for T1, CPMG sequence for T2, and stimulated sequence for diffusion were applied on the samples with the aid of the portable PM25 model of the NMR. The continuous distribution of MDs scale for the excised samples ranged between zero and 100%. The “gold standard” for the experiment was the μCT. HMD% measured on the μCT scale showed impressive correlations with T1 and diffusion data, where R was ~0.92 and 0.96 respectively. Furthermore, the linear correlation between NMR-assisted water diffusion and T1 data was impressive; R was ~0.94 while the correlation between T2 and diffusion data was modest due to an overlap of the water and fat peaks in the T2 spectra. If TE is poorly selected, such that it becomes too short, then the fat and water peaks will overlap in the spectra of T2 (Huang, 2018). However, by selecting moderately long TE, the NMR probe could provide reliable MD measurements. This study will investigate whether or not the three techniques T1, T2, and diffusion (D) are in agreement with each other as well as in agreement with the gold standard (Mammogram images) when used for scanning breast tissue samples with a range of mammographic densities (MDs). To establish the concurrence, the conclusion will be derived from six charts (T1 (%) vs grayscale value), (D (%) vs grayscale value), (T2 (%) vs grayscale value), (T1 vs T2), (T1 vs D) and (T2 vs D), which will show how well the accuracy reproducibility of three techniques compared to mammogram images (gold standard) of the two samples.

2. Material and methods

2.1. Slice mammogram measurements

In this study, 2 slices of breast tissues mammogram images were obtained from two different participants (women) undergo-
ing prophylactic mastectomy with the view of preventing breast cancer, or breast reduction surgery. The HMD, intermediate MD, and LMD regions for the two mammogram images were labelled by the radiologist at the Princess Alexandra Hospital. Subsequently, the grayscale values of the six regions in the two samples were obtained using MATLAB software. The experimental parameters for NMR probing are summarized in Table 1. The two slices were frozen at $-80 \, ^\circ C$ at Translation Research Instititute (TRI) before being transferred to portable NMR room. Subsequently, the samples were left one hour at room temperature ($24 \, ^\circ C$) in order to be deforested. The study has been approved by the Peter MacCallum Human Research Ethics Committee (#008/21), Metro South Hospital and Health Services, Queensland (HREC/16/QPAH107) and Mater Research (RG-16-028-AM02, MR-2016-32), and administratively approved by QUT (#1600000261).

### 2.2. Single-sided NMR-mouse setup

The NMR measurements were performed using the single-sided NMR (PM 25 - Magritek, Wellington, New Zealand). The setup shown in Fig. 1 has a RF surface coil that stimulates and detects the NMR signal. The magnetic field gradient ($g_j$) is permanently installed in the orthogonal direction of the permanent horizontal magnetic field ($B_o$). The magnetic field gradient is equivalent to $7.5 \, \text{T.m}^{-1}$ while $B_0$ is 0.31 T. The portable single-sided NMR instrument has a translation stage that calibrates the sensor to the desired sensing depth. The effective depth of penetration of the PM25 probe is 25 mm. The size of the horizontal sensing slice is dependent on the coil's dimensions; the thickness of the slice varies depending on the amplitude of the applied magnetic field gradient and the strength of the RF magnetic field (Ali, 2018). In this setup (Fig. 1), the excitation frequency (RF) can be scaled to achieve spatial localization of the samples.

### 2.3. Quantifying mammographic density (MD)

The stimulated echo sequence for diffusion (D), the Carr-Purcell-Meiboom-Gill (CPMG) sequence for $T_2$, and saturation recovery sequence for $T_1$ were applied sequentially for the same six regions.

