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Development of a Composite Material Phantom Mimicking the Magnetic Resonance Parameters of the Neonatal Brain at 3.0 Tesla

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ABSTRACT

Objective: Development of a composite material phantom, based on polyvinyl alcohol cryogel (PVA-C) with agarose as an additive, that could effectively mimic the magnetic resonance (MR) relaxation times (T_1 & T_2) of neonatal white matter (WM) and grey matter (GM) at 3.0 Tesla.

Materials and Methods: Samples of PVA-C with and without agarose were prepared with 1 cycle of freezing/thawing. Measurements of T_1 and T_2, at 3.0 Tesla, were carried out on the samples at temperatures ranging from 20°C to 40°C.

Results: Relaxation times similar to neonatal WM and GM can be obtained at a sample temperature of 40°C. Neonatal WM relaxation times required 3% PVA-C and 0.3% agarose, while GM relaxation times required 8% PVA-C and 1.4% agarose.

Conclusion: By adjusting the sample temperature, PVA-C concentration and agarose concentration, the relaxation times of neonatal brain tissues can be obtained using this composite material.

Key Words: phantom; magnetic resonance imaging; neonatal brain; polyvinyl alcohol cryogel; 3.0 T

INTRODUCTION

Various studies have shown that magnetic resonance imaging (MRI) techniques can be used to non-invasively investigate the impact of premature birth and related risk factors on early brain development, and provide prognostic indicators of neuro-developmental outcome.[1-4] Optimization (at a given field strength) and adaptation of MRI sequences developed for adults need substantial revision because the relaxation times (T_1 and T_2) of neonatal brain tissues differ greatly from those of adults and children.[5] Image contrast and information is largely determined by these relaxation times. Experimental testing of these revised techniques would be quite useful, not only for optimizing contrast, but also for exploring the influence of imaging parameters on the efficacy of image processing techniques such as segmentation. However, performing optimization of MRI sequences on human neonates is not ethically appropriate. Although using animals would overcome these ethical problems, the challenge remains in finding a suitable model that matches both the MR relaxation times and morphology of the human neonatal brain. Digital phantoms would also not be optimal because of the difficulties associated with accounting for "non-ideal" signal behaviour from various sources (e.g. imperfect spoiling, eddy currents, non-uniform static and radio-frequency magnetic fields). Thus, a realistic phantom to mimic both the MR parameters and morphological features of the neonatal brain would be a valuable tool.

In order to develop a brain phantom for neonatal MRI, it is necessary to choose a phantom material that can be molded into a complex shape. Polyvinyl alcohol cryogel (PVA-C) is a non-toxic gel that is prepared by mixing water with dry PVA powder and then applying one or more cycles of freezing and thawing.[6] PVA-C has been utilized for

various structural biomedical applications[7,8], demonstrating its potential for complex molding. PVA-C has also been investigated as an MRI phantom material in several studies.[6,9,10] In particular, the MR relaxation times of PVA-C have been found to decrease with increasing PVA content (decreasing water content)[6] and with increasing number of freeze-thaw cycles (FTCs).[9,10] A single compartment, homogeneous MRI phantom with morphology similar to that of the adult brain has previously been constructed from PVA-C[10], thus demonstrating that the shape-retaining properties of PVA-C are adequate for brain phantom construction.

One of the challenges in developing a neonatal brain phantom is emulating the very long relaxation times of neonatal brain tissue, particularly white matter ($T_1 \sim 2800$ ms and $T_2 \sim 260$ ms at 3.0 T).[5] The long relaxation times in neonatal brain tissue compared to an adult brain are, in part, due to the very high water content (> 90%[11]) in the former. To our knowledge, T_1 values reported for gel phantom materials (PVA-C[9,10], carrageenan[12], TX-150[13], gelatin[14], alginate microbeads[15], agarose[16-18], and polyacrylamide[19]) at room temperature generally do not exceed 2 seconds. One exception is 0.5% agarose by weight which is just barely high enough in concentration to hold its shape.[20] The difficulty in achieving a T_1 relaxation time sufficiently long to represent neonatal brain tissue, even with materials that are approximately 97% water, is not unexpected since T_1 of water increases substantially with temperature, and the temperature of brain tissue (37°C) is greater than the phantom temperature (≈20-25°C) used for most applications. Our approach to achieving the required long relaxation times of neonatal tissues involves imaging the phantom material at a higher temperature.

A second challenge in emulating both T_1 and T_2 relaxation times of neonatal brain tissue (or any other tissue) involves the ability to independently alter T_1 and T_2. Previous studies have shown that this can be accomplished using two or more ingredients.[6,12-14,17,20,21]. For example, certain additives, (e.g. graphite[6,14], agarose[12], 2-2-diphenyl-1 picrylhydrazyl[13], aluminum powder[21]) when added in small concentrations have been found to influence T_2 more strongly than T_1. We have chosen to use agarose for this purpose, since it has been shown to homogenously dissolve in phantom materials without producing sediment.[12]

The objective of the present study was to investigate the possibility of emulating neonatal white matter (WM) and grey matter (GM) with a phantom material based on PVA-C, containing agarose as an additive. This is the first stage in our ultimate goal: the creation of a phantom to emulate both MRI properties and morphology of the neonatal brain. In this work, we explore the influence of temperature and PVA-C concentration (1 FTC) on relaxation times, in order to determine if sufficiently long T_1 values to represent neonatal WM can be achieved by altering these two parameters. Then we investigate the influence of agarose concentration for various PVA-C concentrations on the relaxation times measured at an elevated target temperature. Using the results obtained from this study, we will determine the concentrations of PVA-C and agarose required to emulate the relaxation times of neonatal WM and GM with samples held at an elevated temperature.

