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IMPROVED MODELING OF IMAGE-GUIDED THERMAL
ABLATION PROCEDURES TOWARDS PATIENT-
SPECIFIC TREATMENT PLANNING APPLICATIONS

BY

GARRON DESHAZER

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

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DOCTOR OF PHILOSOPHY DISSERTATION
OF
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2016

ABSTRACT

Microwave ablation (MWA) is a minimally-invasive modality that is playing an increasingly vital role in the treatment of cancer and benign disease. These procedures involve the use of a microwave antenna (or an array of antennas) to deliver energy to raise tissue temperature above a thermal threshold to induce irreversible cell damage. Commonly used clinical MWA systems operate at frequencies of 2450 MHz and 915 MHz . Image-guided percutaneous MWA treatments can be guided by intraoperative ultrasound or computed tomography (CT) fluoroscopy, which allows the physician to deliver treatments precisely. As such, image-guided MWA has received substantial attention for the treatment of cancer in the past decade that is performed in combination with other therapies (radiation therapy) or used as an alternative to other more invasive procedures (surgical resection). There has been increasing interest in improving the efficacy and specificity of MWA through improving energy delivery and application techniques in this domain. This review outlines clinical percutaneous MWA technology detailing concepts related to thermal dosimetry, the physics of microwave heating, modeling of MWA in tissue, and future goals of treatment planning in the context of image-guided MWA procedures.

Microwave ablation (MWA) treatment is an important alternative to surgical resection of tumor in cancer treatment; however, the naive planning tools currently available are of limited practical use in real clinical decision making. These geometric planning guidelines are insufficient treatment planning tools for accounting for the level of unpredicted treatment variability seen during MWA procedures. Unanticipated treatment variability may potentially be a cause of cancer recurrence,

and it is difficult to measure treatment variability during MWA procedures on patients. Biothermal models have been employed to simulate these types of procedures and aid in quantifying the level of treatment variability seen in the clinically. In general, there are too many variables to measure and include for a patient-specific physically-based simulation. A physically based simulation that accounts for tissue heterogeneities, perfusion, and temperature dependent effects will provide improved predictive accuracy over existing geometric models. Nevertheless, it is still unclear as to which parameters are important, and if we cannot measure their effect on real patients. A potential solution to this problem would be to create a validated physically based model to simulate and explore the effect of a range of different patient specific variables so that we can focus on the most important ones. This will be a critical component in developing MWA planning and guidance tools for accurate and precise treatment delivery.

Image-guided MWA has emerged as a promising modality for tissue ablation. Currently, available systems in clinical use operate at 915 MHz or 2.45 GHz. Model-based predictive planning tools are under investigation for guiding clinical delivery of ablation treatments. Currently, most MWA modeling approaches have been focused on ablation systems operating at 2.45 GHz. Improving our understanding of the dynamics of 915 MHz MWA ablation will lead to better MWA prediction models of treatments at this frequency. As progress towards this, the finite element method was used to simulate MWA procedures in liver with a clinical 915 MHz ablation applicator. A coupled electromagnetic-thermal solver incorporating temperature dependent tissue biophysical properties of liver was implemented. Model-based

predictions of transient temperature profiles and ablation zone dimensions were compared against experiments in ex vivo bovine liver tissue. Broadband dielectric properties of tissue within different regions of the ablation zone were measured and reported at 915 MHz and 2.45 GHz. The resultant simulated transverse diameter and axial lengths of the ablation zone were in good agreement with ex vivo measurements at 30 W (1.0 mm and 1.0 mm) and 60 W (within 0.5 mm and 2.5 mm). Experimentally measured radial temperature profiles were within 2-8 °C of the simulated profiles. These results will aid in the development of a computational modeling framework for predictive planning of ablation procedures.

While computational models can afford the flexibility for including detailed tissue anatomy and heterogeneity, a balance between model complexity, accuracy, and required computational resources must be struck for practical clinical application. Investigating the contributing factors to ablation variance is therefore important because they provide guidelines for the level of detail needed for patient-specific modeling of microwave ablation procedures. To that end through simulation the impact of 1) heterogeneity of biophysical parameters in tumor vs. healthy tissue, 2) applicator placement relative to the tumor, and 3) proximity to large blood vessels on microwave ablation (MWA) treatment effect area. This will help identify the biophysical properties that have the greatest impact on improving clinical modeling of MWA procedures. Our approach was to develop two-compartment models with variable tissue properties and simulate MWA procedures performed in liver with Perseon Medical's 915 MHz ST applicator. Input parameters for the dielectric and thermal properties considered in this study were based on measurements for healthy

and malignant (primary or metastatic) liver tissue previously reported in the literature. Compartment 1 (C1) represented normal, fatty, or cirrhotic liver, and compartment 2 (C2) represented a primary hepatocellular carcinoma (HCC) tumor sample embedded within C1. To evaluate the sensitivity to tissue parameters, a range of clinically-relevant tissue properties were simulated. To evaluate the impact of MWA antenna position, we simulated various tumor perfusion models with the antenna shifted 5 mm anteriorly and posteriorly. To evaluate the effect of local vasculature, we simulated an additional heat-sink of various diameters and distances from the tumor. Dice coefficient statistics were used to evaluate ablation zone effects from these local heat sinks. The models showed less than 11% of volume variability (1 cm^3 increase) in ablation treatment effect region when accounting for the difference in relative permittivity and electrical conductivity between malignant and healthy liver tissue. There was a 27% increase in volume when simulating thermal conductivity of fatty liver disease versus the baseline simulation. The ablation zone volume increased more than 36% when simulating cirrhotic surrounding liver tissue. Antenna placement relative to the tumor had minimal sensitivity to the absolute size of the treatment effect area, with less than 1.5 mm variation. However, when considering the overlap between the ablation zone and the ideal clinical margin when the antenna was displaced 5 mm anteriorly and posteriorly, there was approximately a 6 mm difference in the margins. Dice coefficient statistics showed as much as an 11% decrease in the ablation margin due to the presence of vessel heat sinks within the model. The results from simulating the variance in malignant tissue thermal and electrical properties will help guide better approximations for MWA treatments. The results suggest that

assuming malignant and healthy liver tissues have similar dielectric properties is a reasonable first approximation. Antenna placement relative to the tumor has minimal impact on the absolute size of the ablation zone; yet it, does cause relevant variation between desired treatment margin and ablation zone. Blood vessel cooling, especially hepatic vessels close to the region of interest may be a significant factor to consider in treatment planning. Further data needs to be collected for assessing treatment planning utility of modeling MWA in this context.