#### 2.3.1. $T_1$ Measurements

A saturation recovery sequence was applied to generate the full $T_1$ recovery curve for each region. This sequence provided a train of 90° RF pulses to counteract the strong inhomogeneity of the magnetic field and to zero the longitudinal magnetization components (Catherine and John, 2019). Each $T_1$ curve was sampled at 30 values of the saturation recovery times ($S_1$) for each region. Then, the Carr-Purcell-Meiboom-Gill sequence was used to sense signals (Bluemich and Perlo, 2008). The relative amount of water and fat signals for each region were measured using a 2-parameter non-linear biexponential least-squares fit (LSF) of equation (2) below:

$$
(t) = K + S_0 e^{-t/T_1} a + S_1 e^{(t/T_1)} b
$$

where $S_0$ is the relative amount of water; $T_1$ a is the recovery time of water molecules.

#### 2.3.2. $T_2$ Measurements

#### 2.3.2.1. Analytical framework. The Carr-Purcell-Meiboom-Gill (CPMG) was used to obtain the CPMG decay for the six regions along the two samples. However, the first and second scans failed to resolve between water and fat peaks because the echo times (TEs) were short, TE = 150 μs and 300 μs respectively. Then, the same region was scanned again with TE = 700 μs which succeeds to resolve the two peaks. This TE value was adopted for scanning the remaining regions. The curves are shown in the results section.

For each region, the following parameters were set for $T_1$ sequence (Table 2):

| Maximum depth of penetration | 25 mm (NMR-Mouse PM25) |
|----------------------------|-------------------------|
| Gold standard              | Mammogram               |
| Number of scanned regions  | 1 region at 5.9 mm depth from the first sample, 5 regions at 4.5 mm depth from the second sample |
| Output                     | Distribution of MDs     |

Fig. 1. Portable NMR Mouse (Tourell, et al., 2018). (a) The side view demonstrates the permanent magnets N & S, direction of static magnetic field as well as the direction of static gradient. The red circle represents the sensing region, while the gray slice denotes the sample’s position; (b) is the top view of the instrument.

$S_1$ is the amplitude of fat content, and $T_1$ b is the recovery time of fat molecules.

The data analysis was performed using Wolfram Mathematica program, and the code was written by Momot (2019).

For each region, the following parameters were set for $T_1$ sequence (Table 2):

Worth noting, The Inverse Laplace Transformation (ILT) was used to reconstruct the $T_2$ spectra which displayed the amplitudes or peaks of fat and water. Equation (2) below shows $T_2$ multicomponent decay (Ali et al., 2019):

$$
S(t_i) = g_j \sum_{i=1}^{m} A(T_i) \exp \left( -\frac{t_i}{T_{2i}} \right) + \epsilon_j
$$

where $\epsilon_j$ represents the noise; the amplitudes of relaxation peak are represented by positive values of $A(T_i)$, $i = 1,...,m$ represents the # of relaxation-time items in the time $T_i$, which is a time constant for relaxation. $A(T_i)$ was obtained by inverting the $T_2$ curve. This was achieved by employing the least-square algorithm to minimize $x^2$ as shown below in equation (3) (Ali et al., 2019):

$$
\min\{x^2\} = \sum_{i=1}^{n} g_i - \sum_{i=1}^{m} A(T_i) \exp \left( -\frac{t_i}{T_{2i}} \right)^2
$$

Given that noise is an inherent property of the NMR signal, the smoothing parameter $\alpha$ was normalized as shown in equation (4) (Ali et al., 2019):

$$
\min\{x^2\} = \sum_{i=1}^{n} g_i - \sum_{i=1}^{m} A(T_i) \exp \left( -\frac{t_i}{T_{2i}} \right)^2 + \frac{1}{\sigma} \sum_{i=1}^{m} \left( A(T_i) - A(T_{i-1}) \right)^2
$$

The code that was initially written by Venkataramanan et al. (2002) was used to solve equation (3) in MATLAB program. The procedure above was repeated for all the $T_2$ distributions for each region in the two samples to minimize their sensitivity to noise.
The corresponding area fractions of the two peaks (fat and water) in each of the T2 distributions were analyzed as shown in equation (6) (Ali et al., 2019):

\[ AF_W = \frac{A_W}{A_W + A_F} \]

(5)

where \( AF_W \) is area fraction for water; \( A_W \) is the amplitude of the water (first peak), and \( A_F \) is the amplitude of the fat (second peak).