MATERIALS AND METHODS

PVA-C Manufacture

Samples containing 3, 6, 10, 15% by weight of polyvinyl alcohol (molecular weight 146 000 – 186 000, #363162 Sigma-Aldrich Canada Limited, Oakville, ON, Canada) were prepared by mixing PVA powder with de-ionized water. The mixture was slowly heated from 20°C to 95°C over two hours using a standard reflux column. The final solution was placed in air-tight cylindrical moulds (diameter = 25 mm, length = 21 mm, wall thickness = 0.3 mm), and after a short settling time, placed into an environmental chamber (Cascade Mechanical Services Limited, Brampton, ON, Canada) for one FTC. This FTC consisted of controlled freezing (20°C to -20°C at 0.1°C/min), a one hour hold time at -20°C, and finally controlled thawing (-20°C to 20°C at 0.1°C/min). The two halves of the moulds were securely tightened using bolts before undergoing a FTC in order to withstand the pressure resulting from expansion of the solution during freezing. The samples were then removed from the moulds, stored in tap water and refrigerated at 4°C.

A second set of samples containing agarose (Type 1, #A-6013 Sigma-Aldrich Canada Limited, Oakville, ON, Canada) as an additive was prepared by mixing PVA and agarose powders with de-ionized water using the same manufacturing process as described above. This set included a total of 32 samples prepared using four different PVA concentrations (3, 6, 11 and 15% [by weight]) with eight different agarose concentrations (0, 0.2, 0.4, 0.6, 0.8, 1.0, 1.4, 1.8% [by weight]).

Warming of Samples for MRI

The PVA-C samples were placed in a plastic container with approximately cylindrical shape (diameter = 11.4 cm, length = 4.6 cm) and filled with water at 20°C. The container was placed in a water bath which was heated slowly to the desired temperature and was held at this temperature for 30 minutes. This sample container was then placed in a styrofoam cylindrical container (diameter = 18.4 cm, length = 11.8 cm, wall thickness = 2.9 cm), which served as a thermal insulator, and then placed in the radiofrequency coil for MRI scans. The temperature of the water in the sample container was measured before and after the set of MRI scans to observe any small temperature changes that may have occurred during the time period. The temperature measurements were averaged to indicate the operating temperature of the samples.

MRI experiments on the first set of samples (no agarose) were performed at five different sample temperatures (20, 25, 30, 35, 40°C). For the PVA-C samples with agarose, experiments were performed at a single sample temperature of 40°C.

Magnetic Resonance Imaging

MRI was carried out on a home-built 3.0 T MRI system custom designed for neonatal and adult head-only scans. The short-bore magnet (length = 135 cm) is equipped with asymmetric gradients with a maximum strength of 30 mT/m. The samples were imaged using a quadrature birdcage coil, with an inner diameter of 27.9 cm.

Image-based measurements of T_1 relaxation times were obtained using a TOMROP pulse sequence[22] with multi-slice acquisition[5] using the following imaging parameters: 5 slices; section thickness = 3 mm; FOV = 120 mm; matrix size= 96×96;

time duration between successive inversion pulses = 2000 ms; time duration between successive excitation pulses = 120 ms; echo time (TE) = 8 ms; and nominal flip angle= 25°. T_1 maps were reconstructed using an automated procedure that does not require prior knowledge of the flip angle within each pixel.[23]

Image-based measurements of T_2 relaxation times were obtained using a 16-segment echo-planar imaging (EPI) sequence[5] with the following parameters: 5 slices; section thickness = 3mm; FOV = 120mm; matrix = 96×96; and TE = 35, 108, 181, 254, 327, 400 ms. The difference between TR and TE was held constant[5] at 5000 ms. T_2 maps were created by performing a pixel-by-pixel log-linear least squares regression, weighted appropriately.

Regions of interest (ROI) were selected on uniform areas (Analyze Software Suite 8.0, Mayo Clinic, Rochester, MN) within the middle slice of each image map. Each ROI was drawn to cover approximately 90% of the sample area, and consisted of approximately 300 pixels.

Regression Analysis

The measured relaxation data for the homogeneous PVA-C samples (with no agarose) were fit to the following empirical model, which assumed that the relaxation times varied linearly with temperature, and that the slope and intercept varied linearly with PVA-C concentrations:

$$T_i = (a_0 + a_1[P]) + (a_2 + a_3[P])t$$

$$T_i = a_0 + a_1[P] + a_2t + a_3[P]t \qquad [1]$$

In the above equation, T_i represents the T_1 or T_2 relaxation time, [P] is the concentration (by weight) of PVA-C in the sample, t is the sample temperature, and a_0, a_1, a_2, a_3 are adjustable parameters. The values of adjustable parameters (with 95% confidence interval) that provide the best fit to the data were determined using the least-squares (Gauss-Newton) method (MatLab, MathWorks, Natick, Massachusetts, USA). The models were then used to predict the PVA-C concentrations necessary to obtain the mean relaxation times from a previous study[5] of neonatal WM and GM at 3.0 T.

