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MR relaxation properties of tissue-mimicking phantoms

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ABSTRACT

High quality tissue-mimicking phantoms (TMPs) have a critical role in the preclinical testing of emerging modalities for diagnosis and therapy. TMPs capable of accurately mimicking real tissue in Magnetic Resonance guided Focused Ultrasound (MRgFUS) applications should be fabricated with precise T1 and T2 relaxation times. Given the current popularity of the MRgFUS technology, we herein performed a systematic review on the MR relaxation properties of different phantoms types. Polyacrylamide (PAA) and agar based phantoms were proven capable of accurately replicating critical thermal, acoustical, and MR relaxation properties of various body tissues. Although gelatin phantoms were also proven factional in this regard, they lack the capacity to withstand ablation temperatures, and thus, are only recommended for hyperthermia applications. Other gelling agents identified in the literature are Poly-vinyl alcohol (PVA), Polyvinyl Chloride (PVC), silicone, and TX-150/ TX-151; however, their efficacy in thermal studies is yet to be established. PAA gels are favorable in that they offer optical transparency enabling direct visualization of coagulative lesions. On the other hand, agar phantoms have lower preparation costs and were proven very promising for use with the MRgFUS technology, without the toxicity issues related to the preparation and storage of PAA materials. Remarkably, agar turned out to be the prominent modifier of the T2 relaxation time even for phantoms containing other types of gelling agents instead of agar. This review could be useful in manufacturing realistic MRgFUS phantoms while simultaneously indicating an opportunity for further research in the field with a particular focus on the MR behavior of agar-based TMPs.

1. Introduction

Tissue Mimicking Phantoms (TMPs) serve as a valuable tool in the process of evaluating diagnostic and therapeutic modalities both in the preclinical setting and clinical routine [1]. Gel phantoms enable ergonomic and cost-effective biomedical research simultaneously contributing to the minimization of animal testing, as well as quality assurance (QA) practices in medicine [1,2]. In the last decade, the increasing utilization of Magnetic Resonance guided Focused Ultrasound (MRgFUS) [3] has resulted in an increased need for high quality TMPs suitable for use with this emerging technology, thus accelerating its clinical adaption. Remarkably, the methods and tools for QA of FUS are still to be standardized. Thereby, gel phantoms with tissue-like behavior could serve as a handy tool in the preclinical validation of emerging applications and quality control of clinical systems while concurrently contributing to establish reliable QA standards in the field of MRgFUS.

FUS induces thermal and mechanical effects in tissue that were proven to be essential in many therapeutic applications [4]. Extracorporeal US can be precisely delivered into a millimeter-sized area of malignant tissue in a totally non-invasive manner [4]. Temperature elevations of up to 90 °C can be produced at the focal point within a few seconds of sonication, causing instant coagulative death of cells [5]. Hence, FUS has emerged as an alternative option to surgical interventions for several oncological applications [6]. The technology has also proven remarkably effective in neurological applications [6].

Thermal ablation with FUS is typically performed under US or Magnetic Resonance Imaging (MRI) guidance [6]. MRI guidance is superior in terms of imaging resolution and soft tissue contrast, thereby offering more accurate delineation of tumour margins [7]. Besides its excellent imaging capabilities, monitoring of the temperature changes during FUS heating is feasible through MR thermometry [8].

The contrast in MR images arises from variability in the proton density (ρ) and longitudinal (T1) and transverse T2 (and T2*) magnetic relaxation times of tissues [8]. Accordingly, temperature monitoring in the MRI setting is based on these temperature-sensitive parameters [8], especially for lipid-rich tissues [9]. In this regard, Waspe et al. [10]

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assessed the feasibility of monitoring temperature changes during FUS by dynamic T2 mapping.

MR parameters have also been shown to greatly affect the contrast between normal soft tissue and FUS lesions. There is a limited number of preclinical animal studies reporting post-sonication relaxation times of FUS lesions [11–13]. *In vivo* experiments in rabbit tissues proved that the T1 and T2 values of thermal lesions depend greatly on the tissue type [11]. Similarly, lesions inflicted in *ex vivo* porcine tissue exhibited different MR appearance depending on the tissue type despite the use of similar acoustic parameters [12], thus confirming that the host tissue properties define the MR appearance of lesions. All inflicted lesions presented T2 values significantly higher than the surrounding untreated tissue and appeared hyperintense in T2-weighted images [12]. A further remarkable finding is that vacuolated and paste-like lesions were estimated to possess higher T2 values compared to thermal lesions [12]. A similar conclusion was reached by Kholmovski et al. [13], who performed radiofrequency ablation in 6 canines, with the acute results revealing higher T2* relaxation times within lesions in normal myocardium. In long-term examination, opposite results were obtained, with the lesions presenting a gradual decrease of the T2* value [13].

Regarding the longitudinal relaxation time T1, various studies [14–16] suggest a trend towards higher T1 values in FUS lesions compared to the surrounding normal tissues. In animal studies performed by Walker et al. [14], the ablated areas appeared hypointense in T1 images in the acute phase post-treatment. Notably, a clinical study that investigated the feasibility of transcranial MRgFUS to treat essential tremor reported T1 gradual shortening at the lesion site, typically beginning at 1-month post-treatment [16].

A tissue like thermal behavior is of paramount importance for phantoms intended for MRgFUS applications since the therapeutic result is evaluated via thermometry based feedback [17]. However, the previously reported data suggest that besides thermal properties, TMPs should also be able to replicate critical MR properties of biological tissues in order to be qualified for use with MRgFUS. So far, studies have predominantly examined the thermal and acoustical properties of FUS phantoms, whereas much less effort was devoted to the investigation of their MR properties [17,18]. At this point, it should be noted that phantom materials that are currently used for imaging purposes might also exhibit potential for use with ablation procedures. Thereby, state-of-the-art research in MR properties of gel phantoms intended for various applications, including those for medical applications and quality assessment purposes, was carried out. Herein, we briefly summarize the collected data, with special emphasis on the materials most widely used for phantom development and their MR relaxation properties.

2. Methodology

The PubMed database was mainly used since it includes a wide variety of sources in the specific field of biomedical sciences covering all time periods, with 7.1 million articles archived. A systematic search of the PubMed papers was carried out using specific vocabulary. The keywords {T1, MRI, US, phantom} were applied without any year range filter, thus not limiting the amount of data and resulted in a total of 608 results. Additional exclusion criteria were not applied, and all articles were considered to eliminate the possibility of missing articles of irrelevant titles which may actually include useful information. A scientific staff member with experience in therapeutic US and TMPs fabrication evaluated the results to ensure all criteria were applied properly and select the relevant articles for inclusion. A total of 39 articles were considered relevant. Supplementarily, another 5 articles were retrieved from Google Scholar searches of similar keywords.