Computational modeling techniques are under investigation for application to patient-specific planning of microwave ablation (MWA) treatments. Knowledge of the antenna design is necessary for accurate simulations; however, the proprietary design of applicators in clinical use is often unknown. Characterizing the specific absorption rate (SAR) during MWA experimentally and comparing to a multi-physics simulation will provide a potential method for more accurately simulating MWA when the antenna geometry is unknown, as in most clinical situations. To accomplish this, an infrared (IR) camera (Mikron M7500) was used to determine the spatial SAR during MWA within a split *ex vivo* liver model. Perseon Medical's short-tip (ST) and long-tip (LT) MWA antenna were placed on top of a tissue sample. Microwave power (15W) was applied for 6 min, while intermittently interrupting power. Tissue surface temperature was recorded via IR camera (3.3 fps, 320x240 resolution). SAR was calculated from initial rate of temperature rise, and intermittently based on slope before and after power shut-down; these data were compared to SAR profiles calculated from simulations. Experimentally measured SAR changed considerably once tissue temperatures exceeded 100 °C, contrary to simulation results. The

simulation and average experimentally measured transverse and axial ablation diameters were 1.28cm and 1.30cm (± 0.0327 cm) and 2.10 cm and 2.66cm (± 0.223 cm); Dice coefficient was on average 0.832 (± 0.0248), suggesting good agreement with the simulated ablation zone. The viability of characterization for MWA antennas via measurements of the specific absorption rate (SAR) within tissue was demonstrated. This method has potential for more accurately simulating MWA when the antenna geometry is unknown, as in most clinical situations.

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PREFACE

Chapter 3 (Manuscript-I) is in the process of submission to *Medical Physics* and is in manuscript format, and as such follows the prescribed formatting of the journal outlined by AIP Publishing. Chapter 4 (Manuscript-II) is published in *Medical Physics* and is in manuscript format, and as such follows the prescribed formatting of the journal outlined by AIP Publishing. Chapter 5 (Manuscript-III) is accepted for publication for the *International Journal of Hyperthermia* and is in manuscript format, and as such follows the prescribed formatting of the journal outlined by Taylor and Francis Group.

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CHAPTER 1

INTRODUCTION

Microwave ablation (MWA) treatment is an important, minimally invasive alternative to surgical resection of tumor in cancer treatment. However, the naive planning tools currently available are of limited practical use in real clinical decision making. These geometric planning guidelines are insufficient treatment planning tools for accounting for the level of unpredicted treatment variability seen during MWA procedures. Unanticipated treatment variability may potentially be a cause of cancer recurrence, and it is difficult to measure treatment variability during MWA procedures on patients. Biothermal models have been employed to simulate these types of procedures and aid in quantifying the level of treatment variability seen in the clinically.

In general, there are too many variables to measure and include for a patient-specific physically-based simulation. A physically based simulation that accounts for tissue heterogeneities, perfusion, and temperature dependent effects will provide improved predictive accuracy over existing geometric models. Nevertheless, it is still unclear as to which parameters are important, and if we cannot measure their effect on real patients. A potential solution to this problem would be to create a validated physically based simulation to simulate and explore the effect of a range of different patient specific variables so that we can focus on the most important ones.

In order to help address the described problem the research reported in this manuscript will focus on discussing steps taken to 1) build and validate a MWA

model, 2) investigate the variability in the physical parameters incorporated in MWA treatments, and 3) extend these methods to other devices with unknown geometry. The results of this research will be a critical component in developing ablation treatment planning and guidance tools for accurate and precise treatment delivery.

Image-guided percutaneous MWA treatments can be guided by intraoperative ultrasound [1,2] or computed tomography (CT) fluoroscopy, which allows the physician to deliver treatments precisely. This precision and associated lower complication rates make ablation therapy a preferred alternative for high-risk patient populations such as the chronically ill and aged, who are not candidates for more invasive procedures such as surgical resection, radiotherapy, or chemotherapy[3,4,5]. However, rates of local recurrence after MWA are noted to be higher than hepatic resection. In some studies, image-guided thermal ablation for hepatocellular carcinoma (HCC) has recurrence rates as high as 50%, and image guided thermal ablation for primary lung cancer has up to a 30% recurrence rate, as confirmed on anatomical and functional imaging and/or repeat biopsy[6]. These recurrence rates are much higher than the reported 5-10% recurrence rates with resection or radiotherapy[7]. Figure 1.1 illustrates the clinical goal for most MWA procedures, which is to ablate the entire tumor with an additional 5-10 mm margin along the entire circumference of the tumor to account for any residual cancerous cells that cannot be detected via imaging [8]. Nevertheless, in some areas where MWA is used to treat primary disease, such as the kidney, there are known risks for intraoperative complications that can lead to interruption and incomplete treatment [9].

Figure 1.1: Illustration of the clinical goal for most MWA procedures ,which is to ablate the entire tumor with an additional 5-10 mm margin along the entire circumference of the tumor

Incomplete treatment implies that the attempted ablation margin was not successfully achieved during the treatment. Data review on over 64 MWA lung cancer treatment cases performed by our research group at Rhode Island Hospital between 2011 and 2015 suggests a correlation between recurrence and lack of specificity in margin control. Furthermore, a potential source of incomplete treatment may be the variability for MWA procedures. I hypothesize that treatment variability can be explained through improved models and measurements of important physical characteristics during MWA.

From the results of a pilot study performed by our group it is suggested that the vendor provided predictive planning tools are not sufficient for predicting treatment margins for all MWA treatments[10]. Currently, planning for MWA is done with vendor specification diagrams that provide estimates of expected ablation treatment region size as derived from experimental measurements in non-perfused animal tissue.