The T_1 relaxation times measured at 40°C for the PVA-C samples with agarose concentrations were fit to the following model, which assumed that T_1 varied linearly with agarose concentrations, and that the slope and intercept varied linearly with PVA-C concentrations:

$$T_1 = (b_0 + b_1[P]) + (b_2 + b_3[P])[A]$$

$$T_1 = b_0 + b_1[P] + b_2[A] + b_3[P][A] \qquad [2]$$

In the above equation, T_1 is the spin-lattice relaxation time of the samples, [A] is the agarose concentration (by weight) and b_0, b_1, b_2, b_3 are adjustable parameters.

The T_2 relaxation times measured at 40°C for the PVA-C samples with agarose concentrations were fit to the following empirical model, which assumed that T_2 varied exponentially with agarose concentrations, and that each parameter varied linearly with PVA-C concentrations:

$$T_2 = (c_0 + c_1[P]) + (c_2 + c_3[P])\exp\{-[A](c_4 + c_5[P])\} \qquad [3]$$

In this equation, T_2 is the spin-spin relaxation time of the samples and c_0, c_1, c_2, c_3, c_4 and c_5 are the adjustable parameters.

Long-Term Stability Tests

Samples containing 3% and 11% PVA, each with different agarose concentrations (0, 0.2, 0.4, 0.6, 0.8, 1.0% by weight), were assessed for long-term stability of their T_1 and T_2 values at 40°C by performing MRI measurements on different days after sample preparation. The 3% PVA-C samples were imaged on 9 different days over a 200 day period after sample preparation, while the 11% PVA-C samples were imaged on seven different days over a 150 day period after sample preparation. The PVA-C samples were stored in tap water and were refrigerated at 4°C in between imaging days. For each of these 12 samples (2 PVA concentrations × 6 agarose concentrations), the coefficient of variation (standard deviation/mean) over the repeated measurements was determined. The mean and standard deviation of the coefficient of variation (over all samples) was computed for T_1 and for T_2.

RESULTS

Homogeneous PVA-C Samples

Measured MRI relaxation times for the samples with different PVA-C concentrations are shown as a function of temperature in Figure 1. Optimized values of the adjustable parameters (a_0, a_1, a_2, a_3 in Eq. [1]) are provided in Table 1. The model function (Eq. [1]) provides a good match to the data within this range of temperatures and PVA-C concentrations, with these two variables accounting for almost all the observed variance ($R^2 = 0.99$ and $R^2 = 0.98$ for T_1 and T_2, respectively). Horizontal lines on these figures represent the mean values of T_1 and T_2 previously obtained for neonatal WM and GM at 3.0 T.[5] The final temperature of the water in the sample container after MRI measurements deviated by less than 0.5°C for temperatures within the range of 20-35°C, and by less than 1.5°C at 40°C.

From Figure 1, it is evident that T_1 values sufficiently long enough to represent the approximate mean value for neonatal WM are obtained with 3% PVA-C at temperatures close to 40°C. At this temperature, the T_1 value of GM can be obtained with values close to 10% PVA-C. However, the corresponding T_2 values ($\approx$ 440 ms and $\approx$ 280 ms for 3% and 10% PVA from Figure 1B) at approximately 40°C are too long for neonatal WM ($T_2 \approx 260$ ms) and GM ($T_2 \approx 140$ ms).[5]

PVA-C Samples with Agarose Additive

Measured T_1 and T_2 values for the PVA-C samples with agarose at 40°C are illustrated in Figure 2. The optimized values of the fit parameters (b_0, b_1, b_2, b_3 in Eq. [2]

and c_0, c_1, c_2, c_3, c_4, c_5 in Eq. [3] are provided in Tables 2 and 3. The model functions (Eq. [2] and Eq. [3]) provide good matches to the data within this range of agarose and PVA-C concentrations, with these two variables accounting for almost all of the observed variance ($R^2 = 0.98$ and $R^2 = 0.99$ for T_1 and T_2 respectively). The T_2 relaxation times (Fig. 2A) decrease with increasing agarose concentration, and this decrease appears to level off at a value close to the mean of reported[5] T_2 values for neonatal GM at 3.0 T (bottom horizontal line).

Figure 3 is a contour plot of T_1 and T_2 at 40°C as described by the empirical equations (Eq. [2] and [3], with best fit parameter values) with PVA-C and agarose concentrations as the independent variables. The shaded area near the bottom left indicate the regions where both T_1 and T_2 are within one standard deviation of the mean (shown as solid black point) of reported values for neonatal WM at 3.0 T.[5] From the plot, it can be seen that these mean relaxation times can be mimicked with [P] ≈ 3% and [A] ≈ 0.3%. The shading near the upper right corner of the figure indicates the region in this contour map where relaxation times are within one standard deviation of the mean value for neonatal GM.[5] This GM region includes only T_2 values that are approximately 10 ms or more above the mean T_2 for neonatal GM (mean ± SD of reported GM $T_2 = 138 \pm 16$ ms). This is consistent with Fig. 2A which shows that with increasing agarose concentration, T_2 levels off slightly above the mean neonatal GM value. Based on this contour plot, using [P] ≈ 8% and [A] ≈ 1.4% would prove a T_1 near the mean value for GM ($T_1 = 2166$ ms) and a T_2 of approximately 150 ms, which is slightly above the mean T_2. The variation (1 SD) in T_1 and T_2 values along contour lines near the regions of interest were found to be approximately 50 ms and 5 ms respectively. These

uncertainties are associated with the uncertainties in the model parameter values (Tables 2 and 3) and are small compared to the variation in neonatal relaxation times for each tissue.