The search results are organized in three sections. The first one briefly introduces the critical properties of phantoms intended for MRgFUS studies to facilitate the reader's understanding. Next, the included articles are classified into five main categories based on the phantom type (i.e., gelling agent used). Critical tissue mimicking properties and any interesting trend in MR properties of each category are listed. The rest of the paper briefly summarizes and discusses the search results and underlines opportunities for further research in the field that would possibly close gaps identified in existing studies. To the best of our knowledge, this is the first attempt to review the MR properties of TMPs.

3. Critical parameters of MRgFUS phantoms

Firstly, TMPs intended for FUS studies should possess similar acoustic behavior, with the speed of sound in the medium, characteristic acoustic impedance, and attenuation coefficient being the most significant properties to be emulated [17,19].

More importantly, the thermal characteristics of biological tissues need to be replicated by phantoms intended for thermal studies with FUS. The thermal profile of a TMP during FUS exposure is mostly governed by specific parameters, among which the most common are the specific heat capacity, thermal conductivity, and thermal diffusivity [17,19]. These parameters are particularly crucial in the process of assessing tissue necrosis during ablation under the guidance of MRI. In fact, since the therapeutic result is evaluated via thermometry based feedback, a tissue like thermal behavior is of paramount importance, whereas rigorous modeling of acoustic properties is not required in this regard.

Besides the thermal behavior of TMPs, MR parameters are also critical in determining their suitability for MRgFUS applications. As previously reported, both the contrast in MR images and temperature monitoring during high intensity FUS (HIFU) exposures are based on changes in the magnetic relaxation times T1 and T2 of tissues [8]. Most importantly, these parameters greatly affect the contrast between normal soft tissue and FUS lesions [11–13]. Accordingly, it is essential for MRgFUS phantoms to produce tissue-like MR signal in the process of evaluating therapeutic protocols.

4. Gel phantoms for evaluating diagnostic and therapeutic modalities

4.1. Agar gels

Agar probably constitutes the most widely used gelling agent for the construction of phantoms for multiple purposes, as confirmed by the current literature search. The widespread use of agar gels may be attributed to several factors, including their ease and low-cost fabrication, as well as their sufficient mechanical strength, which allows them to be formulated in different shapes and layered structures [20]. Another significant benefit of agar as a gelling agent relates to its high melting point of near 78 °C [21], which makes it ideal for thermal studies. Additional benefits of these gels will become apparent through the remainder of the paper.

The standard fabrication techniques of agar gels involve heating up degassed/deionized water in an appropriate buffer to about to 50 °C when the agar powder is slowly added, and then gradually heating the mixture to the melting point of agar, while it is continuously stirred to mitigate aggregation of agar in water [22,23]. The properties of agar gels can be easily and independently varied by adjusting the concentration of other ingredients added during the manufacturing process [20,22,24].

A wide variety of agar-based phantoms simulating thermal and acoustical properties of different types of soft tissue can be found in the literature [17,24–31]. Ultrasonic attenuation was found to vary with the addition of scattering particles such as silicon dioxide [24], magnesium [28], calcium [28], potassium [28], cellulose [29] and graphite [29] particles, as well as with the addition of glass beads [30]. Evaporated milk was proven a dominant absorber of acoustic energy [20]. Notably, glycerol has been proposed as a modifier of ultrasonic velocity [29].

Agar gels can also provide tissue-like signal (i.e., T1 and T2) in MRI [32], and thus, they were predominantly selected for validating new MRI protocols and imaging techniques [23,32–40]. MRI compatible phantoms simulating specific body parts such as brain [41], prostate [42], carotid [32], renal artery [43], and neonatal brain [44] exist in literature. Proper MRI imageability is also required for MRgFUS phantoms since accurate replication of MR relaxation properties is essential for producing tissue-like signal in MRI and more accurately testing and optimizing therapeutic protocols. In this regard, several agar-based TMPs were designed specifically for thermal ablation studies [22,25,27,45].

Literature data clearly indicates that the transverse relaxation time T2 predominantly depends on the agar concentration [23,33,34,46–49]. As described in more detail below, agar also served as the main T2 modifier in phantoms containing other types of gelling agents [46,48].

The addition of MR contrast agents enables better MR visibility while concurrently affecting the magnetic relaxation properties of phantoms [38, 39, 44, 50. Gadolinium-(Gd) based contrast agents were extensively used allowing adjustment of MR relaxation times, more significantly affecting the longitudinal value T1 [38,39,44]. T1 was also varied by incorporating different concentrations of paramagnetic ion salts such as Manganese(II) chloride ($MnCl_2$) [35], Nickel chloride ($NiCl_2$) [36], and Gadolinium(III) chloride ($GdCl_3$) [37]. Moreover, varying concentration of copper (Cu) ions enables changing the T1 values of agar gels [23]. It is important to note that addition of Cu ions requires the presence of another ingredient called Ethylenediaminetetraacetic acid tetrasodium hydrate (EDTA), which combines to Cu ions forming a stable free molecule; Cu-EDTA. Otherwise, Cu ions will be deposited on agar and loss their T1-modifying capacity [23]. In a representative study by D'Souza et al. [49], the concentration of agar (T2 modifier) and Cu-EDTA (T1 modifier) were properly selected, allowing the creation of phantoms simulating the magnetic relaxation properties of prostate and muscle tissue.

By using preservatives, such as thimerosal [49] and sodium azide (NaN_3) [31], bacterial invasion is prevented, thus extending the phantom lifetime. It is also noteworthy that several studies proposed the addition of animal hide gelatin in combination with agarose as a way to prevent the expulsion of an aqueous solution that may be produced in agar only gels [51].

Although agar-based phantoms were proven functional in a wide range of applications, they are accompanied by some limitations. Firstly, they have relatively low toughness and thus are easily fragile [1]. Also, they provide limited optical opacity, which prevents direct visualization of lesion formation in cases of thermal exposures [1]. Extensive results of prior research are summarized in Table 1. The referenced study, purpose of study, phantom recipe, and estimated relaxation times T1 and T2 are listed in this table.

4.2. Gelatin gels

Another category of phantoms that are easily fabricated and were proven factional is the gelatin-based phantoms [52–56]. Again, the gelation process involves solving gelatin powder in aqueous solutions while several soft tissues can be accurately mimicked by adding a proper concentration of other ingredients to the base recipe [52–56]. For instance, evaporated milk [52] and graphite powder [57] can be included to control the acoustic behavior of these gels, whereas the addition of ethanediol and polyethylene powder allows modification of electrical properties [58]. These phantoms can be manufactured in a low cost and easy way, with proper mechanical stiffness by incorporating cross-linkers during the phantom-making process [55].