This approach ignores the effects of tissue perfusion, tumor type and location, and the influence of surrounding anatomy present in actual clinical procedures. Furthermore, the use of 2D ablation zone predictions on 3D anatomy places a considerable burden on the physician's spatial treatment planning skill, and treatment accuracy may be skewed by physician experience. When used for patient specific planning, this leads to inadequate predictions of the treatment coverage. In preliminary work, we showed that such predictions have an average proportional error of 60% in total volume across 20 clinical review cases[11]. To date, planning and intraoperative guidance for MWA remains highly subjective and dependent on individual physician clinical acumen, experience, and understanding of the engineering systems involved. The development of principled computational modeling tools for MWA will allow physicians to execute more complex procedures in shorter times and improve patient safety and treatment accuracy [12].

Biophysical models of tissue heating have been extensively employed for guiding the design and optimization of thermal ablation devices and treatment parameters (e.g. applied power levels, treatment time, single vs. multiple applicators)[13]. These modeling approaches have been extended and adapted for planning ablation procedures. Fuentes et al. used finite element models (FEM) informed by magnetic resonance imaging (MRI) datasets to compute current density and transient temperature profiles for radiofrequency ablation (RFA) planning[14]. Their study used a range of physically realistic blood perfusion parameters in a computer simulation to predict ablation lesions measured *in vitro* in perfused bovine liver models. Their platform has potential for pre-operative evaluation of ablation margin assessment

within tissue (via simulation) with idea of creating a treatment planning tool.

Nevertheless, their developed platform cannot predict MWA treatment outcomes due to the difference in electromagnetic power deposition, heating pattern, and duration of heating between RFA and MWA. Zhai et al. proposed a platform for preoperative surgery planning for percutaneous hepatic MWA that uses an iterative technique for necrosis field simulation and 3D necrosis zone reconstruction [15]. This method has the potential to be useful in assisting clinicians with pre-operatively assessment of insertion trajectory for MWA applicators; however, it had limited accuracy for predicting the size of the ablation zone when compared to post treatment evaluation.

The data presented in this manuscript will aid in developing ablation treatment planning and guidance tools for accurate and precise treatment delivery. Chapter 2 will be a review of MWA, highlighting established key concepts in the context of modeling and treatment planning. Chapter 3 will focus on presenting a method and results for building and validating a model for simulating MWA procedures for a clinically used system (in which the geometry and physical parameters are provided). Chapter 4 will present data on investigating the variability in the physical parameters incorporated in MWA treatments. While computational models afford the flexibility for including detailed tissue anatomy and heterogeneity, a balance between model complexity, accuracy, and required computational resources must be struck for practical clinical application. Investigating the most important contributing physical factors that affect MWA treatments via simulations may potentially provide guidelines for the level of detail needed for patient-specific modeling of MWA procedures. Chapter 5 will discuss a methodology for potentially extending these simulation methods

to other devices with unknown geometry by investigating alternative techniques for providing thermal spatial estimates during MWA procedure. This will involve measuring how the tissue absorbs energy during MWA procedures for that particular antenna.

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CHAPTER 2

MICROWAVE ABLATION REVIEW

Microwave Ablation Cancer Treatments

Microwave thermal ablation (MWA) treatment is an important, minimally invasive alternative to surgical resection. These procedures involve the use of a microwave antenna (or an array of antennas) to deliver energy to raise tissue temperature above a thermal threshold to induce irreversible cell damage. Figure 2.1 illustrates a typical MWA procedure within tissue using a single applicator.

Commonly used clinical MWA systems operate at frequencies of 2450 MHz and 915 MHz . Image-guided percutaneous MWA treatments can be guided by intraoperative ultrasound or computed tomography (CT) fluoroscopy, which allows the physician to deliver treatments precisely[1,2]. As such, image-guided MWA has received substantial attention for the treatment of cancer in the past decade that is performed in combination with other therapies (radiation therapy) or used as an alternative to other more invasive procedures (surgical resection). There has been increasing interest in improving the efficacy and specificity of MWA through improving energy delivery and application techniques in this domain. This review chapter outlines clinical percutaneous MWA technology detailing concepts related to thermal dosimetry, the physics of microwave heating, modeling of MWA in tissue, and future goals of treatment planning in the context of image-guided MWA procedures.

(A)

(B)

Figure 2.1: (A) Schematic and (B) gross specimen of a thermal ablation procedure on liver parenchyma. A central zone of high temperatures (greater than 60°C , can exceed 100°C) is created in tissue immediately around the applicator, and it is surrounded by more peripheral zones of lower tissue heating (Figure originally produced by [3]).

Thermal Dosimetry

Thermal dosimetry is a concept that relates and parameterizes thresholds for thermal damage into other contributing factors that can influence the damage done to tissue. There are basic principles that govern the relationships between thermal exposure, including temperature and time of exposure. In addition, there are thermal damage factors influencing the time-temperature-damage relationships for thermal damage. Thresholds for thermal damage for a range of tissues, and their relationship with temperature-time were derived from cell survival studies[4].

Cell Survival Studies

Numerous in vitro studies show that the rate of cell killing during exposure to heat is exponential and dependent on the temperature and length of exposure. Figure 2.2 (A) shows examples of cell survival curves of Chinese hamster ovary (CHO) generated by Dewey *et al*[5]. Figure 2.2 (B) shows cell survival curves of human

melanoma tumor cell line (HTB-66) [6]. Both curves cover a range from 42–45 °C and the heating times were up to approximately 5 hours.

Figure 2.2: Survival of Chinese hamster ovary (CHO) cells over a range of temperatures (A; Data taken from Dewey *et al* [5]). Survival of human melanoma cells heated over a range of temperatures. (Figure originally produced by Roizin-Towle and Pirro [6].)

These survival curves typically have a shoulder. This shoulder region is important, because it is evidence that shows there is a threshold for thermal damage to cells.

From this study it can be seen that the width of the shoulder region varies with cell line, and is dependent upon temperature. After the initial temperature-time threshold is reached, cytotoxicity starts to occur, and the rate of cell killing begins to have an exponential dependence on temperature. For this study, there is little cytotoxicity for up to 5 hours of heating at 42 °C. At 42.5 °C, however, cell death was achieved after 5 hours of heating. The hamster ovary and human melanoma cell lines showed a reduction in slope of the cytotoxicity curve after 4 hours of heating at 42.5 °C and 3 hours of heating at 43 °C, respectively. This phenomenon is explained by the acquired resistance to heating or thermotolerance.