Long-Term Stability Tests

The coefficients of variation averaged over the twelve samples that were measured at different time points were only 2.72 ± 0.07% and 4.8 ± 1.9% (mean ± SD), for T_1 and T_2, respectively. These values represent insignificant fluctuations over the 150 day (11% PVA-C) or 200 day (3% PVA-C) periods.

DISCUSSION

In this work we investigated the feasibility of creating composite phantom materials to emulate the MRI relaxation times of the neonatal brain at 3.0 T using polyvinyl alcohol cryogel (PVA-C) as a base material and agarose as an additive. Our results demonstrate that it is possible to emulate the long T_1 values of neonatal WM by raising the temperature of low concentration PVA-C to approximately 40°C. By combining this approach with the addition of agarose, both T_1 and T_2 values of the tissues could be approximately emulated. To our knowledge this is the first work to study temperature dependence on the relaxation times of PVA-C, to study MRI properties of very low concentration PVA-C (< 10% by wt), and to study relaxation times of a PVA/agarose composite material at 3.0 T.

Room temperature T_1 values of other firm gel materials[12-19,21] previously investigated for MRI phantoms are too short (approximately < 2 s) to emulate neonatal WM. Although a very long T_1 value (≈ 2700 ms) was reported for 0.5% agarose gel at 1.4 T[20], the authors indicated that the gel did not have the ability to hold its shape at concentrations less than 0.5%; thus, it is very unlikely that 0.5% would have the ability to retain complex shapes within a brain phantom. Increasing the agarose concentration to only 1% resulted in a T_1 value of approximately 1890 ms, which would not be long enough to emulate neonatal WM.

For the present work, we chose to increase sample temperature in order to achieve the required long T_1 values of neonatal WM. Two other potential methods for lengthening T_1 were discovered during research into other topics and should be considered. The first involves "preheating of samples", a technique previously developed

for temperature dosimetry.[24] In this previous study, PVA-C samples (10% & 15% PVA-C with 1 FTC and 10% PVA-C with 2 FTCs) were heated to temperatures up to 72°C, and then cooled to 20°C prior to MRI measurements.[24] This led to lengthening of T_1 and T_2 as measured within 10 hours after preheating; however, the relaxation times for the 10% sample with 1 FTC (most relevant to our work) were not stable as assessed two weeks later. In addition, one would expect that heating of PVA-C to such high temperatures could alter the polymer structure and possibly its mechanical properties. Another possible method of lengthening T_1 involves reducing dissolved oxygen levels in samples. In a previous study, it was reported that removal of dissolved oxygen from bovine serum albumin samples caused only a 5% increase in T_1 from its initial value of 1876 ms.[25] Thus, removal of sample oxygen would not likely provide a sufficient T_1 increase for our purpose.

Although the influence of sample temperature (during MRI) on the relaxation times of PVA-C has not been previously explored, this temperature variation has been reported for agarose samples. One previous study reported that increasing sample temperature from 20°C to 30°C led to a 15% increase in T_1 for 2% agarose.[17] We observed a slight relative increase (22%) in T_1 for 3% PVA-C over the same temperature range.

Agarose has been explored as an additive in carrageenan gel, and was found to significantly shorten the T_2 relaxation time of the gel as the agarose concentration was increased.[12] In that previous study, the T_2 relaxation times of 3% carrageenan gel were shortened from 420 ms to 40 ms as the agarose concentration was varied from 0-1.6% (by weight), with roughly 90% of the T_2 change occurring between 0 and 0.6% agarose.[12] In

our current study, the T_2 relaxation times of 3% PVA-C (at 40°C) were shortened from 480 ms to 148 ms as the agarose concentration was varied from 0-1.8% (by weight), with roughly 94% of the T_2 change occurring between 0 and 0.6% agarose. Increasing the agarose concentration to greater than 0.6% agarose in both materials caused very little additional changes in T_2.

Our results indicate that we can achieve T_1 and T_2 values corresponding to the mean reported 3.0 T values for neonatal WM.[5] However, for emulating neonatal GM, our closest approximation would have T_2 values (150 ms) that are slightly above the mean reported value (mean T_2 = 138 ms, SD = 16 ms). This still provides a reasonable emulation of neonatal GM. It might be possible to achieve a shorter T_2 value while maintaining the required T_1 by increasing the number of FTCs that the PVA-C undergoes. One previous study showed that increasing the number of FTCs from one to two led to a larger relative change (shortening) of T_2 than for T_1.[9]

In our study, the target relaxation times for neonatal WM and GM at 3.0 T were obtained from a previous study at 3.0 T.[5] To our knowledge this is the only report on neonatal WM and GM relaxation times at 3.0 T. In addition, this previous in-vivo study employed the same relaxation time measurement methods used in this study. However, subjects from the previous study ranged in gestational age at birth (range 26-42 weeks, mean 31 weeks) and postmentrual age at scan (range 28-43 weeks, mean 36 weeks), and all suffered from different brain abnormalities.[5] However, the PVA-C concentration, agarose concentration and temperature could be adjusted to alter the relaxation times if necessary to accommodate age-related changes.[11,26,27]

The relaxation times of the PVA-C samples with agarose appear to be stable over a 200 day time period. A previous study reported a 6-month stability period for which the relaxation times of PVA-C would stay relatively constant.[6] However, this assessment was only made for 15% and 20% PVA-C, and it was not reported whether or not the samples were stored in water or kept refrigerated. Further investigations are required to determine if the relaxation times of these PVA-C samples with agarose as an additive are stable over longer periods of time.

