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Simulation-based design and characterization of a microwave applicator for MR-guided hyperthermia experimental studies in small animals

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Abstract

Purpose: The objective of this study was to design and characterize a 2.45 GHz microwave hyperthermia applicator for delivering hyperthermia in experimental small animals to 2 – 4 mm diameter targets located 1 - 3 mm from the skin surface, with minimal heating of the surrounding tissue, under 14.1 T MRI real-time monitoring and feedback control.

Materials and methods: An experimentally validated 3D computational model was employed to design and characterize a non-invasive directional water-cooled microwave hyperthermia applicator. We assessed the effects of: reflector geometry, monopole shape, cooling water temperature, and flow rate on spatial-temperature profiles. The system was integrated with real-time MR thermometry and feedback control to monitor and maintain temperature elevations in the range of 4 – 5 °C at 1 - 3 mm from the applicator surface. The quality of heating was quantified by determining the fraction of the target volume heated to the desired temperature, and the extent of heating in non-targeted regions.

Results: Model-predicted hyperthermic profiles were in good agreement with experimental measurements (Dice Similarity Coefficient of 0.95 – 0.99). Among the four considered criteria, a reflector aperture angle of 120 °, S-shaped monopole antenna with 0.6 mm displacement, and coolant flow rate of 150 ml/min were selected as the end result of the applicator design. The temperature of circulating water and input power were identified as free variables, allowing considerable flexibility in heating target sizes within varying distances from the applicator surface. 2 - 4 mm diameter targets positioned 1 – 3 mm from the applicator surface were heated to hyperthermic temperatures, with target coverage ratio ranging between 76 - 93 % and 11 – 26 % of non-targeted tissue heated.

Conclusion: We have designed an experimental platform for MR-guided hyperthermia, incorporating a microwave applicator integrated with temperature-based feedback control to heat deep-seated targets for experimental studies in small animals.

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Keywords

microwave hyperthermia; small-animal hyperthermia platform; ultra-high field MR-thermometry; model-based characterization; experimental validation

1. INTRODUCTION

Mild hyperthermia, moderate heating of tissue within the temperature range 40- 44 °C for 30-60 minutes, has been clinically applied as an adjuvant therapy for sensitizing tumor cells to radiation and/or chemotherapy. The objective of clinical hyperthermia procedures is to maintain therapeutic temperatures within the targeted tissue for the duration of the procedure, while restricting temperature of non-targeted tissues below a specified threshold [1]. This is often challenging because tissue biophysical properties, especially blood perfusion, vary widely across patients and during the course of the hyperthermic exposure [2]. Treatment outcome following hyperthermia procedures is linked to the ability to deliver desired thermal dose profiles [3], [4]. Thus, practical systems for delivering hyperthermia should include methods for monitoring spatio-temporal temperature profiles so that energy delivery can be adjusted in real-time to achieve the desired thermal dose objectives. Hyperthermia delivery techniques and methods for temperature monitoring were recently reviewed by Faridi et al [5].

In addition to the therapeutic applications that are already in clinical use, the use of mild hyperthermia for modulating the anti-tumor immune response [6]-[8], targeted drug delivery [9]-[11], and other applications, is under investigation as the focus of ongoing research.

Small animals have long been used for experimental tumor models as they can be genetically manipulated to host human disease, making them a powerful tool for researchers investigating the biological effects of anti-tumor therapies, including heating [12]-[14]. Similar to delivery of hyperthermia in humans, investigations in small animals require instrumentation suitable for delivering desired thermal dose profiles to targeted sites. Due to the considerably smaller size of small animals, investigations of therapeutic heating in small-animals often requires the development of instruments optimized for their size. An additional challenge during application of heat to small animals is maintaining core body temperature within normothermic limits.

Hyperthermia may be administered with a variety of energy modalities, including high-intensity focused ultrasound (HIFU) [14]-[19] and electromagnetic energy, such as laser [20], [21], radiofrequency [22] and microwave [23]-[25] modalities. HIFU offers the advantage of non-invasive and precise energy delivery (~2 mm focal spot) due to the short wavelength and large penetration depth of acoustic energy at ultrasonic frequencies. However, the use of HIFU may not always be feasible because acoustic energy does not pass through bone and air in a controlled manner. Another commonly used technique for delivering hyperthermic exposures to small animals is the immersion of the tumor in a temperature-controlled water bath [11]. The water bath is easily administered, but since heating originates from thermal conduction, it can be difficult to achieve therapeutic temperatures within deep targets without overheating the skin and other organs that may be

in thermal contact with the water bath. This places constraints on the use of water-bath for applications where limiting heating to non-targeted tissues is essential e.g. survival studies.

Microwave applicators operating at 2.45 GHz have been applied to mild heating of tumors in various small animal targets, including: bladder [23], lung [25], [26], and implanted tumors in the flank [27], [28] and hind limb [24]. A simulation-based approach was used to design and characterize a water loaded 2.45 GHz microwave applicator for delivering mild hyperthermia to the murine bladder [23]. *In vivo* studies showed that the applicator could be used to heat small tumors, at a depth of 2 - 3 mm beneath the skin, to the hyperthermic range, while maintaining core temperature below 40 °C.

We have previously developed an experimental platform for delivering mild hyperthermia to experimental small animals integrated with ultra-high field 14.1 T MR thermometry [24]. The accuracy of MR thermometry at 14.1 T vs. fiber-optic thermometry was established (maximum discrepancy between MRI and fiber-optic thermometry ~ 0.4 °C) and an MR compatible 2.45 GHz directional water-cooled microwave applicator was employed to heat implanted 4T1 tumors (murine breast cancer) in the hind limbs of mice [24]. While this study demonstrated the feasibility of heating small-animal targets and simultaneously monitoring temperature profiles with 14.1 T MRI, the relatively broad heating profiles of the proof-of-concept applicators is not well suited for experimental studies where limiting heating in non-targeted tumors is essential.