Sapareto-Dewey Thermal Dose Model

With the rapid development of clinical hyperthermia for the treatment of cancer either alone or in conjunction with other modalities, a common way of comparing the heating effect between thermal therapies for an intended isothermal effect was needed. In addition, the non-uniform heating during the procedure caused spatial variations in temperature that need to be quantified and compared. During a typical hyperthermia treatment temperatures can vary from 37°C – 43 °C within the same tumor [4,6,7,8]. Moreover, clinical temperatures could be even higher in some cases, and the duration of treatment and the frequency can also vary.

A method for converting one temperature-time combination to another was presented by Sapareto and Dewey *et al* [9]. The method they proposed, converted temperature-time data into an equivalent number of minutes at 43 °C. From their study the choice of 43°C as the index temperature was based on the temperature needed for several cell lines to break. Equation 2.1 shows the temperature-time conversation equation;

$$CEM_{43^{\circ}C} = \sum_{t=0}^{t^{final}} \Delta t R^{43-T} \quad (2.1)$$

where CEM 43°C is the cumulative number of equivalent minutes at 43°C, t is the time interval (minutes), T is the average temperature during time interval t, and R is the number of minutes needed to compensate for a 1°C temperature change either above or below the breakpoint (either 0.5 above 43 °C or 0.25 below 43°C). The equation shows that if there is a temporal variation in the temperature of specific tissue, the time at each temperature must be determined, and the CEM 43°C is then summed over all time intervals. Consequently, the CEM 43°C is more representative of the entire

history of thermal exposure. It is important to note that the determination of R is based on previously presented experimental data such as Figure 2.2.

A primary advantage of using the CEM 43°C dosimetric unit is that it is not necessary to determine thresholds for damage of a particular tissue at every possible temperature-time combination. If thermal damage is well defined at one temperature-time combination, the results can be extrapolated to define an isoeffect line that will establish exposure time boundaries for that specific tissue at any temperature.

However, there may be extrapolation inaccuracies using the CEM 43°C system at relatively low and high temperatures (below 40°C or above 60°C) due to insufficient data at these temperatures. Additionally, this method is based on the assumption that the R values for the CEM 43°C are constant across a range of tissues. Although a reasonable assumption, more experimental work needs to be done when modeling specific temperature-time effects across different tissues [10]. Moreover, Sapareto et al. and Li et al. suggested that the cellular development of thermotolerance is what causes the “step down” effect in which exposure to temperatures above 43°C prevents the development of thermotolerance, thus allowing faster cell killing after subsequent exposure to temperatures below 43 °C[11,12] This phenomenon affects the calculation of accumulated dose. The development of thermal tolerance by cells also makes it difficult to use CEM 43 °C to calculate total thermal dose when multiple heat doses are applied.

Arrhenius Thermal Damage Model

Many authors in the thermal therapy domain have used curves, derived from cell survival data noted in the previous section, to determine the heat of inactivation of cells. This approach is called the Arrhenius analysis approach. This is done by plotting the rate of cell killing ($1/D_0$). The parameter, D_0 , is defined as the number of minutes to reduce survival by 63% ($1/e$) on the exponential portion of the survival curve [13]. An example of such a curve is depicted in Figure 2.3. The heat of inactivation, K (kcal/mole), is calculated using Equation 2.2

$$K = Ae^{(-E/RT)} \quad (2.2)$$

Figure 2.3: Comparison of Arrhenius plots for a series of rodent and human cell lines, derived from cell survival curve data. The Arrhenius plots consider the rate of cell killing at an exponential rate. The rodent cell lines included in this figure are CHO, AD-%, C3H 10T-1/2; Human cell lines are KB7, MIA-PACA2, glioblastoma, WiDR, AG-1522, HTB66, HTB72, KB8 and A549. (Data from a paper by Roizin-Towle and Pirro [6])

where E is the heat of inactivation (kcal/mole), A is a constant that is assumed to be unchanged over the temperature range studied, R is the molar gas constant (1.987×10^{-3} Kcal/mole-K) and T is the absolute temperature in K.

These Arrhenius curves typically have a major change in their slope at a point (the break point) in which the slope tends to be steeper below the break than above it. The inactivation energy for the temperature range above the break point is typically around 120–150 kcal/mole. This energy range is consistent with the heat of inactivation of proteins and enzymes [7]. The change in slope of the Arrhenius plot below the breakpoint is generally thought to be related to the development of acquired thermotolerance during heating[8]. When heating is delivered at temperatures above the breakpoint, thermotolerance does not occur *during* the heating period. It should be kept in mind, however, that thermotolerance does develop *after* heating at temperatures above and below the breakpoint. It can be seen from the Arrhenius plots that human cells have a higher breakpoint than rodent cells and therefore develop thermotolerance at a higher temperature. These characteristic differences in the Arrhenius plot between human and rodent cells indicate that human cells are more thermally resistant than rodent cells. This type of thermal sensitivity analysis is necessary in understanding the relationship between applied thermal energy and biochemical effects.

Arrhenius data have also been derived from a large number of *invivo* studies. In this case, the endpoint is usually the time to reach an isoeffect, at a defined temperature. Moritz and Henriques *et al.* and Stoll and Greene *et al.* performed such studies they analyzed time–temperature relationships needed to create skin burn effects in human and pig skin, over a wide range of temperatures(Figure 2.4 and Table 2.1) [14,15]

Figure 2.4: Time–temperature combinations to achieve varying thresholds of thermal damage to human skin. Data obtained from Moritz and Henriques and Stoll and Greene[14,15].

Table 2.1: Activation energies calculated from double exponential fits to data from Figure 2.4. The breakpoints were 47 °C for man and pig and 42.58 °C for mouse.