Similarly,

\[ AF_F = \frac{A_F}{A_W + A_F} = 1 - AF_W \]

(6)

where \( AF_F \) is area fraction for fat; \( A_F \) is the amplitude of the fat (second peak), and \( A_W \) is the amplitude of the water (first peak).

2.3.2.2. Diffusion measurements. A stimulated echo sequence was applied, while the CPMG block was coupled for detection. The diffusion interval \( \Delta \) was set at 10 ms, while \( \delta \) was varied from 0.05 ms to 1 ms with 32 step points. Subsequently, the diffusion curve (signal versus \( \delta \)) was plotted for each region. The relative apparent amounts of fat and water were quantified via a two-parameter biexponential least-squares fit of the following equation:

\[ S = S_0 \cdot e^{-\frac{\delta^2 D_{LS}^2}{(\Delta-\delta)^2} \cdot \Delta} + S_1 \cdot e^{-\frac{\delta^2 D_{LS}^2}{(\Delta-\delta)^2} \cdot \Delta} \]

(7)

where \( S_0 \) and \( S_1 \) represent the amplitudes of water and fat, respectively, \( \Delta \) is the diffusion interval, while \( \delta \) denotes the path for longitudinal magnetization. Signals corresponding to fast and slow molecular diffusion are linked to water and fat components, in their respective order.

The data analysis was performed using Wolfram Mathematica program, and the code was written by Momot (Momot, 2019).

For each region, the following parameters were set (Table 4): 0.004 which is <0.05; therefore, the correlation is statistically significant. Fig. 3 shows a graphical linear plot of Diffusion (%) versus grayscale value. The Pearson Correlation Coefficient, \( R = 0.99 \) at 95% confidence interval, and the p value is 0.001 which is <0.05; therefore, the correlation is statistically significant (see Figs. 8 and 9).

4. Discussion

Breast MRI is used for early BC detection and patients with high BC risk. It has a higher temporal and spatial resolution and a better signal-to-noise ratio (NSR) than other imaging modalities such as mammmography, positron emission tomography (PET), and ultrasonography. In addition, breast MRI has no risk of ionizing radiation exposure and enables simultaneous assessment of both breasts (Iranmakani, et al., 2020).

From the experimental results, it can be observed that the Pearson Correlation coefficients, \( R \), of T1 (%) versus Grayscale value, diffusion (%) versus Grayscale value, T2 (%) versus Grayscale value, T1 (%) versus diffusion (%), T2 (%) versus diffusion (%), and T2 (%) versus T1 (%), was 0.91, 0.91, 0.93, 0.97, 0.95, 0.99 respectively at 95% confidence interval. In all cases, \( R > 0.90 \) and \( p < 0.05 \), implying that the correlations are statistically significant. This means the water content based on spin–lattice relaxation time T1, spin–spin relaxation time T2 and diffusion are in agreement with each other as well as in agreement with the gold standard. The amount of water based on diffusion increases proportionately with an increase in the water content based on T1 and T2 techniques. Clearly, the water content displayed an excellent quantitative correlation with the tissue content over the range of MDs investigated where higher MD in the mammogram images corresponds to higher water con-

| Table 2 |

Parameter settings for the T1 technique.

| Saturation recovery sequence | CPMG block |
|-----------------------------|------------|
| Eacho time (TE) (µs) | Repetition time (ms) | Max recovery time (ms) | Number of echos | Number of complex points | Number of scan | Dwell time (µs) |
| 60 | 2000 | 3000 | 64 | 16 | 4 | 0.5 |

| Table 3 |

Parameter settings for the T2 measurements.

| Eacho time (TE) (µs) | Repetition time (ms) | Number of eachos | Number of complex points | Number of scan | Dwell time (µs) |
|--------------------|---------------------|------------------|------------------------|----------------|----------------|
| 700 | 7000 | 1500 | 32 | 8 | 0.5 |
tent in NMR measurements and vice versa. This means that the accuracy reproducibility of MDs based on the three techniques $T_1$, $T_2$ and diffusion are reliable.