The objective of this study was to employ computational models to characterize the design of the proof-of-concept microwave applicator to focus heating ($4\text{ }^{\circ}\text{C} < T < 5\text{ }^{\circ}\text{C}$) within 2 – 4 mm targets located at 1 - 3 mm from the applicator surface, with minimal heating of adjacent regions ($T < 4\text{ }^{\circ}\text{C}$). Such an applicator would be suitable for *in vivo* experimental studies in small-animals, for delivering mild hyperthermia to 2 – 4 mm diameter tumors located at depths ranging between 1 – 3 mm beneath the skin. As a first step, we employed MRI thermometry to characterize temperature profiles during heating with a prototype microwave hyperthermia applicator in order to assess the validity of computational models of microwave heating, and to identify antenna geometry and thermal cooling parameters that have the greatest impact on temperature profiles. Next, the experimentally validated computational models were employed to identify antenna geometry and circulating water flow parameters with the objective of maximizing therapeutic heating within simulated targets, while limiting heating in other regions. Finally, the most promising applicator design was fabricated and experimentally evaluated in tissue-mimicking phantoms during experiments performed under real-time MR thermometry. During these experiments, we evaluated the ability of the designed applicator to effectively heat targets at distances 1 – 3 mm from the applicator surface.

2. METHODS

2.1 Computational model of the microwave hyperthermia applicator

We employed multi-physics computational models to optimize 2.45 GHz water-cooled directional microwave applicators, similar to the design presented in [24], for non-invasive heating of targets in small-animals from a lateral position. As illustrated in figure 1, the

applicator consists of a coaxial monopole antenna, with an eccentric monopole element displaced from the coaxial cable's central axis, and a hemi-cylindrical metallic reflector to restrict energy deposition to approximately one half of the angular expanse. Water is circulated through the reflector tube to limit waste heating along the length of the applicator, and provide adequate impedance matching of the antenna to the feedline transmission line. Computational models were implemented to mimic applicator positioning within the experimental environment.

Here, we implemented 3D electromagnetic-bioheat transfer simulations with COMSOL Multiphysics, v 5.3. The model consists of the applicator positioned centrally within a 27 mm diameter cylindrical agar phantom, to mimic experimental procedures where the agar phantom is enclosed in a large Eppendorf tube (O.D. 30 mm; I.D. 27 mm) that fits snugly within the 30 mm imaging coil of a Bruker 14.1 T Advance III scanner. The model consists of two steps: computing the electric field radiated into the tissue and subsequently computing transient temperature profiles due to the absorbed electric field heat source. The model solves the time-harmonic Helmholtz equation to determine electric fields radiated to the tissue, subject to the following boundary conditions. The metallic parts of the applicator are defined as perfect electric conductors (PECs; i.e. conductivity, $\sigma \rightarrow \infty$). Scattering boundaries were applied on all the outer surfaces of the model, and act to absorb electromagnetic energy at the model boundaries. A coaxial port boundary condition was applied at the proximal surface of the coaxial cable's dielectric region to specify the excitation.

Two types of heat transfer models were implemented; one model simulated heating in a homogenous agar phantom and was used for experimental validation of the computational model and design optimization of the applicator. A second model, *in vivo* model, included concentric layers of skin, fat and muscle, and used the Pennes' bioheat transfer equation to account for the effects of blood perfusion and metabolic heat generation [29]. Given the promising application of thermal models in previous studies [23], [29], [30], we employed a similar approach. Temperature dependant metabolic heat and perfusion rates after anesthesia were incorporated in the thermal models and was used to assess the impact of heterogeneity and physiological changes on the temperature profiles of the microwave applicator developed in this work. The electromagnetic power loss density, determined from the electromagnetic simulations, was used to specify the heat source. A convective heat transfer boundary condition at the outer wall of the catheter was used to approximate heat transfer due to circulating water within the applicator. For *in vivo* simulations, we considered a multi-layer geometry incorporating multiple tissue types. The thickness of skin layer in mice ranges from 0.2 – 0.4 mm in males, and 0.13 – 0.2 mm in females, and the thickness of sub-cutaneous adipose tissue ranges between 0.05 – 0.17 mm in males, and 0.15 – 0.23 mm in females [31]. In our multi-layer model, we employed the largest thicknesses from these ranges for skin (0.4 mm) and sub-cutaneous fat (0.23 mm) layers. Table 1 lists material properties used in simulations.

The applicator's heating pattern, as assessed by specific absorption rate (SAR) profiles, can be controlled by modifying the reflector's aperture and shape, as well as position of the monopole element, as shown in previous studies [35], [36]. The length of the monopole

radiating element was restricted to 6 mm, for optimally matching the antenna at 2.45 GHz. Figure 2 depicts the antenna geometry parameters we investigated in this study: reflector angle (θ_r), monopole element shape (line or S-shape) and displacement from the center (m) to control the applicator's SAR pattern.

To assess the impact of microwave applicator geometry on the heating pattern, we modeled and implemented two applicators, one with $\Theta_{r1} = 150^\circ$, $m = 0.6$ mm (applicator 1), and another with $\Theta_{r2} = 120^\circ$, $m = 1$ mm (applicator 2).

Besides the antenna geometry, the temperature (T_{cool}) and flow rate of water circulated within the applicator were expected to have an impact on temperature profiles, particularly, the extent of tissue adjacent to the applicator that could be thermally spared. To assess the effect of convective heat transfer on thermal profiles, we conducted microwave heating experiments in tissue mimicking phantom employing three flow rates, corresponding to different convective heat coefficient (h), and three cooling temperatures (T_{cool}). Temperature profiles during these experiments were measured using MRI thermometry.

2.2 Experimental assessment of computational models

Preliminary microwave heating experiments were conducted, with temperature profiles measured using 14.1 T MRI thermometry, with the objective of providing a dataset for assessing the validity of computational models, and identifying the antenna geometry and circulating water flow parameters that have the greatest impact on thermal profiles. Specifically, we compared the measured and simulated $T = 6^\circ\text{C}$ and 8°C hyperthermic isotherms using the Dice Similarity Coefficient (DSC) defined using equation below, where X and Y are the measured and simulated isotherms.

$$DSC = \frac{2 |X \cap Y|}{|X| + |Y|} \quad (1)$$

We conducted several microwave heating of tissue mimicking agar phantom integrated with real-time MR thermometry. During each of these experiments, one parameter of either geometry or convective heat transfer was considered as a variable while other parameters were kept constant. Table 2 summarizes the experimental settings of the described experiments. During these experiments, input power varied in the range of 4 – 11 W at the applicator.