Species	Temperature range (°C)	Activation energy (kcal/mole)
Man	44–47	182.2
	47–60	95.78
Pig	44–47	150.75
	48–56	106.38
Mouse	41.5–42.5	273.89
	42.5–44.5	138.26

The relative resistance of human tissues to thermal damage is significant when it comes to relating thermal exposure to thermal damage from the skin burn data shown above. Nevertheless, factors, such as time and temperature, can be controlled during clinical thermal energy delivery methods such as hyperthermia. Temperature and time greatly contribute to the rate of cell killing. This fact has led groups to investigate methods of normalizing data of heating at different temperatures for different periods of time to a common unit that would allow for comparison of different heating techniques (i.e. Sapareto and Dewey model)

Physics of Microwave Heating

Governing Physical Equations

The equations that govern microwave heating of a material are Maxwell's equations, which govern the propagation of the microwave radiation, and the forced heat equation, which governs the absorption and diffusion of heat by the material. If the material is assumed to be homogeneous, isotropic, and ohmic, (that is the current and the displacement current, D , are proportional to the electric field, E ,) and that the magnetic flux density, B , is proportional to the magnetic field strength, H , then Maxwell's equations of electromagnetism are given by

$$\begin{aligned}\nabla \cdot D &= \nabla \cdot (\epsilon E) = \rho & \nabla \cdot B &= \nabla \cdot (\mu H) = 0 \\ \nabla \times E &= -\frac{\partial}{\partial t}(\mu H) & \nabla \times H &= \frac{\partial}{\partial t}(\epsilon E) + \sigma E\end{aligned}\tag{2.3}$$

where σ (S/m) is the electrical conductivity, ϵ (1) is the electrical permittivity, and μ (H/m) is the magnetic permeability[16,17]. In general, all the material properties are temperature-dependent. For the heating of a three dimensional system, the electromagnetic wave propagation described in equation set 2.3 are functions of the spatial coordinate, x, y, z , and time with the net free charge, ρ , being zero[18]. As a result, Maxwell's equations reduce to

$$\nabla \times \mu_r^{-1}(\nabla \times \mathbf{E}) - k_0^2 \left(\epsilon_r - \frac{j\sigma}{\omega\epsilon_0} \right) \mathbf{E} = \mathbf{0}\tag{2.4}$$

Where, μ_r is the relative permeability ratio, $\mathbf{E}$ is the electric field, k_0 is the propagation constant in free-space, ϵ_r is the relative permittivity ratio, σ is the electrical conductivity, ϵ_0 is the permittivity in free-space, and ω is the frequency in radians/second. As described earlier, several of the material parameters in equation 2.4

are dynamic with temperature. Thus this equation is temperature-dependent and is coupled with the forced heat transfer equation:

$$\rho c(T) \frac{\partial T}{\partial t} = k(T) \nabla^2 T + Q \quad (2.5)$$

where, k (W/m-K) is the thermal conductivity, c (J/kg-K) is the specific heat, Q (W/m³) is the heat deposition term, and ρ (kg/m³) is the density and is often assumed to be constant. The first term on the right hand side of equation 2.5 is known as the thermal conductive term. This term describes the thermal conductance from local thermal gradients that result from physical interactions between particles of different temperatures within the medium of interest. The second term describes resultant thermal energy deposited via electromagnetic field propagation from a microwave energy source. [19].

When investigating the energy transmitted via an electromagnetic field, Poynting's theorem can be used. Poynting's theorem describes conservation of energy in a volume contained within a closed surface and can be expressed as

$$\frac{\partial}{\partial t} \int_V (\epsilon E \cdot E + \mu_0 H \cdot H + w_{cp}) dV + \int_S (E \times H) \cdot dS = 0 \quad (2.6)$$

The volume integral in equation 2.6 has terms representing the instantaneous energy stored in the electric field, in the magnetic field, and that possessed by charged particles, and as such shows the instantaneous total energy within the enclosed volume. The Poynting vector term $(E \times H)$, represents the power density, thereby describing the surface integral as the instantaneous total power passing out through the closed surface. Consequently, equation 2.6 shows that the time and rate of change of the total energy inside the volume (V) is equal to the total power passing through the

surface (S). Since the time averaged energy stored in the electric and magnetic fields is zero for sinusoidal fields, then from equation 2.6 it follows that

$$-\int_S \langle P \rangle \cdot dS = \int_V \langle P_{cp} \rangle dV \quad (2.7)$$

Where the total average power ($-P = -E \times H$) passing into V through S, and P_{cp} is the total average power transferred to the charged particles within V. For steady state-sinusoidal fields

$$\langle P_{cp} \rangle = Q = \sigma \frac{|E_0|^2}{2} \quad (2.8)$$

The absorption of the power transferred, the specific absorption rate (SAR), is described by:

$$SAR = \frac{d}{dt} \left[\frac{dW}{dm} \right] = \frac{d}{dt} \left[\frac{dW}{\rho dV} \right] \quad (2.9)$$

SAR (W/kg) is defined as the time derivate of the increment energy (dW) absorbed by or dissipated in incremental mass (dm) contained within a volume element (dV) of a medium of density ρ . From equation 2.8, the whole region SAR and local SAR can be calculated with the following expressions[20]

$$SAR_{wr} = \int_V \frac{\langle P_{cp} \rangle dV}{M} = \frac{Q dV}{M} \quad (2.10)$$

$$SAR_{local} = \frac{Q}{\rho} = \sigma \frac{|E_0|^2}{2\rho}$$

Dielectric Properties of Biological Tissue

The transmission of electromagnetic energy is determined by the dielectric permittivity and magnetic permeability of the media in which the waves propagate. As such, the propagation of electromagnetic energy through biological tissue is an adaptation of the principles discussed in equations 2.4 and 2.5. The magnetic permeability of biological tissues is approximately the same as vacuum. The dielectric

permittivity contains both a real and imaginary component, which are used to define the more common terms: relative permittivity and conductivity (see equation 2.5).

Relative permittivity, ϵ_r , is the real part of the complex permittivity and quantifies the ability to store electrical energy relative to vacuum. It is frequently referred to as dielectric constant. However, since permittivity is quite variable depending on frequency, temperature and other factors in biological tissues, the term relative permittivity is a more accurate expression.