Similar to agar phantoms, gelatin-based gels doped with an MRI contrast agent, most commonly a Gd-based agent, constitute a handy tool for MRI applications [56]. In cases where US compatibility is desired, acoustic modifiers should also be added in these phantoms. Farrer et al. [55] used porcine gelatin powders with three different bloom values (125, 175, and 250) for the construction of MRgFUS phantoms of different mechanical stiffness, in which evaporated milk was the main attenuation component. The estimated T1 and T2 values varied for the different bloom types of gelatin [55]. An interesting trend was also observed by Hofstetter et al. [52], who developed a gelatin-based MRI/US compatible phantom containing psyllium husk as the ultrasonic scattering agent. Interestingly, both relaxation times were found to be decreasing with increasing concentration of psyllium husk. Again, evaporated milk was included replacing a percentage of the water component to enhance ultrasonic absorption [52].

Another typical material found in gelatin phantoms is oil [53,54]. These phantoms are commonly referred to as oil-in-gelatin phantoms and are mainly involved in elastography studies, in which the elastic modulus depends on the volume percentage of oil [54]. Remarkably, the oil concentration was shown to have a noticeable effect on the MR relaxation properties of oil-in-gelatin dispersions [53,54]. In a study by Madsen et al. [54], the use of safflower oil was proven suitable particularly for US elastography [54]; however, the resultant relaxation properties of phantoms differed considerably from those of soft tissue [54]. Advantageously, Yuan et al. [53] selected pure vegetable oil to develop an oil-in gelatin human thigh phantom intended for radio-frequency heating because its thermal and MR properties are comparable to that of human fat. In this category of phantoms, thimerosal served as the preservative component [54].

Typically, gelatin phantoms possess a relatively low mechanical strength, as well as a low melting temperature making them impractical for thermal regimes exceeding 50 °C [59]. These limitations can be fairly addressed with the addition of a bonding agent such as formaldehyde [60] or glutaraldehyde [61]. These chemicals act as cross-linkers of gelatin [54], thus increasing the stiffness and temperature tolerance during thermal exposures in gelatin phantoms [62]. In fact, the typical melting point of gelatin of about 32 °C [63] can be increased to more than 60 °C when using a cross-linking agent [62,63]. Though this technique has essential benefits, it may cause unfavorable changes in other critical parameters [55].

Phantoms composed of mixtures of agar and gelatin have emerged as alternative candidates for elastography [63] and MRI [51,62] applications. Employment of agar results in stiffer phantoms (i.e., higher Young's modulus) with increased geometrical stability while at the same time enabling the embedment of inclusions to gelatin gels [63]. To be more specific, a different dry-weight gelatin concentration between background and inclusions could result in over-time size changes of inclusions due to osmotic effects [63]. This phenomenon does not occur in the case of agar, and thus, a phantom of proper stability can be produced by incorporating different agar concentrations between background and inclusions [63]. It is also noteworthy that several studies proposed the addition of animal hide gelatin in combination with agarose as a way to prevent the expulsion of aqueous solution which may be produced in agar only gels [51].

Cu ions have the capacity to lower T1 values of agar/gelatin phantoms [51,63]. They are usually added in the form of ionic salts such as Cupric chloride ($CuCl_2$). As previously described for the agar gels, addition of EDTA is required for preventing the arrestment of ions to gelatin molecules [51,63]. A representative example is a study by Madsen et al. [63], who developed an agar/gelatin elastography phantom consisting of agar as the stiffness agent, Cu-EDTA as the T1 modifier, formaldehyde as the cross-linking agent, and glass beads as the attenuation and backscatter component. Sodium chloride (NaCl) was also included to offer tissue-like NMR coil loading. Alternatively, Blechinger et al. [62] selected glycerol instead of paramagnetic ions to attain the desired T1 in an animal hide gel/agar phantom. Variations in glycerol concentration significantly varied T1 values, whereas T2 was minimally affected. In fact, T2 was strongly affected by the animal hide gel concentration [62], confirming that the relaxation times can be varied independently. In line with the previously reported data, the resultant phantom showed durable stability, without any fluid

Table 1
T1 and T2 relaxation times of agar-based phantoms, along with the MR technique used for relaxometry mapping and the temperature at which measurements were conducted (if provided by the relevant study). IR = Inversion Recovery; ME = Multi-Echo; SE = Spin-Echo; FSE = Fast SE; T2-w = T2-weighted; T1-w = T1-weighted; TSE = Turbo SE; CPMG = Carr-Purcell-Meiboom-Gill; TIRSE = Turbo Inversion Recovery SE; SR = Saturation Recovery; DESPOT = Driven Equilibrium Single Pulse Observation of T1/T2; UTE-MRF = Ultrashort Echo time MR fingerprinting.

Agar-based phantoms				
Recipe	**T1 rel. time (ms)**	**T2 rel. time (ms)**	**Purpose**	**Ref.**
3% agarose in water 3 % fibrous cellulose 7% glycerol 0.05 % methylene blue	1679 ± 15 3 T MR scanner *IR* seq. TI: 50–5000 ms	41 ± 1 3 T MR scanner *ME SE* seq. -	Tumour mimic for MRgFUS studies	[45]
0.5 % agar in water 5–30 μl gadopentetate acid meglumine	735–1667 3 T MR scanner *IR SE* seq. TI: 100–2100 ms	236–311 3 T MR scanner *ME SE* seq. TE: 8–56 ms	Phantom for testing fast T1 mapping method	[38]
2 % w/v agar 4 % w/v wood powder	844 1.5 T MR scanner *T1-w IR FSE* seq. TI: 200–1600 ms	66 1.5 T MR scanner *T2-w FSE* seq. TE: 23–101 ms	TMP for MRgFUS applications	[22]
0.6 % agar solution 0–0.15 mM $MnCl_2$	700–1800 3 T MR scanner *2D IR TSE* seq. TI: 30–2000 ms	–	Brain MRI phantom	[41]
4% agarose gel	1207 ± 168 1.5 T MR scanner *IR* seq.	66 ± 9 1.5 T MR scanner *ME* seq.	CT/MRI prostate phantom	[42]
2 % w/v agar 25% v/v evaporated milk 1.2% w/v silica	852 1.5 T MR scanner *IR SE* seq. TIs: 66–750 ms	66 1.5 T MR scanner *T2-w FSE* seq. ETs: 18–99 ms	Brain TMP for US surgery	[25]
1 L of distilled water 35 g high gel strength agar 80 mL glycerol. 30 g cellulose particles (size: 50 μm) 20 mL of formaldehyde (2 wt%)	1090 ± 140 (0.5 T) 1150 ± 162 (1.5 T)	42 ± 3 (0.5 T) 50 ± 6 (1.5 T)	Carotid Phantom for MRI applications	[32]
82.97 wt% distilled water 3.0 wt% agar 11.21 wt% glycerol 0.53 wt% silicon carbide (400 grain) 0.88 wt% aluminum oxide (0.3 μm) 0.94 wt% aluminum oxide (3 μm) 0.46 wt% benzalkoniumchloride	1504 ± 10 3 T MR scanner *IR* seq. -	40.0 ± 0.4 3 T MR scanner *CPMG* SE seq. TEs: 10–80 ms	Multimodality renal artery phantom	[43]
0.3 % w/v agarose + 0.03 mM Gd-DTPA 0.6 % w/v agarose + 0.10 mM Gd-DTPA	1654 ± 9 1134 ± 7 1.5 T MR scanner 2D *TIRSE* seq. TIs: 25–3970 ms 19 °C	376 ± 4 200 ± 7 1.5 T MR scanner 2D *CPMG ME SE* seq. TEs: 20 –640 ms 19 °C	TMP simulating T1 and T2 of neonatal brain	[44]
0.3–4 wt% agarose 0.5–8 mM Ni^{2+}	180–1400 10.7 MHz (0.25 T) MR analyzer *SR* seq.	34–200 10.7 MHz (0.25 T) MR analyzer *SE* seq.	TMP for MR imaging	[34]
agarose gel 0.0–2.0 mM gadolinium 0, 10, 20, 100% peanut oil (content ratio)	$50 < T_1 < 350$ 3 T MR scanner *DESPOT* seq	–	Method for fast MR mapping	[39]
agarose & varying concentration of $MnCl_2$	397 (±12)–759 (±19) 3 T MR scanner *UTE-MRF* seq.	37 (±3)–85 (±7) 3 T MR scanner *UTE-MRF* seq.	Evaluation of methods for MR parameter mapping	[35–37]
agarose & varying concentration of $NICl_2$	200 < T1 < 1500 1.5 T MR scanner *IR SE* seq. TI: 50–3000 ms	41–80 (1.5 T) 1.5 T MR scanner *ME SE* seq.		
agarose & varying concentration of GdCl3	200–1600 (1.5/3 T) *2D IR single echo SE seq.* TI: 50–3800 ms or *Look-Locker* seq.	-		
2 % w/v agar 2 % w/v silicon dioxide 40 % v/v evaporated milk	776 1.5 T MR scanner *IR SE* seq. TIs: 50 –800 ms	66 1.5 T MR scanner *T2-w FSE* seq. TEs: 10.8–150.8 ms	MRI bone phantom for thermal exposures	[27]
0.5–4.0 % w/v agarose	1000 (±92) – 1481 (±151) 5 MHz NMR spectrometer	23 (±9) – 240 (±15) 5 MHz NMR spectrometer	TMP for NMR imaging	[23]