MR thermometry was implemented using a FLASH sequence with the following parameters: FOV = 30 mm, image size = 128×128 , flip angle = 15° , TR/TE = 30.15/4.0 ms, slice thickness = 1 mm, scanning duration = 3.87 s. During the experiments, MR thermometry scans were acquired either three transaxial or sagittal slices, or one transaxial and sagittal slice simultaneously. Models were implemented to mimic the experiments taking into account the two different applicator geometries and various heat transfer parameters.

2.3 Parametric design of the microwave hyperthermia applicator

The goal of the parametric design process is to adapt the microwave hyperthermia applicator design for treating targets of varying size located at varying depths within the small-animal's body. To evaluate the quality of a candidate applicator design, the following metrics were employed: (1) the fraction of the target volume covered within the desired hyperthermic range and (2) the fraction of surrounding non-target regions heated above a threshold.

A two-stage design process was employed; 1) SAR-based geometry design; controlling electromagnetic power transfer to the tissue, 2) temperature profile-based selection of convective cooling parameters; assessing the impact of thermal parameters.

In the first stage, electromagnetic simulations were employed to identify the optimal S-shaped monopole displacement, m , and reflector aperture angle, Θ_r . The parameter m was varied in the range of 0 - 1 mm with the increment of 0.2 mm and Θ_r was varied between 100 – 180° with increments of 10°. Candidate designs that delivered less than 30 % of applied power to the agar phantom (i.e. 70% of microwave power was absorbed within the applicator), were discarded from further consideration, as they would require excessively large applied input powers to heat tissue, which would compromise the efficacy of surface cooling due to microwave absorption within circulating water. Similarly, candidate designs that delivered more than 70% of power to the agar phantom were also discarded, as these designs yielded broad heating patterns.

In the second stage, heat transfer simulations were employed to assess the most promising antenna designs, namely combinations of m , 0.4 and 0.6 mm, and Θ_r , 160° to 100° with decrement of –10°, with convective heat transfer coefficient restricted to $h=2000$ [W m⁻² K⁻¹] (correspondence to flow rate of 150 ml/min). The combination of m and Θ_r experiencing higher coverage and safety rates compared to the remaining combinations, were saved as parametric design process applicator called *applicator 3*.

To determine the versatility of designs for delivering hyperthermia to a wide range of target sizes at varying distances from the applicator, input power and T_{cool} were introduced as control variables that could be selected by the user, and that are independent of the antenna geometry. The impact of varying these cooling parameters was assessed using transient heat transfer simulations over a period of 5 mins.

Finally, the end result of this parametric design process, *applicator 3*, was incorporated in the *in vivo* model to assess the feasibility of delivering localized hyperthermia in the presence of tissue heterogeneity taking into account the effect of anesthesia, blood perfusion and metabolic heat generation on the transient temperature profiles of *applicator 3*.

Applicator 3 (with $\Theta_r = 120^\circ$, $m= 0.6$ mm) was fabricated, as illustrated in figure 3. We used a 3D template with an open angle of $\Theta_r = 120^\circ$ and an ID equal to the reflector OD (2.4 mm) to precisely machine the reflector dimensions. The monopole element was moved outward slightly greater than 0.5 mm relative to the ruler precision. The fabricated applicator has a resonance close to 2.45 GHz, and is well matched (i.e. $s_{11} < -10$ dB) over a 300 MHz bandwidth as shown in figure 3 (d). The performance of this fabricated prototype was

experimentally evaluated during 5 min and 30 min microwave heating experiments conducted under real-time MR thermometry.

During these experiments, a binary control scheme (i.e. bang-bang control) was employed, similar to Farr *et al.*¹². The objective was to modulate the input power to keep the average temperature change of the pre-defined target ROI within the range 4 - 5 °C, while ensuring the maximum temperature change in the phantom did not exceed 8 °C (corresponding to 45 °C *in vivo* presuming 37 °C as a normothermic temperature). We considered circular target ROIs with diameters of 2, 3 and 4 mm while specifying the distance between the applicator edge and ROI boundary as 1, 2, and 3 mm. Real-time temperature monitoring was performed using Thermoguide (IGT, Pessac, France), an MRI based temperature imaging software. To assess the performance of the end result of parametric design process geometry and thermal design, we employed two cost functions to quantify the quality of the hyperthermic exposure: coverage and safety. The coverage metric defines the fraction of the target volume heated to the target temperature range (i.e. 4 °C < T < 8 °C). The safety metric is defined as the volume of the surrounding tissues (i.e. non-targeted regions) with temperature rise below 4 °C. Both the coverage and safety metrics are computed during the interval of time over which the binary controller was activated (See Fig. 10). Coverage and Safety were defined using the following functions:

$$\text{Coverage} = \int \frac{4^{\circ}\text{C} < \text{Control ROI} < 8^{\circ}\text{C}}{\text{Control ROI}} dv \quad (2)$$

$$\text{Safety} = \int \frac{\text{Surrounding tissue} < 4^{\circ}\text{C}}{\text{Surrounding tissue}} dv \quad (3)$$

Since these metrics are competing, a desired applicator design and/or treatment delivery parameters has to be selected to balance the coverage and safety as prescribed by the constraints of the specific subject.

3. RESULTS

3.1 Primary experimental characterization of microwave hyperthermia applicators

MRI thermometry maps and radial temperature profiles within agar phantoms after 5 min microwave heating are shown in figure 4. These data illustrate that the reflector aperture angle, Θ_r , and the monopole shape and displacement, m , considerably affect the peak temperature and width and depth of the hyperthermic zone and provide degrees of freedom for modulating thermal profiles. Using the S-shaped monopole leads to more uniform heating along the applicator length, as demonstrated by the radial temperature profiles in different transaxial planes illustrated in figure 4 (d) and 4 (h). Further, the S-shape monopole affords thermal sparing of tissue immediately adjacent to the applicator, which is not feasible with the line-shaped monopole.