The effective conductivity, σ , of a material is defined from the imaginary part of the complex permittivity and is used to describe how well a material absorbs microwave energy. It is important to note that effective conductivity describes contributions from moving charges (electrical current) and time-varying electric fields (displacement current), specifically the rotation of dipoles in the material as they attempt to align with an alternating electric field [21]. The latter contribution dominates for most biological tissues in the microwave spectrum. This rotation of dipoles generates heat inside of lossy materials such as biological tissues, which will be described next.

Interactions of Microwaves within Tissue

The most significant effect of an electromagnetic field applied to biological tissue is conversion of microwave energy to thermal energy. Heat transfer in tissue can be quantified using a variation of the forced heat equation (equation 2.5), known as the bioheat equation [22].

$$\rho C_p \frac{\partial T}{\partial t} = \nabla \cdot (k \nabla T) + Q + Q_{bio} \quad (2.11)$$

As previously discussed, Q is the applied heat rate via microwave to heat energy conversion, which is dictated by the effective conductivity. More specifically, the effective conductivity dictates how efficiently microwave energy is converted to heat, and is dependent primarily on the type of tissue, its water content, and the frequency of the applied field. The water content within biological tissue is the greatest constituent to the heating effect. The atomic structure of water produces an electric dipole moment. When an electromagnetic field is applied water molecules continually rotate to align with the applied field. Kinetic energy increase as a result of this continuous realignment, thus elevating temperature. Consequently, conversion of microwave energy to thermal energy is directly correlated the amount of water within the region of interest [23].

Microwave field penetration into a tissue medium is also dependent on the dielectric properties of the tissue. The penetration depth, d (m), of the electromagnetic field of a plane wave travelling in a homogenous, isotropic medium, is quantified as the distance required for the electric field to attenuate to $1/e$ (approximately 37%) of its initial value[20]. More specifically, it is quantified by the relation

$$d = \frac{1}{\omega \sqrt{\mu \epsilon} \left\{ \frac{1}{2} \sqrt{1 + (\sigma / \omega \epsilon)^2} - 1 \right\}^{\frac{1}{2}}} \quad (2.12)$$

where ω is angular frequency (rad/s) which is equal to $2 \pi f$, where f is frequency (Hz), μ is magnetic permeability (H /m), and ϵ is dielectric permittivity (F /m).

Assuming good dielectric ($[\sigma / \omega \epsilon]^2 \ll 1$) tissue (i.e. liver, kidney, and muscle) the penetration depth can be approximated with the more simplified relation

$$d \gg \frac{2}{\sigma} \sqrt{\frac{\epsilon}{\mu}} \quad (2.13)$$

which is a good first assumption for most tissues and microwave ablation frequencies. It is important to remember that penetration depth is inversely related to conductivity, but heating rate is proportional to conductivity. Therefore, deeper penetration occurs at the expense of slower heating. Energy conservation through the conversion of microwave energy to heat explains this, and is the major cause of field attenuation. Consequently, balancing penetration heat production and penetration depth is important for analyzing the most appropriate frequencies for specific applications. Higher frequencies have faster heating rates but shallower field penetration which is favorable for procedures that desire fast controlled heating such as thermal ablation [24]. Lower frequencies have slower heating rates but deeper field penetration which may be more desirable heating applications such as regional hyperthermia of larger volumes [25].

It is important to note that much of the energy radiated by microwave antennas in lossy media such, as biological tissues, is absorbed near the antenna (also called the Fresnel zone). As such, the radiated energy may not propagate as a plane wave. In this case, the previously mentioned calculations of penetration depth can only be viewed as approximations. This is where simulations of electromagnetic and thermal interactions can provide more accurate temporal heating estimates[26]. Moreover, coupled electromagnetic-thermal simulations may be more enlightening than simple calculations considering only electromagnetic penetration. Curto et al. assessed the differences in MWA at 915 MHz and 2.45 GHz (the most common clinically used frequencies) and corroborated their simulation findings with experiments[27]. In this study 2.45 GHz yield larger ablation zone due to greater power deposition in

proximity to the antenna (for 5-10 minute heating durations). In addition, Luyen et al. showed faster heating rates with MWA antennas operating at 10.0 GHz antenna when compared to a 1.9 GHz antenna, suggesting that higher frequencies may offer the advantage of smaller antenna size [28]. However, at 10 GHz there was a slightly delayed onset of heating farther from the antenna, suggesting that heat conduction plays a greater role at higher microwave frequencies in achieving a comparably sized ablation zone. Accurate modeling techniques are becoming increasingly important for analyzing the relationship among antenna design, power deposition, and heating efficiency of MWA.

Modeling Microwave Ablation in Tissue

Modeling Framework

There are several different modeling approaches that have been discussed in the literature for simulating MWA procedures for the purpose of design and optimization of MWA devices [29-33]. Commonly used techniques include the finite element method (FEM), finite difference time domain, and the method of moments. Nevertheless, all approaches generate power deposition and heat dissipation solutions within the region of interest, and some incorporate potential confounders simultaneously. For all modeling methods, a mathematical framework that can simulate the two important physical processes in ablation are: 1) how energy radiated from the ablation device is deposited within the nearby tissue, and 2) how heat is then distributed within the tissue to cause a thermal damage effect. Figure 2.5 illustrates a comprehensive theoretical modeling framework for microwave tissue ablation [34].

Figure 2.5: Flow of operations for a comprehensive theoretical model for microwave tissue ablation. The treatment may be terminated based on a thermal coverage of a pre-specified region or after a given treatment time.

Developing a MWA model involves integrating a prior knowledge of the physical characteristics of the tissue of interest into the solution. The requisite differential equations discussed previously are governed by the electromagnetic and thermal tissue properties of the target and their dependence on temperature [35,36], and the input power source of the ablation device at a specified frequency. Moreover, boundary conditions are also established within the simulation. As stated in the previous section, several terms in Maxwell's equations and the bioheat transfer equation implicitly depend on the relative permittivity, electric conductivity, thermal conductivity, specific heat, and other properties at the material interface between different media [37,38,39]. For every material boundary within the simulation a stable solution is generated, i.e. from the port in which the microwave signal is sent, through main conductor, and all the way to the medium in which the antenna is immersed. As

the complexity of the simulation increases with the added variables, computational time increases as well. Furthermore, each variable also introduces additional uncertainty that must be carefully managed to preserve the accuracy of the simulation. Figure 2.6 is an illustration of a modeling geometry used for simulating a MWA experiment.