(*continued on next page*)

Table 1 (*continued*)

Agar-based phantoms				
Recipe	**T1 rel. time (ms)**	**T2 rel. time (ms)**	**Purpose**	**Ref.**
	1390 (±84) – 2743 (±71) 60 MHz NMR spectrometer *IR* seq.	27 (±3) – 278 (±43) 60 MHz NMR spectrometer *CPMG SE* seq.		
1.3% w/v agar 0–26.7 % w/v granulated sugar	921 (±16) – 2239 (±55) 3 T MR scanner *IR* seq.	68 ± 2–73 ± 3 3 T MR scanner *ME* seq.	Evaluation of methods for breast diffusion-weighted MRI	[40]
0.24–2.38 % Agarose 0.18–5.55 mM $NiCl_2$	256–1870 1.4 T Minispec relaxometer 22 °C 250–1872 3 T MR scanner *IR* seq. 21 ± 2 °C	50–288 1.4 T Minispec relaxometer 22 °C 42–231 3 T MR scanner *SE* seq. 21 ± 2 °C	Phantom for global T1 mapping quality assurance	[33]
Prostate 50 % v/v agarose solution (2% dry w/v) 50 % v/v condensed milk 7.9 % v/v n-propyl alcohol (per agarose) 0.06 w/v % CuCl2 salt (per total volume) 0.103 w/v % Ethylenediamine tetra acetic acid (EDTA) (per total volume) 1 g/l of 45–53 μm diameter glass beads thimerosal	937 ± 13 40 MHz Minispec relaxometer *IR* seq. 21 °C	88 ± 3.8 40 MHz Minispec relaxometer *CPMG SE* seq. 21 °C	TMP multi-imaging modality	[49]
Muscle 50 % v/v agarose solution (6% dry w/v) 50 % v/v condensed milk 7.9 % v/v n-propyl alcohol (per agarose) 0.048 % w/v CuCl2 salt (per total volume) 0.082 % w/v EDTA (per total volume) 5 % w/v microscopic glass beads thimerosal	686 ± 9 40 MHz Minispec relaxometer *IR* sequence 21 °C	36.7 ± 1.9 40 MHz Minispec relaxometer *CPMG SE* seq. 21 °C		

extrusions, most probably due to the addition of formaldehyde and n-propanol offering antibacterial activity, also given the agar-enhanced rigidity. The proposed gelatin-based phantoms and their T1 and T2 relaxation times are summarized in Table 2.

4.3. Polyacrylamide (PAA) gels

Another candidate material for fabrication of stable TMPs is PAA [50,64–69]. PAA is probably the most popular material for fabricating heat-responsive phantoms, primarily due to its high melting point [64]. It is also of paramount importance that these phantoms offer optical transparency [65], enabling visual confirmation of coagulation in the phantoms. Common catalysts added for activating PPA polymerization are the ammonium persulfate (APS) and tetramethylethylenediamine (TEMED) [50,68–70].

Thermoresponsive proteins such as Bovine serum albumin (BSA) were found to enhance acoustic absorption in PAA phantoms [66]. When these proteins are heated at lethal temperatures undergo irreversible changes in MR values and become opaque, thus enabling discrimination of the heated area both visually and via changes in MRI signal intensity [66,67]. Specifically, white-opaque lesions are formed when BSA is coagulated at temperatures between 60 °C and 70 °C. Additional ingredients such as evaporated milk, corn syrup [71], glass beads [72], and silica particles [68] can be used to adjust the acoustical properties of PAA-BSA phantoms in the range of human tissues.

Bazrafshan et al. [70] developed an MR visible liver mimicking phantom intended specifically for Laser interstitial thermal therapy (LITT) applications. The PAA gel was doped with BSA protein for visualization of thermal effects. Poly-vinyl alcohol (PVA) microspheres were also incorporated to enhance photon scattering. The addition of two different MR contrast agents; Magnevist and Lumirem, allowed modification of the T1 and T2 relaxation times, respectively [70]. NaN_3 was used to prevent microbial growth [70]. Notably, a PAA-based phantom for LITT applications may also contain bovine hemoglobin as a photon absorber [50].

TMPs containing thermochromic ink that exhibits progressive color change upon heating can also be used for visual monitoring of thermal ablation [68]. Eranki et al. [68] developed a PAA-based thermochromic TMP intended for HIFU applications. Both BSA protein and a thermochromic ink that under heating changes color from white to magenta were added. Proper concentration of these inclusions allowed visualization of well-defined regions of permanent color change upon heating, which correlated well with MRI thermometry data and regions of hypointensity on T2-weighted images [68]. Similar to agar-based phantoms, silicon dioxide served as the attenuation component [68]. In this category of phantoms, NaCl is usually included to adjust electrical conductivity [68,70]; however, the relaxation values of PAA gels were found independent of the NaCl concentration [73].