Figure 5 shows the impact of varying the circulating water flow rate and temperature, T_{cool} , on radial temperature profiles when using applicator 1 in an agar phantom. Figure 5 (a)

demonstrates that using a water flow rate of 150 ml/min enables sparing of regions adjacent to the applicator surface, while this region is heated to the hyperthermic range when using lower and higher flow rates. The effect of three different values of T_{cool} on radial temperature profiles is shown in figure 5 (b). Increased T_{cool} leads to higher maximum temperatures, as well as decreased radial penetration of hyperthermic zones, thereby increasing the risk of overheating the skin surface.

3.2 Experimental assessment of computational models

Simulated and experimentally measured temperature maps are illustrated in figure 6. The DSC between the simulated and measured $T = 6\text{ }^{\circ}\text{C}$ and $8\text{ }^{\circ}\text{C}$ isotherms were 0.97 ± 0.02 and 0.98 ± 0.01 , respectively, which suggests that computational model predicts temperatures that are in alignment with experimental measurements. We have previously comparatively assessed the validity of simulated transient temperature profiles in multiple ROIs with MR thermometry and the maximum error between simulated and MR measured temperatures were $0.7\text{ }^{\circ}\text{C}$ [37].

3.3 Simulation-based parametric design and simulations under *in vivo* conditions

Figure 7 displays normalized SAR profiles of a range of candidate applicator designs with varying Θ_r and m . Based on these simulations, the number of candidate designs was narrowed down to 8 from an initial 30 combinations of Θ_r and m , by considering only those applicators where the power deposited within the phantom ranged between 30 – 70 % of the applied power.

At the end of thermal simulations, applicators with $m = 0.4\text{ mm}$ and $\Theta_r = 140^{\circ}$ and $m = 0.6\text{ mm}$ and $\Theta_r = 120^{\circ}$ yielded higher Coverage and safety values compared to the rest of combinations. While both of these geometries could be employed for delivering hyperthermia to the target with similar coverage and safety values, the applicator with $m = 0.6\text{ mm}$ and $\Theta_r = 120^{\circ}$ was selected as the end result of the parametric design process, *applicator 3*, because of its adaptability to larger number of target sizes and distances from the surface. Figure 8 depicts variations of temperature profiles in phantoms following heating with the optimal applicator design ($\Theta_r = 120^{\circ}$ and $m = 0.6\text{ mm}$), when using different combinations of applied power and T_{cool} . Figure 8 further illustrates that *applicator 3* ($\Theta_r = 120^{\circ}$ and $m = 0.6\text{ mm}$), enables a range of temperature profiles that can be achieved with other applicator geometries, simply by adjusting the applied power level and T_{cool} . Importantly, adjusting applied power level and T_{cool} for other applicator geometries, provided only limited flexibility in modifying hyperthermic profiles.

Figure 9 depicts transient temperature profiles of *in vivo* model using *applicator 3* which restricts the extent of heating to the tumor site with minimal collateral heating.

3.4 Experimental evaluation of optimal applicator design

Figure 10 illustrates MRI thermometry profiles following 7 W, 5 min heating of agar phantom using *applicator 3* ($\Theta_r = 120^{\circ}$ and $m = 0.6\text{ mm}$). Temperature profiles are shown for exposures with and without feedback-control. Figure 10 (b) shows the average transient

temperature during the application of binary temperature control (figure 10 (c)) which kept the average temperature of ROI ($r = 1\text{ mm}$ and $D = 2\text{ mm}$) in the target hyperthermic range.

To evaluate the performance of *applicator 3* for delivering hyperthermia to the target, control targets were defined, with $r = 1, 1.5$ and 2 mm , and $D = 1 - 3\text{ mm}$ from the applicator surface (figure 11). Tables 3 and 4 include coverage and safety rates in transaxial and sagittal planes of each of the controlled hyperthermic experiments conducted with $T_{cool} = T_{phantom}$ and $T_{cool} = T_{phantom} - 5^{\circ}\text{C}$.

Figure 12 illustrates the operation of the feedback-controlled power delivery approach and transient temperature profiles during 30 min of heat exposure. Figures 11, 12 and tables 3 and 4, illustrate the capability of *applicator 3* to deliver and maintain hyperthermic temperature to the targets of diameter 2 - 4 mm within 1 - 3 mm distance from the applicator surface.

4. Discussion

Localized hyperthermia treatment requires (1) precise energy delivery to the targeted tissue and (2) maintaining the temperature in the hyperthermic range for 30- 60 minutes. In this work, we have optimized a previously presented non-invasive 2.45 GHz directional water-cooled microwave applicator to limit the extent of hyperthermic zone to 1 – 3 mm targets and preserve surrounding tissue. Real-time MR temperature monitoring and feedback control enabled maintaining temperature within the hyperthermic range. An advantage of the described system is it enables precise delivery of hyperthermia to small target sites with an easy to implement microwave applicator. Specifically, hyperthermic profiles to 1 – 3 mm targets could be controlled through selection of applied power level and T_{cool} . Compared to small-animal hyperthermia systems employing focused ultrasound, which may offer extended control of heating to deep seated targets, the presented system may afford simplified hyperthermia delivery, as it does not require careful selection of phased array excitation parameters [15], [16].

We evaluated the impact of geometrical and thermal design of the microwave applicator on the temperature profiles. The evaluation of experimentally measured temperature profiles using the fabricated applicators with different geometrical design indicated that the reflector angle, Θ_r , and monopole displacement from the center, m , modify the width and depth of the heating pattern and peak temperature. Specifically, increasing m moves the radiating monopole closer to the targeted tissue, which results in greater electromagnetic power absorbed within the tissue. Conversely, increasing Θ_r results in more power remaining within the catheter. In addition to Θ_r and m , the monopole antenna shape impacted the ability to shift the onset of the hyperthermic zone from immediately adjacent to the applicator surface, to deeper regions within tissue. This may be important because of the need to thermally spare the skin surface for several applications (figure 4). During experimental evaluation of thermal parameters, using a convective heat transfer rate of 150 ml/min increased radial penetration of the peak temperature from the surface of the applicator compared to flow rates of 50 ml/min and 300 ml/min (figure 5). This enables increased skin cooling and treatment of tumors up to 4 mm from the skin surface. The

choice of T_{cool} relative to $T_{phantom}$ has a considerable impact on the temperature profile. High values of T_{cool} leads to convective heating, in addition to direct microwave heating, which increases the tissue temperature, particularly at the applicator boundary, and broadens the extent of the hyperthermic zone (figure 5). Temperature rise also appears along the applicator length due to convective heating which heats up the whole tissue sample. Therefore, circulating water with higher temperature relative to tissue sample is not suitable for localized hyperthermia delivery to small animal targets. Using lower T_{cool} reduces the peak temperature, as well as the width of the hyperthermic zone.