The information obtained in this present study represent the first step in the design and construction of a multi-region MRI brain phantom with morphology and with relaxation times appropriate for neonatal brain tissue. To utilize such a phantom for testing and optimizing MRI techniques (e.g. 3D imaging), it would be necessary to hold the phantom temperature at 40°C for at least a period of roughly one hour or more. In the present study, with the phantom materials held in a stryofoam container (2.9 cm wall thickness), the temperature of the samples that were initially close to 40°C dropped by less than 1.5°C over the 45 minute imaging duration. However, heat loss could be reduced by increasing the wall thickness of the stryofoam. Assuming a neonatal brain phantom with a 10 cm diameter, imaged in the same RF coil used in this study (27.9 cm inside diameter), one could construct a cylindrical insulator with wall thickness of approximately 9 cm (approximately 3 times thicker than that used here) which would substantially reduce heat loss. If necessary, a vacuum-based insulated container could also be used, which should provide superior insulation.

In summary, we have shown that it is possible to emulate relaxation times similar to neonatal brain tissues at 3.0 T using polyvinyl alcohol cryogel (PVA-C) as a base

phantom material with agarose as an additive. This can be achieved by increasing the temperature of the phantom material to approximately 40°C. At this temperature, it was computed that neonatal WM can be mimicked with a PVA-C concentration of 3% and an agarose concentration of 0.3%. Neonatal GM can be approximately mimicked (with T_2 values slightly above the target mean reported value) with PVA-C concentration of 8% (computed from the results of this study) and an agarose concentration of 1.4%

TABLE 1. Coefficients of Eq. [1], for each parameter

	a_0	a_1	a_2	a_3	R^2
T_1	1170 ± 186	-19.2 ± 20	50.1 ± 6.0	-1.73 ± 0.64	0.99
T_2	391 ± 64	-17.7 ± 6.8	3.31 ± 2.2	-0.120 ± 0.22	0.98

Note – The coefficient values were determined by fitting the data to Eq. [1] using the nonlinear least-squares method (Gauss-Newton method). Values are presented as $a_i \pm \sigma$, where the 95% confidence interval is $(a_i - \sigma,\ a_i + \sigma)$.

TABLE 2. Coefficients for Eq. [2], for T_1

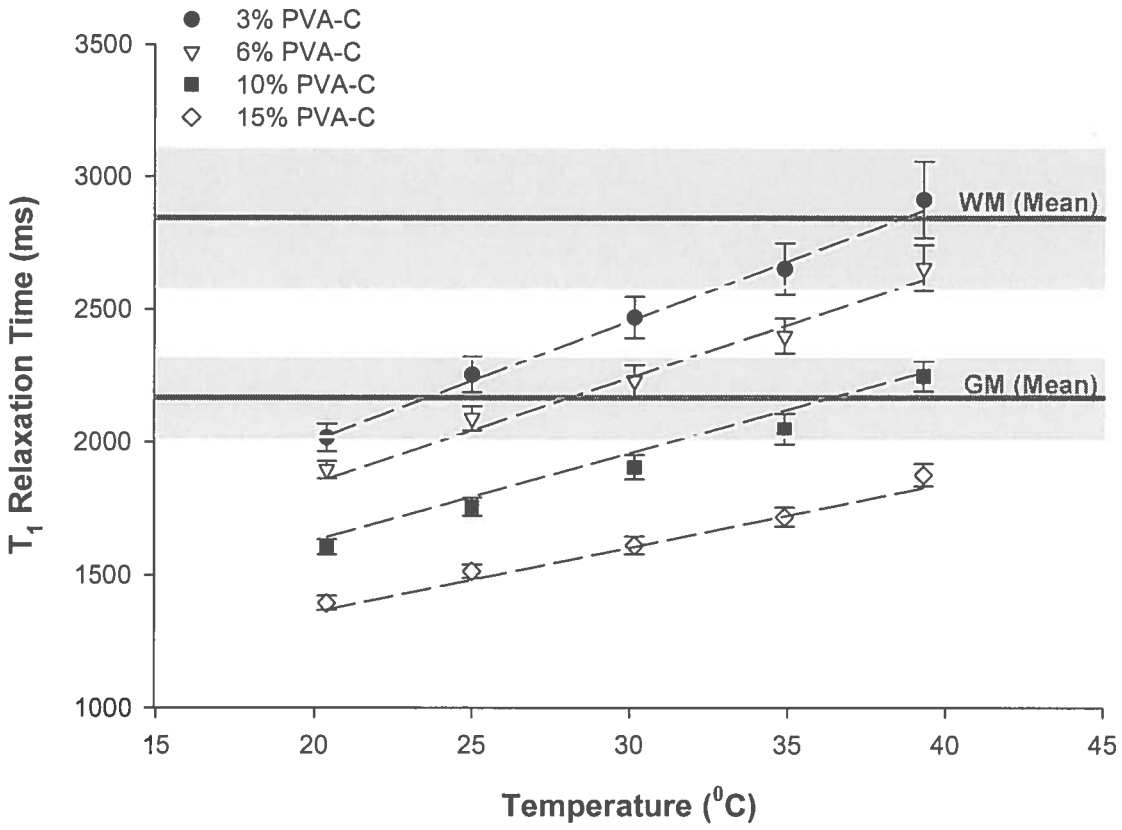
b_0	b_1	b_2	b_3	R^2
3160 ± 90	-88.2 ± 9.0	-249 ± 92	5.21 ± 9.4	0.98

Note – The coefficient values were determined by fitting the data to Eq. [2] for T_1 using the nonlinear least-squares method (Gauss-Newton method). Values are presented as $b_i \pm \sigma$, where the 95% confidence interval is $(b_i - \sigma,\ b_i + \sigma)$.