Egg-white is another heat-responsive material that was proposed for irradiation studies with FUS as a less expensive alternative to BSA [69]. Careful selection of egg white concentration is critical to maintaining adequate optical clarity in phantoms. A suitable egg white (my mass) concentration of 10 to 40% was proposed by Takegami et al. [69] for sufficient visualization during HIFU exposures. Although the acoustic properties of the proposed phantom were found to be similar to those of soft tissues, MR relaxation properties were not investigated.

Toxic materials are typically employed complicating the preparation of PAA gels and generating safety concerns [74]. Specifically, the procedure involves polymerization of acrylamide, a toxic monomer, which requires proper care and may be hazardous when PAA-gels are not stored under proper environmental conditions [74]. Another limitation relates to the use of BSA or egg white, which undergo permanent changes when coagulated, thus making the phantoms unsuitable for repeated use. The relevant studies are listed in Table 3.

4.4. Carrageenan gels

Carrageenan constitutes a common additive that can be used as a bonding material for phantom fabrication [48]. Although, as a polysaccharide, it generally presents similar characteristics with agar,

Table 2
T1 and T2 relaxation times of gelatin-based phantoms, along with the technique used for relaxometry mapping and the temperature at which measurements were conducted (if provided by the relevant study). T2-w = T2-weighted; T1-w = T1-weighted; SPGR = Spoiled gradient recalled echo; IR = Inversion Recovery; CPMG = Carr-Purcell-Meiboom-Gill; STIR = Short T1 Inversion Recovery; ME = Multi-Echo; GRE = Gradient Recalled Echo; TSE = Turbo Spin Echo; MPME = Multi-Pathway Multi-Echo.

Gelatin-based phantoms				
Recipe	**T1 rel. time (ms)**	**T2 rel. time (ms)**	**Purpose**	**Ref.**
Tumour 225 bloom gelatin in saline water 5 % oil-in-gelatin dispersion	1034.7	T2* 113.1	TMP for RF heating and MRI thermal monitoring	[53]
Muscle 225 bloom gelatin in saline water 10 % oil-in-gelatin dispersion	1084.9 1.5 T MR scanner T1-w *SPGR* seq. TR: 50–3000	64.5 1.5 T MR scanner T2*-w *SPGR* seq. TE: 7.5–160.7		
13.3 wt% gelatin 1 g/L thimerosal 0.35 g/L formaldehyde 50 % safflower oil 4 g/L glass beads	560 **or** 1610	230 **or** 416	Tissue-Mimicking Heterogeneous Elastography Phantoms	[54]
or 20 g/L glass beads	40 MHz Bruker relaxometer *IR* seq. 22 °C	40 MHz Bruker relaxometer *CPMG* seq. 22 °C		
11.1 % w/v porcine gelatin powders (125/ 175/ 250 bloom) 50 % v/v water–50 % v/v evaporated milk vyse defoamer solution	970 ± 3 (125 bloom) 853 ± 3 (175 bloom) 1093 ± 5 (250 bloom) 3 T MR scanner *STIR* seq. TI: 50–2500 ms	T2* 58 ± 7 (125 bloom) 55 ± 7 (175 bloom) 67 ± 12 (250 bloom) 3 T MR scanner *ME GRE* seq. TE: 2.83–80 ms	TMPs for use with MRgFUS	[55]
50 vol% water–50 vol% evaporated milk 111 g/L 250-bloom gelatin powder 3.33 g/L DOWACIL 75 0.5–16 g/L psyllium Husk	974–1038 3 T MR scanner 2D *IR TSE* seq. TI: 50–2500 ms 21 °C	T2: 97–108 3 T MR scanner 2D *TSE* seq. TE: 13.1–262 ms 21 °C T2*: 49–89 3D *GRE* seq. TE: 3.96–62.92 ms 21 °C	Phantom for US and MRI imaging	[52]
0.17 vol% defoamergelatin & varying concentration of gadolinium	150 < *T*1 < 5003 T MR scanner *MPME* seq.	100 < *T*2 < 2203 T MR scanner *MPME* seq.	New method to quantitatively map MR parameters	[56]
Gelatin/ Agar phantoms				
1.11–3.64 wt% agar 3.60–5.70 wt% 200 bloom gelatin 0.113–0.116 wt% $CuCl_2$-$2H_20$ 0.33–0.34 wt% EDTA tetra-Na hydrate 0.77–0.80 wt% NaCl 0.24–0.33 wt% formaldehyde	369–498	28–63	Heterogeneous elastography phantoms	[63]
1.45–1.50 wt% German plus 0–5.6 wt% glass bead	60 MHz Bruker relaxometer *IR* seq. 22 °C	60 MHz Bruker relaxometer *CPMG* seq. 22 °C		
Thalamus 2.3 wt% agar 7.5 wt% gelatin 0.028 wt% CuCl2 0.13 wt% EDTA-tetra Na 0.1 wt% NaCl 0.24 wt% HCHO 0.1 wt% thimerosal	T1 of water in phantom: 1065 ± 30	T2 of water in phantom: 98.06 ± 0.20	Anthropomorphic MRS head phantom	[51]
Tumour 2 wt% agar 7.5 wt% gelatin 0.0223 wt% CuCl2 0.101 wt% EDTA-tetra Na 0.1 wt% NaCl 0.24 wt% formaldehyde 0.1 wt% thimerosal	1215 ± 1 1.9 T Bruker spectrometer *IR* seq. 22 °C	149.6 ± 0.2 1.9 T Bruker spectrometer *CPMG* sequence 22 °C		
0–50 vol% (of liquid components) glycerol 40 vol% animal hide gel–60 vol% agar	200 < *T*1 < 1100	50 < *T*2 < 80	TMPs for MRI phantoms	[62]
8.3 vol% n-propyl alcohol 0.0065 mass ratio of p-methylbenzoic acid /animal hide gel 0.017 mass ratio of formaldehyde	10 MHz spectrometer *IR* seq. 22 °C	10 MHz spectrometer *CPMG SE* seq. 22 °C		

Table 3
T1 and T2 relaxation times of PAA-based phantoms, along with the technique used for relaxometry mapping and the temperature at which measurements were conducted (if provided by the relevant study). ME = Multi-Echo; TSE = Turbo Spin Echo; IRTF = Inversion Recovery Turbo Flash; MCSE = Multi-Contrast Spin Echo.