Temperature profiles predicted by the 3D computational model were comparatively assessed with MRI thermometry data from experiments in tissue-mimicking phantoms. The hyperthermic isotherms of measured and simulated temperature profiles were highly correlated ($DSC = 0.95 - 0.99$) for multiple input powers (figure 6). The validated computational models were then utilized for design and characterization of the applicator based on the normalized SAR and temperature profile. For the SAR-based parametric design (figure 7), monopole shape was restricted to S-shape because of the ability to thermally spare regions between the applicator edge and the hyperthermic zone. This gap lowers the risk of skin burn during *in vivo* hyperthermia treatments. From thermal simulations, using a convective heat transfer coefficient of $h=2000$ [W/m²K] (corresponding to a flow rate =150 ml/min), $\Theta_r = 120$ °C and $m = 0.6$ mm was selected (*applicator 3*), because compared to other Θ_r and m combinations, this selection enabled heating of a wider range of target sizes at greater distances from the skin, while maintaining a similar safety rate. It is worth noting that the range of thermal profiles that can be achieved by *applicator 3*, by appropriate selection of T_{cool} and applied power, spans the range of temperature profiles achieved by the majority of the eliminated designs, which have distinct antenna geometries (figure 8).

The ultimate goal of the parametric design process was to identify an applicator design suitable for delivering localized hyperthermia to small animal targets *in vivo*. The temperature profiles predicted by computational models using *applicator 3* when considering a multi-layer perfused skin, fat and muscle layer and metabolic rate after anesthesia (mimicking *in vivo* treatments) demonstrate the suitability of using the design presented in this work for localized heating of small-animal targets. Comparing the temperature profiles simulated under *in vivo* conditions (figure 9) in a multi-layer medium, including blood perfusion and metabolic heat generation, with temperature profiles in the homogeneous phantom (figures 6 and 8), it is apparent that, for the same applied power level, the shape of the hyperthermic zones remain similar, suggesting that the shape of the hyperthermic profiles are not substantially impacted by dielectric heterogeneity. However, for the same applied power level, the peak temperature and the volume raised to the hyperthermic temperature in *in vivo* simulations compared to homogeneous phantoms is decreased, which may be attributed to the additional heat sink terms. We anticipate that applying power using the binary feedback control algorithm would facilitate increased peak temperatures and hyperthermic treatment zones, although these may still remain below the size of hyperthermic zones that could be achieved in homogenous phantoms. It is noted that we employed a simplified model where the skin, fat, and muscle layers were geometrically modeled as concentric cylinders. While these simulations illustrate the impact of heterogeneity and blood perfusion and metabolic heat generation on thermal profiles

compared to those simulated in homogeneous agar phantoms, models incorporating the anatomy of the animal [23], [38] may provide a more comprehensive prediction of temperature profiles for a particular administration of heating.

Integrating *applicator 3* with binary temperature-based feedback control of applied power, localized the heating to the targeted region of interest (figure 10). Real-time MR temperature monitoring using *applicator 3* with the application of temperature feedback control enabled precise delivery of hyperthermia to target ROIs over a narrow temperature range (4 - 5 °C) (figure 11). The average temperature within the targeted ROI reached the hyperthermic range within a few minutes; for example, hyperthermic temperatures for target ROIs with $r = 1$ mm and $D = 1$ mm were obtained after 43 s, and for target ROIs with $r = 2$ mm and $D = 3$ mm, after 207 s. In this study, binary feedback control was employed to terminate the input power when average temperature change of the pre-defined target ROI reached 5 °C. The uniform distribution of hyperthermic temperatures in the selected ROIs, compared to non-uniform distribution previously reported for MR-guided pancreatic hyperthermia in mice [14], may facilitate *in vivo* hyperthermia treatment for target sizes of 2 - 4 mm in diameter in 1 - 3 mm distance from the applicator yielding high target coverage (table 3 and 4). The placement of the monopole antenna could change the maximum temperature of the target by 1 - 2 °C. However, average temperature of the target ROI remains in the hyperthermic zone with relatively high coverage and safety rates (safety = 74 - 77 %; coverage = 80 - 94 %).

Figure 12 illustrates the feasibility of using *applicator 3* integrated with feedback control for delivering hyperthermia over a 30 min period. During 30 min of heating, hyperthermic zones remained confined to the target while maintaining the safety rate of non-targeted surroundings. We calculated the safety and coverage metrics over an average of 60 s prior to the timepoints shown in figure 12. The safety metric ranged between 77 - 79 %, and the coverage metric ranged between 70 - 90 %. These data illustrate the ability of the proposed system to maintain localized heating to targeted regions over an extended duration of time. While baseline drift is known to be a potential source of error during MRI thermometry for long durations [15], we observed the maximum drift over 60 min to be 0.4 °C; further, this level of drift could be corrected with established drift compensation techniques [39]-[41].

A limitation of this work is the absence of *in vivo* experiments. The dissimilarity between *in vivo* and phantom studies are tissue heterogeneity, blood perfusion, metabolic heat generation and small animal movement inside the MR scanner. Although the optimal system described here was not employed to deliver hyperthermia to small animals, we expect accurate energy *in vivo* delivery according to the temperature profiles of validated 3D *in vivo* computational models. In this study, we applied feedback control relevant to temperatures measured in one transaxial plane, however, temperature was monitored in sagittal plane simultaneously to avoid temperature rise above 8 °C. Coverage and safety rates in sagittal plane were similar to those measured in the transaxial control plane.