Figure 2.6: An example MWA simulation geometry within liver generic dipole antenna. The presented geometry is and 2D axisymmetric model created within Comsol Multiphysics finite element software package[34].

Input Parameters

Table 2.2 provides a list of some of typical thermal and electrical inputs used for a microwave procedure performed on a bovine liver model. Liver animal models are commonly for simulation and validation of MWA procedures on patients in the context of evaluating antenna performance [40,41] However, as previously discussed there is evidence of a dynamic temperature dependency of several thermal and electrical properties of tissue during MWA.

Table 2.2. List of static properties used in the homogenous liver simulations

	ϵ (1)	μ	σ (S/m)	κ (W/m*K)	ρ (kg/m ³)	C_p (J/kg*K)
Air	1	1	0	.0257	1.205	1000
Liver/Tumor	ϵ liver	1	σ liver	.564	1038	3400
Dielectric	2.1	1	0	0.5	1050	3600
Copper	1	1	5.998×10^7	400	8700	385

The dynamic nature of dielectric tissue properties is evident from studies that have measured these properties during MWA experiments within liver and other tissue across a broad range of temperatures[42]. For example, temperature dependent measurements dielectric properties of liver tissue at 2450 MHz were performed by Ji and Brace *et al.* [43]. Figure 2.7 illustrates the measured results from this study.

Figure 2.7: Experimental results (dots) of relative permittivity and conductivity versus temperature during microwave ablation at 2450 MHz. Also shown are the best-fit sigmoidal curves (solid lines), along with the upper and lower envelopes (dashed lines) used for numerical simulation. Figure originally produced by Ji and Brace [43].

Figure 2.7 shows tissue dielectric properties changing slowly below 70 °C as observed in previous studies by Lazebnik *et al* Stauffer *et al*[44,45]. However, a rapid decrease

in both relative permittivity and conductivity is shown from 70 °C - 100 °C. At above 100 °C, tissue relative permittivity and conductivity drops to values at about 10% of those at room temperature and remains there. From these measurements, mathematical parameterizations (based on best fit sigmoidal curves) have been derived to be incorporated as inputs for modeling MWA within tissue.

For thermal conductivity, there are several approximation techniques that have been employed in modeling MWA within tissue. For example, linear approximation are commonly used to reflect increases in thermal conductivity from the starting reference temperature (37 °C) up to temperatures of 100°C[46]. Determination of the slope of increase is based on experimental data previously reported from experiments within the tissue of interest. Similarly, temperature dependent specific heat capacity of tissue is implemented using the parameterization derived from previously reported data. For specific heat, it is important that the parameterization reflects steep drops at temperatures above 90 °C that corresponds to the loss of tissue water[47].

Boundary Conditions

First-order electromagnetic scattering boundary conditions are often used within the simulated MWA medium. These are governed by the PDEs described earlier. Moreover, thermal insulation boundary condition can also be applied at the model as well. In addition, some MWA procedures use cooling systems to avoid excessive charring during MWA procedures within tissue. Often either fixed temperature boundary conditions or a convective cooling boundary condition is placed along the shaft of the antenna to model the cooling. A similar approach has been used for modeling blood vessel cooling when modeling *in vivo* MWA close to a vasculature.

Model Output

Several metrics have been used as output metrics for MWA zone evaluation. As previously discussed, Arrhenius tissue damage model has been used to estimate extents of the ablation zones. Appropriate isotherms are often used as a first approximation to evaluate model output accuracy. Figure 2.8 is an example result of a MWA prediction of a procedure performed within the liver.

Figure 2.8: Comparison of (a) ablation zone in created *ex vivo* bovine liver and (b) theoretically predicted temperature profiles using comprehensive theoretical simulation including dynamic changes in tissue properties. The 60 °C isotherm is in good agreement with visible boundary of coagulated tissue. (Figure original produced by [48])

Treatment Planning for Microwave Ablation

There are groups that have developed simple tools for planning microwave ablation procedures; however these are all limited in clinical utility as they provide little more than visualizations of vendor specified geometric guides relative to the patient anatomy near the antenna. Although this approach does provide some 3D information about likely treatment zone margins near the target, these estimates are known to be inaccurate in clinical situations. Figure 2.9 shows an illustration of these commonly used clinical treatment planning tools

Figure 2.9. Example of current geometric planning available for percutaneous microwave thermal ablation from the operator's manual of Perseon and NeuWave ablation systems.

Recently, there has been renewed interest in the development of accurate modeling techniques for predictive planning of MWA and other thermal therapies. Such models may help physicians in selecting treatment parameters (e.g. number of antennas, applied power levels, insertion paths) that maximize the likelihood of a desired treatment outcome. Predictive modeling tools are of particular clinical relevance due to the shortage of practical techniques for intra-operative monitoring of thermal damage. There have been attempts for developing treatment planning systems for thermal therapies. Challenges with the use of biophysical models for treatment planning include lack of knowledge of patient-specific tissue biophysical properties and clinical impracticality due to computational time constraints.

Imaging data that is collected prior to and during ablation treatments has strong potential to inform biophysical models for treatment planning[49]. Computational models guided by imaging data offer the ability to determine the impact of tissue heterogeneity, blood perfusion, source/applicator positioning relative to the target, vascular cooling, and other parameters that can affect the size and shape of the

treatment effect region. A novel treatment planning system for high frequency ultrasound (HIFU) that uses this type of framework has been developed by Amin *et al* [50]. Their group used pre-treatment imaging (CT, MRI or ultrasound) for the segmentation of the target and surrounding anatomy. From these segmentations, 3D anatomical models of the target and overlaying tissues were developed. That information was then used for ultrasound simulation of beam intensity distribution and HIFU temperature profiles. Figure 2.10 is an illustration of this inputs and results of this platform.