PAA-based phantoms				
Recipe	**T1 rel. time (ms)**	**T2 rel. time (ms)**	**Purpose**	**Ref.**
70.0 % v/v deionized water 7.0 % v/v 40% acrylamide/bis-acrylamide 5.0 % v/v Magenta (thermochromic ink) 3.0 % w/v BSA 1.1% w/v Silicon dioxide 0.9 % w/v NaCl 0.15 % w/v APS 0.15 % v/v TEMED	–	225 ± 14 1.5 T MR scanner 152 ± 8 3 T MR scanner *2D ME TSE* seq. TE: 50–450 ms	TMP for HIFU applications	[68]
37.9 vol% distilled water 30 vol% Rotiphorese® acrylamide 16 wt% BSA 10 vol% PVA microsphere 0.04 vol% Magnevist®	275 < *T*1 < 500for 25–75°C	46 < *T*2 < 52for 25–75 °C	Liver-mimicking MRI phantom	[70]
3.3 vol% Lumirem® 0.08 vol% TEMED 1.75 vol% APS 0.9 wt% NaCl 0.03 wt% NaN3	1.5 T MR scanner *IRTF* seq. TI: 100–2500 ms	1.5 T MR scanner *MCSE* seq. TE: 10.6–339.2 ms		
60 vol% distilled water 30 vol% Rotiphorese® acrylamide 5 vol% PVA microsphere 3.92 ± 0.42 vol% bovine hemoglobin	246.6–597.2 for 25–75 °C	40.8–67.1 for 25–75 °C	A liver mimicking MRI phantom for thermal therapy studies	[50]
0.098 ± 0.023 vol% Magnevist® 2.980 ± 0.067 vol% Lumirem® 0.084 vol% TEMED 1.5 vol% APS 0.9 wt% NaCl 0.03 wt% NaN3	1.5 T MR scanner *IRTF* seq. TI: 120–1000 ms	1.5 T MR scanner *MCSE* seq. TE: 10.6–339.2 ms		

carrageenan gels were proven less fragile than agar-based gels [48]. They are elastic and can be easily shaped to form strong phantoms of any configuration without the addition of other reinforcing materials [48]. It should though be noted that carrageenan phantoms are not suitable for HIFU exposures since they can only withstand temperatures of up to about 60 °C before liquefaction [48].

The addition of carrageenan in agar gels seems to solve the problem of low toughness in agar-only gels [2,46–48]. Yoshida et al. [48] developed an MRI phantom using carrageenan as a solidifier and agarose as the T2-modifying component. T1 values were adjusted by addition of proper $GdCl_3$ concentration. Furthermore, inclusion of NaCl affected both T1 and T2 values, with T1 being affected in a slightly larger degree [48]. Accordingly, in a study by Yoshimura et al. [46], both relaxation times T1 and T2 were found to be increasing, respectively, upon increasing concentration of $GdCl_3$ and agarose at a fixed concentration of carrageenan. Again, carrageenan served as the solidifying agent allowing the creation of a robust phantom, while agarose served as the T2 modifier [46]. Neumann et al. [47] have proposed a carrageenan phantom mimicking thorax tissue, in which T1 was adjusted by adding proper amount of gadoterate meglumine. Again, NaN_3 may be added in this phantom type acting as an antiseptic [47,48]. The proposed carrageenan phantoms are summarized in Table 4.

4.5. Other gelling agents

Other former candidates that were identified include PVA [75–77], Polyvinyl Chloride (PVC) [78–80], silicone [81,82] and TX-150/151 [83,84]. These materials served as gelling agents in phantoms intended for imaging applications. Detailed results can be found in Table 5.

PVA is a water-soluble rubbery synthetic polymer with which cryogels can be formed through a repeated freeze-thaw method [75–77]. PVA cryogels doped with Gd-based contrast agents were proposed for MR imaging studies [75]. It should be noted that different types of contrast agents can be used to offer compatibility with multiple imaging modalities. For instance, a PVA-based brain phantom containing Barium sulfate ($BaSO_4$) as CT contrast agent, Copper sulfate ($CuSO_4$) as MR contrast agent, and talcum as US contrast agent was recommended by Chen et al. [76] for multimodal imaging. In such cases, the MR contrast agent acts as the main relaxation time modifier. A notable trend observed by Surry et al. [77] is that increasing number of freeze–thaw cycles during phantom preparation results in lower T1 relaxation times.

Another common synthetic chemical polymer is PVC. Soft PVC phantoms are relatively low-cost, with long-term easy storage [79]. The fabrication process involves heating up a mixture of PVC powder and softener until polymerization under constant stirring [78–80]. PVC gels mimicking soft tissue are useful in MR and US elasticity imaging [79]. Chatelin et al. [79] found that their MR relaxation properties are slightly influenced by the variation of the mass ratio PVC /plasticizer. In this study, cellulose served as a source of echogenicity without consistent influence on relaxation values [79]. Another study [80] confirmed that the MR properties of PVC gels can be regulated to mimic different soft tissues by adjusting the ratio of the softener to polymer [80]. Remarkably, inclusion of glass beads moderately lowered T2. Mineral oil was also incorporated to facilitate needle insertion applications but did not produce any apparent effect on T1 or T2 [80].

More recently, a polysaccharide material called TX-150 has been introduced as a candidate gelling agent for the construction of water-based TMPs for MRI applications [83,84]. Groch et al. [84] prepared a lesion phantom for MRI, in which increasing weight % concentration of TX-150 in degassed water shortened both relaxation times. This study suggests that T1 and T2 can be altered independently by incorporating metal phthalocyanines and 2-2-diphenyl-1 picrylhydrazyl, respectively [84]. A modified form of this polysaccharide; TX-151 was used in the development of an MRI compatible breast phantom by Mazzara et al. [83]. The amount of gelling agent had a weak influence on relaxation times. Aluminum powder served as the dielectric component having insignificant effect on T1 values. On the other hand, T2 was significantly shortened upon addition of aluminum and largely affected by varying

Table 4
T1 and T2 relaxation times of carrageenan-based phantoms, along with the technique used for relaxometry mapping and the temperature at which measurements were conducted (if provided by the relevant study). SR = Saturation Recovery; SE = Spin-Echo; T2-w = T2-weighted; T1-w = T1-weighted; IR = Inversion Recovery; TSE = Turbo Spin Echo.