5. Conclusion

We employed a model-based approach for the design and characterization of 2.45 GHz water-cooled microwave applicators for delivering hyperthermia to small-animal targets

under 14.1 T MRI guidance. Computational models of microwave heating were experimentally validated and used to comparatively assess the range of applicator parameters that affect thermal profiles, namely: monopole antenna shape and displacement, reflector aperture angle, circulating water temperature, and flow rate. The result of the parametric design process, *applicator 3*, employed a reflector with aperture angle $\Theta_r = 120^\circ$ and an S-shaped monopole displaced 0.6 mm from the antenna's central axis. Adjusting the applied microwave power and circulating water temperature enabled using the selected applicator design to deliver hyperthermic profiles to a range of target ROIs. In experiments using *applicator 3*, a binary feedback control scheme was employed to deliver heating to target ROIs targets 2 - 4 mm in diameter positioned 1 - 3 mm from the applicator surface. In these experiments, 76 - 93 % of the target ROI was heated to the target temperature while 74 - 89 % of non-targeted regions were maintained below the hyperthermic threshold.

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References

- [1]. Datta NR et al., "Local hyperthermia combined with radiotherapy and/or chemotherapy: recent advances and promises for the future," *Cancer Treat. Rev.*, vol. 41, no. 9, pp. 742–753, 11 2015. [PubMed: 26051911]
- [2]. Hurwitz M and Stauffer P, "Hyperthermia, radiation and chemotherapy: the role of heat in multidisciplinary cancer care," in *Seminars in oncology*, 2014, vol. 41, pp. 714–729. [PubMed: 25499632]
- [3]. van Rhoon GC, "Is CEM43 still a relevant thermal dose parameter for hyperthermia treatment monitoring?," *Int. J. Hyperthermia*, vol. 32, no. 1, pp. 50–62, 2016. [PubMed: 26758036]
- [4]. Ohguri T et al., "Relationships between thermal dose parameters and the efficacy of definitive chemoradiotherapy plus regional hyperthermia in the treatment of locally advanced cervical cancer: data from a multicentre randomised clinical trial," *Int. J. Hyperthermia*, vol. 34, no. 4, pp. 461–468, 2018. [PubMed: 28679349]
- [5]. Faridi P, Bossmann SH, and Prakash P, "Image-Guided Cancer Thermal Therapies," in *Magnetic Nanomaterials*, 2017, pp. 195–220.
- [6]. Mahmood J et al., "Immunotherapy, radiotherapy, and hyperthermia: A combined therapeutic approach in pancreatic cancer treatment," *Cancers*, vol. 10, no. 12, p. 469, 2018.
- [7]. Frey B et al., "Old and new facts about hyperthermia-induced modulations of the immune system," *Int. J. Hyperthermia*, vol. 28, no. 6, pp. 528–542, 2012. [PubMed: 22690925]
- [8]. Toraya-Brown S and Fiering S, "Local tumour hyperthermia as immunotherapy for metastatic cancer," *Int. J. Hyperthermia*, vol. 30, no. 8, pp. 531–539, 2014. [PubMed: 25430985]
- [9]. Gasselhuber A et al., "Targeted drug delivery by high intensity focused ultrasound mediated hyperthermia combined with temperature-sensitive liposomes: computational modelling and preliminary in vivo validation," *Int. J. Hyperthermia*, vol. 28, no. 4, pp. 337–348, 2012. [PubMed: 22621735]
- [10]. Centelles et al MN., "Image-guided thermosensitive liposomes for focused ultrasound drug delivery: Using NIRF-labelled lipids and topotecan to visualise the effects of hyperthermia in tumours," *J. Controlled Release*, vol. 280, pp. 87–98, 2018.
- [11]. Willerding L et al., "Method of hyperthermia and tumor size influence effectiveness of doxorubicin release from thermosensitive liposomes in experimental tumors," *J. Control. Release Off. J. Control. Release Soc.*, vol. 222, pp. 47–55, 1 2016.

- [12]. Ruggeri BA, Camp F, and Miknyoczki S, "Animal models of disease: pre-clinical animal models of cancer and their applications and utility in drug discovery," *Biochem. Pharmacol*, vol. 87, no. 1, pp. 150–161, 1 2014. [PubMed: 23817077]
- [13]. Bredlau ALet al., "Thermal Therapy Approaches for Treatment of Brain Tumors in Animals and Humans," *Crit. Rev. Biomed. Eng*, vol. 44, no. 6, pp. 443–457, 2016. [PubMed: 29431091]
- [14]. Farr N et al., "Hyperthermia-enhanced targeted drug delivery using magnetic resonance-guided focussed ultrasound: a pre-clinical study in a genetic model of pancreatic cancer," *Int. J. Hyperth. Off. J. Eur. Soc. Hyperthermic Oncol. North Am. Hyperth. Group*, pp. 1–8, 7 2017.
- [15]. Bing C et al., "Localised hyperthermia in rodent models using an MRI-compatible high-intensity focused ultrasound system," *Int. J. Hyperthermia*, vol. 31, no. 8, pp. 813–822, 2015. [PubMed: 26540488]
- [16]. Fite BZet al., "Magnetic resonance thermometry at 7T for real-time monitoring and correction of ultrasound induced mild hyperthermia," *PloS One*, vol. 7, no. 4, p. e35509, 2012. [PubMed: 22536396]
- [17]. Staruch R, Chopra R, and Hynynen K, "Hyperthermia in bone generated with MR imaging–controlled focused ultrasound: Control strategies and drug delivery," *Radiology*, vol. 263, no. 1, pp. 117–127, 2012. [PubMed: 22438444]
- [18]. Poorman MEet al., "Open-source, small-animal magnetic resonance-guided focused ultrasound system," *J. Ther. Ultrasound*, vol. 4, no. 1, p. 22, 2016. [PubMed: 27597889]
- [19]. Lee JEet al., "Assessing high-intensity focused ultrasound treatment of prostate cancer with hyperpolarized ¹³C dual-agent imaging of metabolism and perfusion," *NMR Biomed*, p. e3962, 2018. [PubMed: 30022550]
- [20]. Norred SE and Johnson JA, "Magnetic resonance-guided laser induced thermal therapy for glioblastoma multiforme: a review," *BioMedRes. Int*, vol. 2014, 2014.
- [21]. Vogl TJet al., "MR-based thermometry of laser induced thermotherapy: temperature accuracy and temporal resolution in vitro at 0.2 and 1.5 T magnetic field strengths," *Lasers Surg. Med*, vol. 44, no. 3, pp. 257–265, 2012. [PubMed: 22407543]
- [22]. Zhang F et al., "Intrabiliary RF Heat-enhanced Local Chemotherapy of a Cholangiocarcinoma Cell Line: Monitoring with Dual-Modality Imaging—Preclinical Study," *Radiology*, vol. 270, no. 2, pp. 400–408, 2 2014. [PubMed: 24471389]
- [23]. Salahi S et al., "Miniature microwave applicator for murine bladder hyperthermia studies," *Int. J. Hyperthermia*, vol. 28, no. 5, pp. 456–465, 2012. [PubMed: 22690856]
- [24]. Curio Set al., "An integrated platform for small-animal hyperthermia investigations under ultra-high-field MRI guidance," *Int. J. Hyperth. Off. J. Eur. Soc. Hyperthermic Oncol. North Am. Hyperth. Group*, pp. 1–11, 7 2017.
- [25]. Motomura Tet al., "Evaluation of systemic external microwave hyperthermia for treatment of pleural metastasis in orthotopic lung cancer model," *Oncol. Rep*, vol. 24, no. 3, pp. 591–598, 2010. [PubMed: 20664962]
- [26]. Yang Yet al., "Microwave hyperthermia enhances the sensitivity of lung cancer cells to gemcitabine through reactive oxygen species-induced autophagic death," *Oncol. Rep*, vol. 41, no. 5, pp. 3100–3110, 5 2019. [PubMed: 30976815]
- [27]. Petryk AAet al., "Comparison of iron oxide nanoparticle and microwave hyperthermia alone or combined with cisplatin in murine breast tumors," *Proc. SPIE-- Int. Soc. Opt. Eng*, vol. 7901, 2 2011.
- [28]. Petryk AA, Giustini AJ, Gottesman RE, Tremblay BS, and Hoopes PJ, "Comparison of magnetic nanoparticle and microwave hyperthermia cancer treatment methodology and treatment effect in a rodent breast cancer model," *Int. J. Hyperth. Off. J. Eur. Soc. Hyperthermic Oncol. North Am. Hyperth. Group*, vol. 29, no. 8, pp. 819–827, 12 2013.
- [29]. Rodrigues DB, "Target-specific multiphysics modeling for thermal medicine applications," 2013.
- [30]. Salahi S, Target-Specific Microwave Antenna Optimization for Pre-Clinical and Clinical Bladder Hyperthermia Devices, vol. 73 2012.
- [31]. Hew J et al., "The effects of dietary macronutrient balance on skin structure in aging male and female mice," *PloS One*, vol. 11, no. 11, p. e0166175, 2016. [PubMed: 27832138]
- [32]. Balanis CA, *Advanced engineering electromagnetics*. John Wiley & Sons, 1999.