TABLE 3. Coefficients for Eq. [3], for T_2

c_0	c_1	c_2	c_3	c_4	c_5	R^2
152 ± 11.6	-0.54 ± 1.14	389 ± 20	-23.8 ± 2.2	3.84 ± 0.68	-0.090 ± 0.1	0.99

Note – The coefficient values were determined by fitting the data to Eq. [3] using the nonlinear least-squares method (Gauss-Newton method). Values are presented as $c_i \pm \sigma$, where the 95% confidence interval is $(c_i - \sigma,\ c_i + \sigma)$.


3% PVA-C
6% PVA-C
10% PVA-C
15% PVA-C
3500
3000
2500
2000
1500
1000
WM (Mean)
GM (Mean)
T1 Relaxation Time (ms)
15
20
25
30
35
40
45
Temperature (0C)

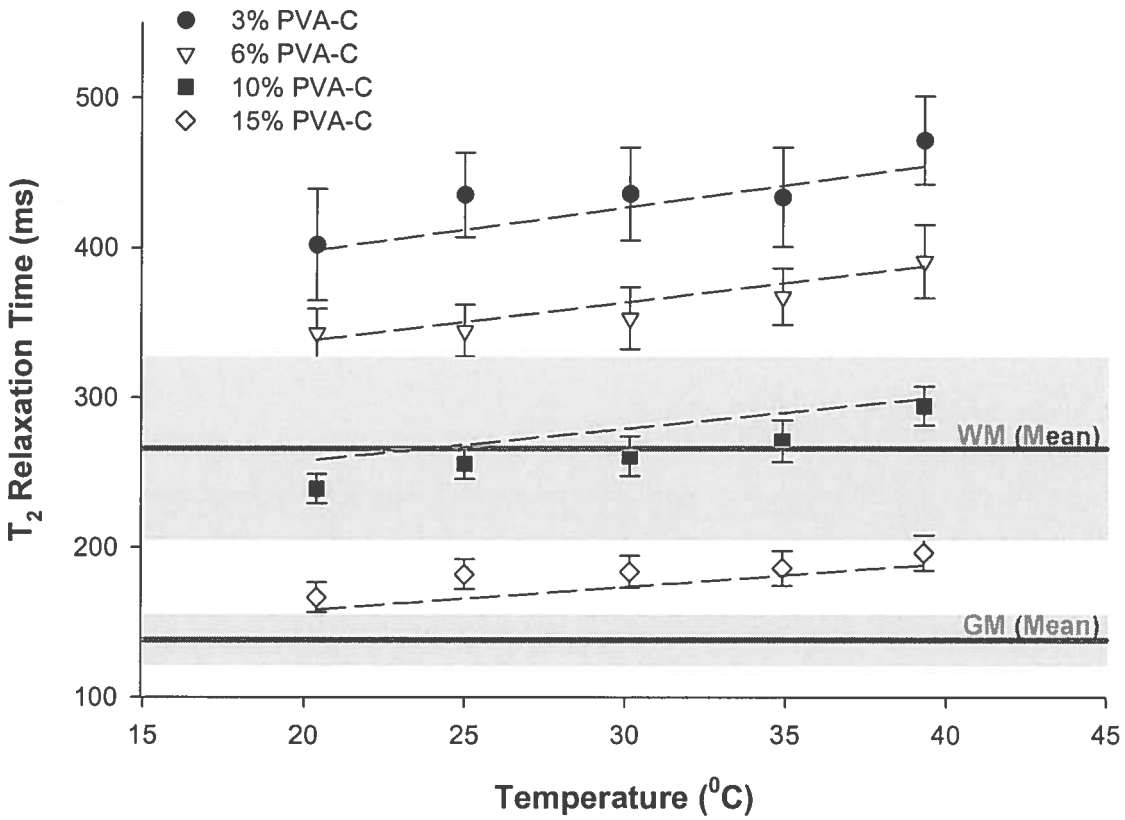
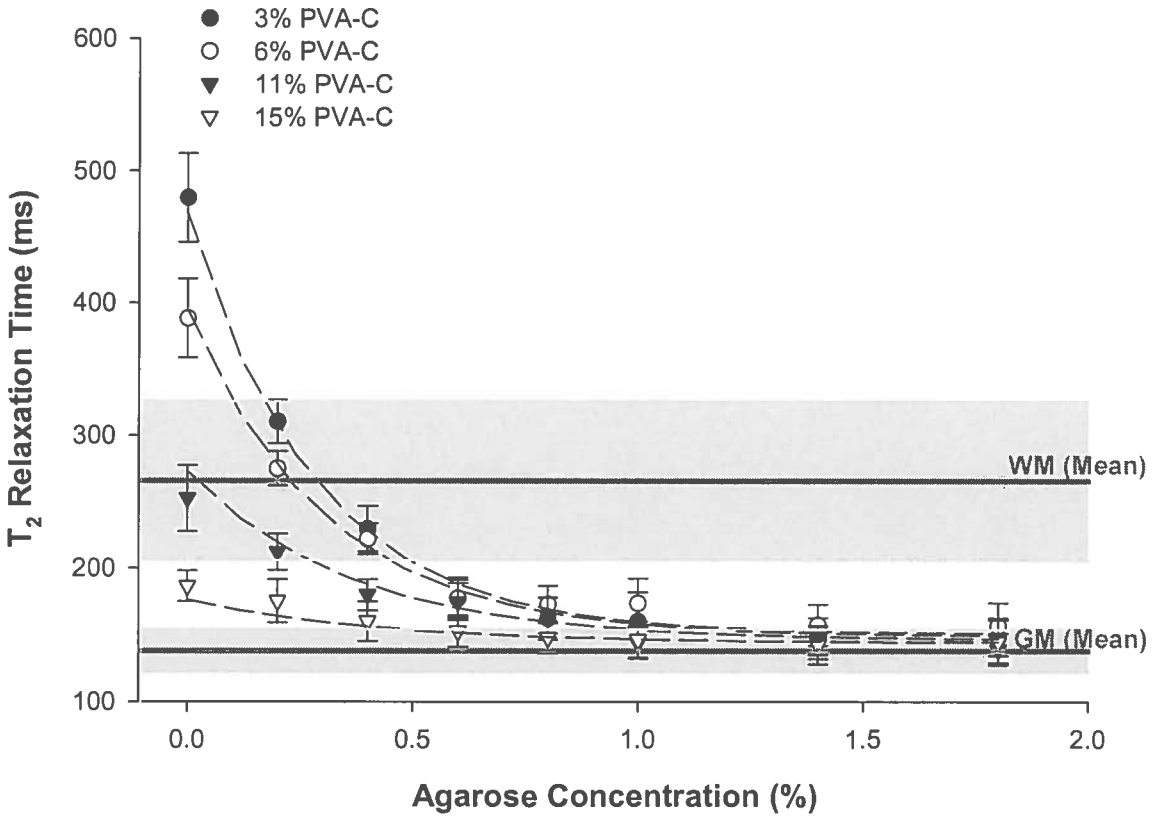