Fig. 12 demonstrate the effect of echo Time on The resolution of the ILP decay. Three scans with three different TE values were performed on the first sample in order to observe the best TE value that would resolve the water and fat peaks in the ILP spectrum. The ILP decay curve with $TE = 700\ \mu s$ was adopted for subsequent $T_2$ scans since it displayed no overlaps between the water and fat peaks (Fig. 12). As such, it is evident that the selected of echo time (TE) of 700 $\mu$s was long enough to show distinctive water and fat peaks for the breast samples under investigation. In contrast, Huang et al. (2018) could not discriminate between the water and fat peaks due to the short CPMG echo time adopted (60 $\mu$s) leading to an overlap of water and fat peaks in the ILPs of $T_2$ spectra. This, indeed, reduces the accuracy of calculating the amplitude
of water peaks in T₂ spectra. Consequently, the superiority of the present measurements is a direct result of the choice of the sequence parameters.

Evidently, all the experimental T₁ curves are bioexponential; they reveal the amount of water and fat in the breast tissue. In contrast, the study conducted by Tourell et al. (2018) did not reveal the amplitudes of the two components since the T₁ curves were monoexponential. The measurements were based on the apparent T₁ of HMD and LMD regions. However, the current study has successfully determined the amplitudes of the two components. From the analysis, the water/fat ratio can be deduced from T₁ measurements, or the three techniques altogether.

In the water and fat peaks in T₂ spectra, it is possible to discriminate between the LMD, HMD, and intermediate MD regions of the excised samples. The HMD regions represent relatively larger amount of water molecules. This means that the transverse coherent magnetization components of protons in water molecules are highest in the HMD regions, followed by the intermediate MD, and then, the LMD regions. These differences are reflected in the water and fat peaks of the T₂ spectra. The analysis has also revealed that the water-to-fat ratio increases as the MD of excised breast samples increases. Overall, the experimental analysis has quantitatively shown that the pulse sequences can be used in the portable NMR instrument to provide quantitative measurements of MD on a continuous scale throughout the breast tissue sample. The measurements revealed more intricate details of breast tissue composition than the ones based on paired LMD/HMD classifications as reported by Tourell et al. (2018). Among the limitations of the current study is that it measured MD from the excised samples of participants undergoing prophylactic mastectomy, and hence, it is unclear whether the outcomes provide representative measurements for patients in both the upper and lower MD quartile of the BI-RADS scale. Further, the ILP might have introduce numerical errors while reconstructing the T₂ distributions, thereby reducing the accuracy of T₂ measurements. This problem was recently reported by Ali et al. (2019). Possibly, the L-bend was not always identifiable due to the effect of noise in the data. Most likely, the T₂ distributions were either under- or over-smoothened, especially where sub-optimal ILT values were observed. Such errors stem from the ILT framework employed, which should be investigated in future studies. Nevertheless, this research is novel in the sense that it represents the first time when T₁, T₂, and NMR diffusion are employed sequentially for each region of interest to quantitatively measure the distribution of MDs in breast tissue samples.

5. Conclusion

This research has demonstrated that the three techniques (T₂, T₁, and NMR-aided diffusion) are fairly in agreement with one other in quantifying HMD, intermediate MD, and LMD regions of breast tissue sample. Certainly, these regions, which represent changes in MD, are useful quantitative indicators of breast cancer progression stages. Furthermore, the outcomes lend support to the utilization of NMR probes to quantify MD affordably and conveniently. The method is also safe since it is free from ionizing radiation. The impressive correlation between the measurements indicate the fundamental essence of selecting the portable-NMR parameters for measuring MD. The results have important implications in clinical settings and more so, to breast cancer patients. For instance, they can be used in the early prediction of MD and subsequent risk analysis of breast cancer. The study could also be
extended to predicting the utility of hormonal therapy with the view of preventing breast cancer.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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