- [33]. Haemmerich D and Schutt DJ, "RF ablation at low frequencies for targeted tumor heating: In vitro and computational modeling results," *IEEE Trans. Biomed. Eng.*, vol. 58, no. 2, pp. 404–410, 2011. [PubMed: 20934940]
- [34]. Hasgall PA, Neufeld E, Gosselin MC, Klingenböck A, and Kuster N, "IT'IS Database for thermal and electromagnetic parameters of biological tissues," Version 30, 2015.
- [35]. McWilliams BT, Schnell EE, Curto S, Fahrbach TM, and Prakash P, "A Directional Interstitial Antenna for Microwave Tissue Ablation: Theoretical and Experimental Investigation," *IEEE Trans. Biomed. Eng.*, vol. 62, no. 9, pp. 2144–2150, 9 2015. [PubMed: 25794385]
- [36]. Sebek J, Curto S, Bortel R, and Prakash P, "Analysis of minimally invasive directional antennas for microwave tissue ablation," *Int. J. Hyperth. Off. J. Eur. Soc. Hyperthermic Oncol. North Am. Hyperth. Group*, vol. 33, no. 1, pp. 51–60, 2017.
- [37]. Faridi P and Prakash P, "Experimental Validation of Computational Models of Microwave Tissue Heating with Magnetic Resonance Thermometry," in *2018 IEEE/MTT-S International Microwave Symposium-IMS*, 2018, pp. 1282–1284.
- [38]. Raaijmakers EAL et al., "An MR-compatible antenna and application in a murine superficial hyperthermia applicator," *Int. J. Hyperth. Off. J. Eur. Soc. Hyperthermic Oncol. North Am. Hyperth. Group*, pp. 1–7, 9 2017.
- [39]. Bing C et al., "Drift correction for accurate PRF-shift MR thermometry during mild hyperthermia treatments with MR-HIFU," *Int. J. Hyperth. Off. J. Eur. Soc. Hyperthermic Oncol. North Am. Hyperth. Group*, vol. 32, no. 6, pp. 673–687, 2016.
- [40]. Grissom WA et al., "Hybrid referenceless and multibaseline subtraction MR thermometry for monitoring thermal therapies in moving organs," *Med. Phys.*, vol. 37, no. 9, pp. 5014–5026, 2010. [PubMed: 20964221]
- [41]. Alivar A, Faridi P, Prakash P, and Natarajan B, "An enhanced hybrid MRI thermometry technique for monitoring microwave thermal therapy," in *Medical Imaging 2019: Image-Guided Procedures, Robotic Interventions, and Modeling*, 2019, vol. 10951, p. 109512P.

Figure 1.
Geometry of the distal tip of the microwave hyperthermia applicator illustrating the monopole radiating element and metallic hemi-cylindrical reflector

Figure 2. Schematic (left column) and photograph (right column) of fabricated microwave applicator geometry, (a) transverse view of reflector geometry, (b-c) longitudinal view of S (with 4mm monopole element parallel to the outer catheter wall according to Sebek et al. [36]) and line-shape monopole radiation element with m displacement from the center of coaxial cable

Figure 3.

(a) Photograph of fabricated prototype of *applicator 3* (outer catheter is not enclosed), (b) Cutting the reflector cylinder to the desired angle using a 3D printed template, (c) monopole element displacement from the center (m) measured with a 0.5 mm precision ruler, (d) applicator 3 reflection coefficient.

Figure 4.