FIG. 1. Relaxation times of PVA-C samples vs. temperature. T_1 and T_2 are shown in parts A and B, respectively. Error bars represent standard deviations obtained in averaging over all pixels in each region of interest. The broken lines represent the least-squares fit of the data to the multiple regression model described by Eq. [1]. The solid gray lines in (A) represent the mean T_1 values for neonatal white matter (WM) and gray matter (GM) previously reported[5] (shaded regions indicate SD = 260 ms and 147 ms, respectively). The corresponding lines in (B) represent the mean T_2 values for neonatal WM and GM previously reported[5] (shaded regions indicate SD = 60 ms and 16 ms, respectively).


3% PVA-C
6% PVA-C
11% PVA-C
15% PVA-C
600
500
400
300
200
100
T_2 Relaxation Time (ms)
WM (Mean)
GM (Mean)
0.0
0.5
1.0
1.5
2.0
Agarose Concentration (%)

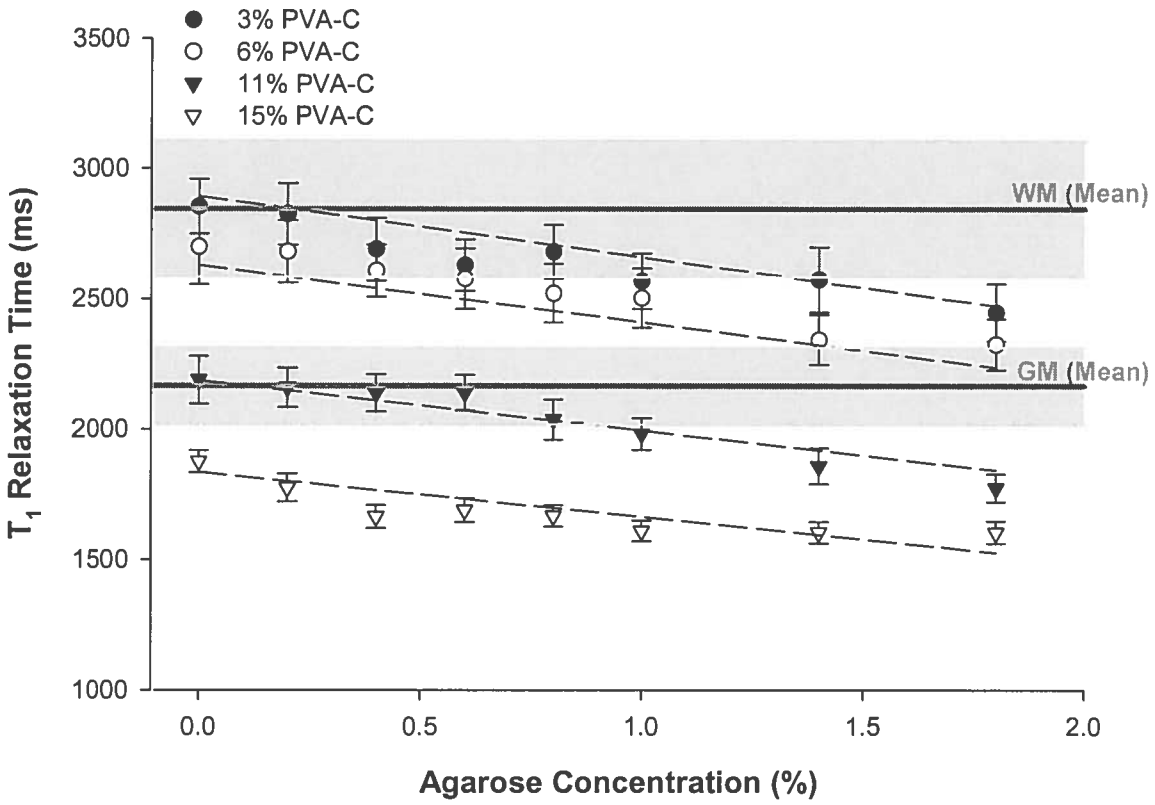


FIG. 2. Relaxation times of PVA-C samples vs. agarose concentration at a sample temperature of 40°C. T_2 and T_1 are shown in parts A and B, respectively. Error bars represent standard deviations obtained in averaging over all pixels in each region of interest. The broken lines represent the least-squares fit of the data to the multiple regression models shown in Eq. [3] (A) and Eq. [2] (B). The solid lines in (A) represent