Recipe	T1 rel. time (ms)	T2 rel. time (ms)	Purpose	Ref.
Carrageenan phantom				
5 wt% carrageenan 0.2 mM $MnCL_2$ 0.19 wt% NaCl 0.1 wt% NaN_3	429 (1.5 T)	84.9 (1.5 T)	MRI phantom	[88]
Carrageenan/ Agarose phantoms				
3 % carrageenan in distilled water	$100 < T1 < 2100$	$20 < T2 < 420$	Phantom compatible for MRI and hyperthermia	[48]
0–1.6 % agarose 0–140 μmol/ kg $GdCl_3$ 0–0.7 % NaCl 0.03 % NaN3	1.5 T MR scanner *SR* seq. TR: 140–16 474 ms 25 ± 1 °C	1.5 T MR scanner *SE* seq. TE: 15–300 ms 25 ± 1 °C		
3 wt% carrageenan in distilled water 0–1.6 wt% agarose 0–140 μmol/ kg $GdCl_3$ 0.03 wt% NaN_3	202–1904 1.5 T MR scanner *SR* seq. TR: 140–16 474 ms 25 ± 1 °C	38–423 1.5 T MR scanner *SE* seq. TE: 15–300 ms 25 ± 1 °C	Tissue mimicking MRI phantom	[46]
3 % carrageenan in distilled water	790 ± 28	65 ± 1	MR/ CT liver phantom	[47]
1.3 % agarose 2.37 ppm gadoterate meglumine 20 mM Na^+	3 T MR scanner *T1-w IR TSE* seq. TI: 250–5000 ms	3 T MR scanner *T2-w TSE* seq. TE: 15–240 ms		

aluminum (Al) concentration [83]. The relaxation time T1 was found to be decreasing with increasing Gd-DTPA concentration. Authors concluded that variation of these additives allows the creation of phantoms with a wide range of tissue-comparable MR relaxation times [83].

5. Discussion

Due to the increasing popularity of the MRgFUS technology, there is a critical need for TMPs that can replicate all the critical characteristics of human tissues, including acoustical, thermal, and MR properties. So far, TMPs have been widely characterized in terms of thermal and acoustical properties; however, more limited data is available about their MR properties. Thereby, this study aimed to review the MR relaxation properties of different phantom types through a systematic search of the literature. Although various physical properties of the referenced phantoms were discussed through the article, particular focus was placed on their T1 and T2 relaxation values.

In this article, the several phantoms previously proposed for a wide range of applications were briefly reviewed by category of gelling agent. However, the included studies could also be classified according to the intended application of the proposed phantom. Some studies were designed to investigate the physical parameters of phantoms intended

Table 5
T1 and T2 relaxation times of other tissue-mimicking materials, along with the technique used for relaxometry mapping and the temperature at which measurements were conducted (if provided by the relevant study). ME = Multi-Echo; FSE = Fast Spin Echo; IR = Inversion Recovery; T1-w = T1-weighted; T2-w = T2-weighted, GE = Gradient Echo; TSE = Turbo SE.

Recipe	T1 rel. time (ms)	T2 rel. time (ms)	Purpose	Ref.
PVA phantoms				
10 % PVA cryogel, 90 % water	1317 ± 23 106 ± 16	T2: 98 ± 8 T2*: 191 ± 36 T2: 122 ± 30 T2* 4.5 ± 0.56	MRI phantom	[75]
10 % PVA cryogel 50 μl/ml gadolinium solution	3 T MR scanner *3D fast-field ME* seq. TI: 20–2000 ms	3 T MR scanner T2*: *3D fast-field ME* seq. T2: *TSE* seq.		
10 wt% PVA in water solution 1–4 freeze–thaw cycles	718–1034 1.5 T MR scanner *2D FSE-IR* seq. TI: 50–3200 ms	108–175 1.5 T MR scanner *2D FSE* seq. TE: 15–195 ms	TMP for MR and US imaging	[77]
6 % PVA 1 freeze–thaw cycle 2 % BaSO4 0.025 % CuSO4	1004 –1213	163–182	Brain phantom for multimodal imaging	[76]
1 % talcum **or** 4 % PVA with 3 FTCs	1900–2600 3 T MR scanner *T1-w SE* seq.	1100–1665 3 T MR scanner *T2-w GE* seq.		
PVC phantoms				
12.3×10^{-2} g/mL PVC powder/ softener	206.81 ± 17.50 (3 T)	20.22 ± 5.74 (3 T)	Multi-purpose breast TMP	[78]
mass ratio PVC /plasticizer: 40–70%. 0.6, 0.8, and 1% concentrated cellulose	258–223 1.5 T MR scanner *TSE* seq. TI: 23–2,970 ms	50–44 1.5 T MR scanner *SE* seq. TE: 3.5–200 ms	TMP for MR and US elastography	[79]
0–1 ratio of softener to PVC polymer, 0/5 % mass fraction of mineral oil 0/1 % mass fraction of Glass beads	426.3–450.2 7 T RF volume coil *SE* seq. TI: 50–2500 ms	21.5–28.4 7 T RF volume coil *SE* seq. TE: 11–80 ms	TMP for multimodal imaging	[80]
Silicone phantoms				
–	410–765 (1.4 T)	50–165 (1.4 T)	Multimodality imaging Phantom	[81]
–	1002 ± 8 3 T MR scanner *Look-Locker IR* seq. TI: 30–4000 ms	58 ± 1 3 T MR scanner *ME SE* seq. TE: 40–400 ms	MR compatible cardiac left ventricle model	[82]
TX-150/ TX-151 phantoms				
7.00 wt% TX-151 polysaccharide material 83.50 wt% water 0.303 wt% NaCl 9.20 wt% Al powder 0.0–0.8 mM Gd-DTPA	174 (±10) – 1405 (±59) 1 T MR scanner 447 (±15) – 2949 (±213) 1.5 T MR scanner	30.4 (±0.2) – 36.3 (±0.1) 1 T MR scanner 19.6 (±0.1) – 24.8 (±0.6) 1.5 T MR scanner	Tissue mimicking MRI phantom	[83]

(*continued on next page*)

Table 5 (*continued*)

Recipe	T1 rel. time (ms)	T2 rel. time (ms)	Purpose	Ref.
0.08 mM GdDTPA 41.75 g water 0.1515 g NaCl g TX-151	746 ± 13–803 ± 28 (1 T) 1523 ± 147–1567 ± 77	25.4 ± 0.1–162.4 ± 10.2 (1 T) 18.8 ± 0.0–72.8 ± 3.2		
0–14.2 wt% Al	(1.5 T) *SE* seq. TR: 50–3000 ms 18 °C	(1.5 T) *SE* seq. TE: 20–160 ms 18 °C		
3–18 wt% TX-150 in degassed water	586 ± 30–2211 ± 37 20.9 MHz (0.5 T) NMR pulsed spectrometer *IR* seq. 20 °C	57–287 0.5 T MR scanner *SE* seq. 20 °C	Lesion phantom for MRI	[84]

specifically for thermal therapy studies, whereas the vast majority of included articles have proposed TMPs for imaging or QA purposes.

As confirmed by the search results, agar is probably the most common gelling agent for widespread applications. In fact, the majority of identified studies reporting MR properties of phantoms (~43%) involve the use of agar-based gels [22,23,25,32–45,49]. Agar has been quite extensively used as a gelling agent in FUS phantoms simulating different soft tissues, with additional materials added to adjust their thermal and acoustical properties [17,25–27]. In this regard, critical properties that have been sufficiently investigated include the speed of sound, acoustic attenuation, acoustic impedance, thermal diffusivity, specific heat capacity, and thermal conductivity [17,22,25]. In addition, their tissue-like MR signal makes them the material of choice for validating new MRI protocols and imaging techniques [23,32–40]. In such cases, modifiers of acoustic properties such as glycerol [32,43], cellulose particles [32], milk [49], and glass beads [49], are also added and adjusted to provide tissue-like US visibility.