MR thermometry temperature measurements after 3 and 5 minutes of heat exposure in a transaxial slice S2 with 10.6 W (b and f) and 7.2 W (c, d and g, h) input power, respectively using, (b - d) applicator 1, (f - h) applicator 2, (d) and (h) show the radial temperature profile in the direction of maximum heating labeled in (c) and (g), (three horizontal lines in sagittal views of the applicators inserted inside the phantom, (a) and (e), are showing three transaxial MR thermometry slices, S1, S2 and S3).

Figure 5. Temperature profiles measured with MR thermometry while (a) water flow rate and (b) T_{cool} are adjusted.

Figure 6.

Experimentally measured (first row) and simulated (second row) temperature profiles after (a-b) 5 min of heat exposure with an input power of 7.2 W in transaxial view, (c-d) and (e-f) 3 min of heat exposure with an input power of 10 W in transaxial and sagittal view, respectively. Circulating water temperature (T_{cool}) is equal to phantom temperature ($T_{phantom}$) with flow rate of 150 ml/min. Full white circles and rectangles show the antenna position.

Figure 7. Normalized SAR profile of applicator designs employing varying combinations of Θ_r and m (profiles are shown here for 12 out of a total 30 combinations that were investigated).

Figure 8.

Simulated temperature profiles among the 8 remaining combinations of Θ_r and m from SAR patterns that are well-suited for hyperthermia delivery to small tumors at $t = 300$ s with input powers of $P = 5, 6, 7, 8, 9$ and 10 W, $T_{cool} = 15^\circ\text{C}$ or 20°C while $T_{phantom}$ is 20°C . The red dashed border indicates the selected optimal design. Each column shows that temperature pattern achieved with the optimal design, by appropriately choosing applied power and T_{cool} , spans the range of temperature profile achieved by applicators with other Θ_r and m combinations; emphasizing that the optimal design embraces all the possible hyperthermic temperature profiles.

Figure 9.
Transient temperature profiles of *in vivo* simulation using *applicator 3*

Figure 10.

(a) temperature profile measured by MR thermometry with $P = 7$ W at the applicator at $t = 300$ s, (b) Average temperature profile during feedback-controlled heating, (c) Input power termination (21 W at power meter was equal to 7 W) and average temperature of the target ROI during feedback-controlled heating. T_{cool} and $T_{phantom}$ were both 18.5 °C with water flow rate of 150 ml/min.

Figure 11.

Temperature maps during 5 min heating ($P=8$ W) to maintain average temperature change of control ROIs with radius (a) 1 mm, (b) 1.5 mm and (c) 2 mm, in the range of 4 - 5 °C utilizing binary feedback control. D indicates the distance between the applicator edge and closest ROI boundary.

Figure 12.

(a) Average temperature of target sized 3 mm in diameter located at 1 mm from the applicator boundary incorporating binary feedback control to trigger the input power ($P=7$ W), (b) transient temperature profiles during 30 min heat exposure

Table 1.

Material properties used in simulations

	Relative permittivity ϵ_r	Conductivity σ (S /m)	Density ρ (kg /m ³)	Heat capacity C (J /Kg °C)	Thermal cond. k (W /m °C)	Metabolic heat rate M_A (W /m ³)	Blood perfusion ω (kg/s /m ³)
Polyimide	3.4 [32]	-	-	-	-	-	-
Water	78.6	1.45	-	-	-	-	-
Agar phantom	57.99 [Measured]	2.3 [Measured]	1300 [Measured]	4182 [33]	0.6 [33]	-	-
Muscle	52.7	1.74	1090	3421	0.49	1734[29]	2.161[29]
Fat	10.8	0.268	911	2348	0.21	1734[29]	2.161[29]
Skin	38	1.46	1109	3391	0.37	2002[29]	1.359[29]
Blood	-	-	1050	3617	-	-	-

^aAll material properties are from [34] except the indicated ones from [29], [32], [33] and measured properties in our laboratory.

Table 2.

Experimental settings to assess the significance of the impact of each parameter

Variable	Geometry	T _{cool} (°)	Water flow rate (ml/min)
Water flow rate	applicator 1	T _{phantom} = 16.5	50 150 300
T _{cool}	applicator 1	13.5 16.5 29.5	150
Geometry	applicator 1 applicator 2	T _{phantom} = 16.5	150
Geometry	applicator 1 applicator 2	T _{phantom} = 16.5	150

Table 3.

Coverage and safety of the controlled hyperthermia experiments in phantoms at a time following activation of the binary controller with $T_{cool} = T_{phantom}$

P= 8 W		Sagittal		Axial		Coverage [%]				Safety [%]		SS
r (mm)	D (mm)	Max (°C)	Ave (°C)	Max (°C)	Ave (°C)	Sagittal		Axial		Sagittal	Axial	t [s]
						Max	Ave	Max	Ave			
1	1	6.8	4.2	7.7	4.3	100	86	99	88	89	80	43
	2	7.1	4.3	7.6	4.4	100	86	100	87	88	79	73
	3	6.9	4.1	7.5	4.2	99	84	99	84	87	78	112
1.5	1	6.7	3.9	7.5	3.9	100	84	100	84	88	80	58
	2	7.4	4.2	8.1	4.3	98	75	98	77	87	79	104
	3	6.8	3.9	7.7	4.1	91	74	97	76	87	79	178
2	1	6.9	3.8	7.4	4	99	93	99	86	84	77	120
	2	7.2	4	8	4.2	93	81	95	83	80	76	190
	3	7.7	4.5	7.8	4	93	77	96	80	77	74	207

Table 4.

Coverage and safety of the controlled hyperthermia experiments at a time following activation of the binary controller with $T_{cool} = T_{phantom} - 5\text{ }^{\circ}\text{C}$

P= 8 W		Sagittal		Axial		Coverage [%]				Safety [%]		SS
r (mm)	D (mm)	Max ($^{\circ}\text{C}$)	Ave ($^{\circ}\text{C}$)	Max ($^{\circ}\text{C}$)	Ave ($^{\circ}\text{C}$)	Sagittal		Axial		Sagittal	Axial	t [s]
						Max	Ave	Max	Ave			
1	1	6.6	4.2	7.4	4.2	100	77	99	73	89	80	104
1.5	1	6.8	4.1	7	4.3	96	72	98	74	89	79	66
2	1	7.2	3.9	7.9	4	91	74	95	76	84	77	208