the mean T_2 values for neonatal white matter (WM) and gray matter (GM) from a previous study[5] (shaded regions indicate SD = 60 ms and 16 ms, respectively). The corresponding solid lines in (B) represent the mean T_1 values for neonatal WM and GM from a previous study[5] (shaded regions indicate SD = 260 ms and 147 ms, respectively).

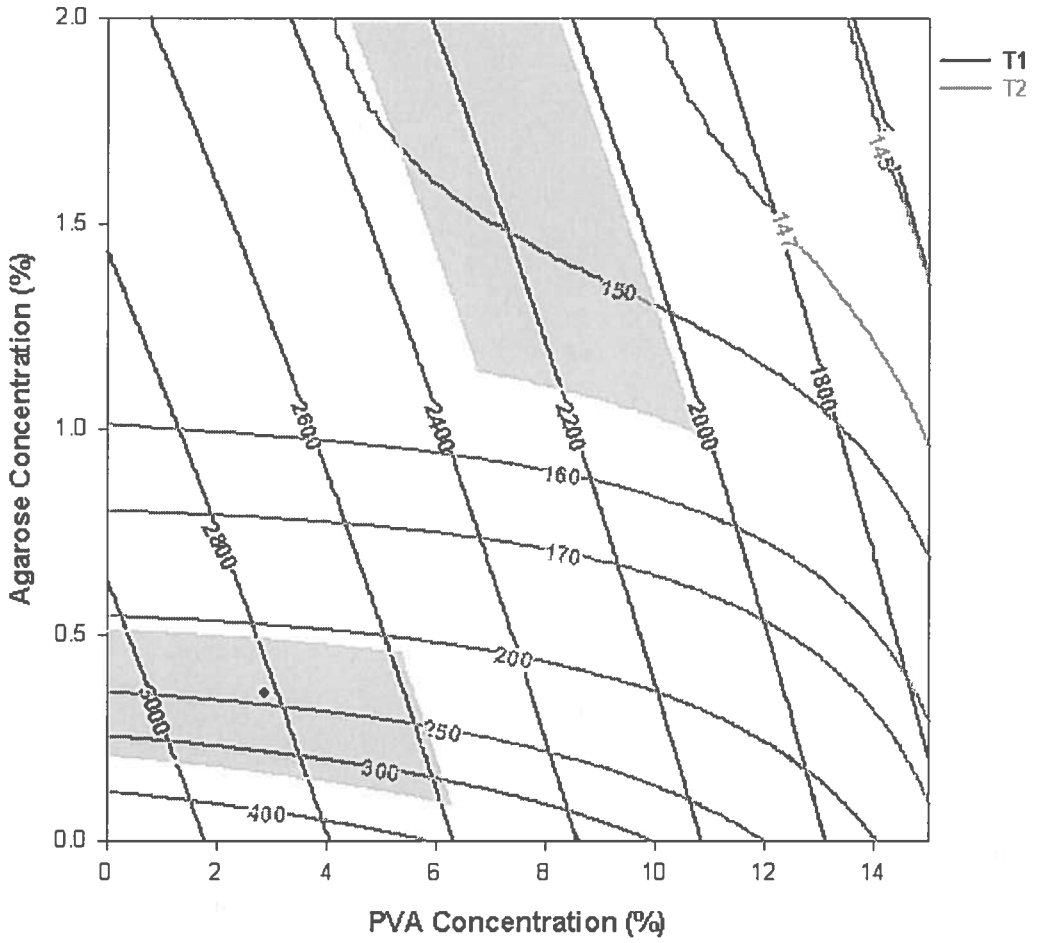


FIG. 3. Contour plot illustrating lines of constant T_1 and T_2, as functions of PVA and agarose concentration, at 40°C, based on our empirical equations (Eq. [2] and [3]). The shading boundaries near the bottom left indicates the regions where relaxation times are within one standard deviation (above or below) the mean value obtained in a previous study[5] for neonatal WM at 3.0 T. The black circle in the WM region, at [P]=3% and [A]=0.3%, corresponds to the mean neonatal WM relaxation times (T_1 = 2844 ms; T_2 = 266 ms). The shading near the upper right corner of the figure indicates the region within this contour map where relaxation times are within one standard deviation of the mean value for neonatal GM. [5] This GM region includes only T_2 values that are approximately

10 ms or more above the mean reported T_2 for neonatal GM (mean ± SD of reported GM T_2 = 138 ± 16 ms)

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