Regarding thermal studies, PAA [50,68], agar [17,25–27], and gelatin [53,55] constitute the preferable gelling agents, each one having its own benefits and limitations. The ability of all three to accurately simulate physical properties of various biological tissues upon addition of proper concentration of inclusions has been demonstrated [1,2]. Both agar and PAA materials are characterized by temperature tolerance sufficiently high to maintain their physical and mechanical properties during HIFU exposures [21,64]. On the other hand, gelatin phantoms lack the capacity to withstand ablation temperatures. Their low melting temperature makes them unsuitable for thermal studies in which temperatures exceed 50 °C, and thus, are only recommended for hyperthermia applications [59].

Upon proper use and storage, gelatin gels can maintain long-term stability; however, they generally possess relatively low mechanical strength, which is strongly dependent on temperature variations [52]. Although their insufficient mechanical stability and temperature tolerance can be improved with the addition of a bonding agent such as formaldehyde [60] and glutaraldehyde [61], this may negatively affect their physical properties. Likewise, agar has been employed in gelatin phantoms to provide geometrical stability and allow the creation of inclusions without undesirable osmotic phenomena [63]. Thereby, the synergy of agar and gelatin seems to provide essential benefits related to long term stability and increased shelf life [63].

Except from being tissue equivalent and temperature resistant, phantoms intended for thermal ablation studies should ideally offer visualization of the coagulative regions, thus facilitating evaluation of therapeutic protocols. Visual capacity is also of great importance for visual assessment of the motion accuracy in robotic applications [85,86]. Therefore, the optical transparency of PAA gels makes them favorable over agar gels [65]. However, synthesis of PAA gels is generally considered more complicated since it requires special care due to the use neurotoxic ingredients [74].

On the other hand, agar phantoms are easily prepared and stored, cost-effective, harmless, and with durable stability [2,22,23]. At this point, it should be noted that carrageenan can be used as a mechanical stabilizer in agar gels, enabling even more robust anatomical models [46,48]. It should though be pointed out that carrageenan cannot withstand ablation temperatures, and thus, it is unsuitable for HIFU therapies [48].

Other mimicking materials identified in the literature are the PVA [75–77], PVC [78–80], silicone [81,82], and TX-150/TX-151 gels [83,84]. Although various studies report some very promising results, the physical properties of these materials have not been sufficiently investigated, and their efficacy in thermal studies is yet to be established. This would of course require further evaluation of those characteristics critical for thermal applications, and particularly MRgFUS. In addition, proper gelation and solidification of such materials typically require multiple steps [75–77] leading to more complicated fabrication processes and sometimes to increased costs. Regarding TX-150, its gelation parameters are not well defined, thus causing difficulties in the fabrication process [83]. Moreover, TX-150 gels normally undergo bacterial degradation in just a few days. It is though notable that the addition of metal phthalocyanines was shown to create more stable and durable phantoms [84].

Potential modifiers of MR relaxation times become apparent through the collected data. T2 relaxation time was predominantly tailored by varying the gelling agent concentration. In fact, agarose served as the predominant T2 modifier in all the proposed agar-based phantoms [23,33,34,46–48], as well in phantoms containing other types of gelling agents [46–48]. Varying animal hide gel concentration also provides T2-modifying capacity [62], whereas both T1 and T2 of gelatin phantoms were found to vary for different types of gelatin [55]. This does not imply in the case of TX-151 gels, for which the amount of gelling agent seems to cause insignificant influence on relaxation times [83]. Regarding synthetic polymers, the MR properties of PVC gels can be adjusted to mimic different soft tissues by adjusting the ratio of the softener to polymer [80], whereas for PVA phantoms, smaller T1 values were observed with increasing number of freeze–thaw cycles [77].

Ingredients added as modifiers of acoustical properties also have a significant effect on the MR behavior of TMPs. Firstly, inclusion of glass beads was proven to slightly lower T2 of PVC phantoms [80]. A similar trend was reported in a study by Huber et al. [87], wherein the inclusion of glass beads lowered both T1 and T2 relaxation times of an agar/gelatin-based phantom. Another interesting trend observed is the decrease of T2 with increasing concentration of psyllium husk in gelatin-based phantoms [52]. Regarding the longitudinal relaxation time T1, it can be varied by incorporating different concentrations of paramagnetic ion salts, such as $MnCl_2$ [35], $NiCl_2$ [36], and $GdCl_3$ [37], or copper ions [23]. Finally, both T1 and T2 can be modified with the addition of proper type and concentration of MRI contrast agents [50].

Another remark emerging from the gathered data is that the same phantom ingredient may act differently on the MR relaxation properties when companied with different gelling agents. For instance, addition of NaCl in agar-based phantoms markedly affected T1 and T2 values [48]. On the contrary, the relaxation values of a PAA phantom were found independent of the NaCl concentration [73]. Therefore, the previously reported trends should be considered with caution, considering synergic components and how they may interrelate.

Preservatives are required to prevent bacterial invention and offer long-term use. NaN_3 is maybe the most widely used preservative since it was selected to lengthen the lifetime of various phantom types, including agar [31], PAA [70], and Carrageenan [47,48] phantoms.

Even though an ideal phantom would possess all the characteristics of the simulated tissue, this is extremely difficult. Thus, phantom recipes

are adjusted to simulate only the critical properties of tissue depending on the intended phantom application. In the current study, focus was placed on the MR properties of a wide range of TMPs. In synergy with other studies reviewing acoustical and thermal properties, the reported data is expected to facilitate the selection of appropriate materials for the construction of high-quality MRgFUS phantoms.

6. Conclusions and future prospects

In conclusion, agar-based phantoms appear to be very promising for use with the MRgFUS technology, without the toxicity issues related to PAA materials. Agar gels can be formed in any configuration through a simple manufacturing process while maintaining sufficient mechanical strength upon solidification. In addition, their lifetime can easily be extended with the addition of preservatives. In this category of phantoms, cheap and easy to obtain ingredients can be added as modifiers of acoustical and thermal properties. Their MR relaxation times can be predominantly tailored by varying the agar concentration to accurately match those of human tissue. However, the literature lacks targeted research on specific trends between added ingredients and resultant MR properties of these phantoms. The effect of varying concentration of common inclusions such as silicon dioxide and evaporated milk on the resultant MR relaxation properties of these phantoms is still to be investigated. Overall, the provided data could be useful in manufacturing more effective and realistic MRgFUS phantoms, while simultaneously indicating an opportunity for further research in the field with a particular focus on the MR behavior of agar-based TMPs.

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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