Figure 2.10: (Upper left) Screen capture of the tools for DICOM image segmentation , (lower left) tissue model simulation, (right) and ultrasound beam simulation. (Original figure in [50]).

There have been several proposed systems for MWA pre-procedural planning [51,52]. Similar to the illustration in Figure 2.11, these MWA planning systems allow for 2D and 3D visualization of antenna position with respect to the target volume and surrounding anatomy. This may provide some additional

Figure 2.11: 3D visualization of applicator placement with respect to tumor location and surrounding anatomy

information that can be used by clinicians when discussing treatment approach, of which is not available in current planning standards. Although valid approaches, the referenced platforms lack imaging datasets as the basis for informing their MWA models of zone extents.

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CHAPTER 3

Manuscript-I

PROGRESS TOWARDS DEVELOPMENT OF A TREATMENT PLANNING PLATFORM FOR SIMULATING 915 MHz MICROWAVE ABLATION

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Introduction

Microwave ablation (MWA) is a minimally-invasive modality that is playing an increasingly vital role in the treatment of cancer and benign disease. Over the past decade, MWA has been adopted as an alternative form of treatment for several primary and secondary tumor sites in liver ¹, lung ², kidney ³, and bone ⁴. These procedures require the use of a microwave antenna (also referred to as the ablation applicator) to deliver energy to raise the temperature of tissue above a threshold where irreversible cell damage occurs. Tissue injury following thermal exposure is a function of the time-temperature history during heating ⁵. Other energy modalities in clinical use for tumor ablation include radiofrequency current, lasers, ultrasound, cryoablation, and non-thermal irreversible electroporation. Although MWA has its advantages as a cancer treatment, there are still many unknowns with regard to the energy dissipation from the antenna, as well as biophysical effects in tissue adjacent to the antenna and at the treatment margin.

Mathematical models of the processes that occur during MWA have been employed during the design and optimization of devices for MWA ^{6, 7, 8, 9, 10}. These models use numerical techniques to solve the partial differential equations which govern electromagnetic propagation, power deposition, and bioheat transfer ^{11, 12}. Commonly used numerical techniques for solution of these equations include the finite element method (FEM), finite difference time domain (FDTD), and the method of moments (MoM). Analytical methods for approximating microwave power deposition and bioheat transfer have also been reported ¹³. Recently, there has been renewed interest in the development of more accurate modeling techniques for predictive

planning of ablation treatments. Such models may help physicians to choose the treatment parameters (e.g. number of antennas, applied power levels, antenna insertion paths) which maximize the likelihood of a desired treatment outcome. Predictive modeling tools are of particular clinical relevance due to the shortage of practical techniques for intra-operative monitoring of thermal damage. While MRI does provide a means for volumetric thermometry, at present the added cost and technical complexity make it impractical for routine clinical use^{14, 15}.

Microwave systems and antenna designs for thermal ablation have evolved from systems originally designed for interstitial hyperthermia (moderate heating of targeted tissue for $\sim 40 < T < 46$ °C) as an adjuvant to radiation/chemotherapy¹⁶. Currently, clinical ablation systems operate at frequencies of 915 MHz and 2.45 GHz. Computational models of interstitial microwave hyperthermia devices, which account for electromagnetic energy deposition and bioheat transfer at temperatures slightly above core temperature, have been extended for modeling of the higher temperatures required in thermal ablation. Recent accomplishments include: (a) measurement and incorporation of dynamic changes in tissue dielectric properties as a function of tissue temperature within computer models^{17,18}, (b) accounting for electrical and thermal changes in the tissue properties due to the movement and phase change of water during ablation^{19, 20, 21}, (c) modeling the temperature-dependent changes in blood perfusion^{22,23}, and (d) modeling the heat-induced tissue shrinkage²⁴. However, most measurements of the temperature dependence of the electromagnetic properties of tissues in addition to modeling studies have been focused at 2.45 GHz. Most computational models of microwave ablation systems for 915 MHz have assumed

static tissue dielectric properties and energy deposition profiles during ablation^{23, 25, 26,}
²⁷. Furthermore, there are no definitive measurements of the thermal and dielectric properties of tissue residues at temperatures well above 150 °C which occur near the antenna during MWA.

There is a need for improved models to determine the spatiotemporal profile of electromagnetic energy deposition and bioheat transfer during 915 MHz microwave ablation. These models will provide further insight into the dynamics of ablation treatments, and thereby enable improved device and system design. Furthermore, accurate theoretical models have a strong potential for characterizing the thermal dose distribution during ablation, as well as for prospective treatment planning. The objective of this study is to formulate, develop, and experimentally verify a computational modeling platform for simulating microwave ablation with a 915 MHz clinical ablation antenna (Perseon Short Tip (ST) antenna). The impact of dynamic changes in tissue electrical and thermal properties on predicted ablation volume outcome will be investigated. The proposed modeling platform will provide more insight into simulating the biophysical phenomena during 915 MHz microwave ablation.

Methods

Modeling the Physical Processes during Microwave Ablation

During MWA, an antenna is introduced into the target tissue under image guidance, and the induced electric field heats the tissue. As the tissue temperature increases, temperature-dependent electrical and thermal properties of the tissue may

change: (1) impedance matching between the ablation device and the tissue; (2) the pattern of microwave heating by the antenna; and (3) bioheat transfer. At temperatures in excess of 60 °C, tissue desiccation, water vaporization, and shrinkage have a significant impact on the induced temperature profile²⁸.

In this study, we employed the FEM (implemented with COMSOL Multiphysics, v4.4) to simulate MWA with the 915 MHz Perseon ST antenna. First, we assigned values for the material properties of the tissue as well as components of the antenna at the initial temperature. The Helmholtz wave equation was then solved to determine the electric field radiated by the antenna. Next the temperature was determined with Pennes' bioheat equation. Then the material properties were determined at the new temperature. This process was repeated iteratively while reducing the size of the time step until the electric field and temperature converged. Then this process was repeated for steps until reaching the specified duration for the treatment. Equations 3.1 and 3.2 show the two processes in each step.

$$\nabla \times \mu_r^{-1}(\nabla \times \mathbf{E}) - k_0^2 \left(\epsilon_r - \frac{j\sigma}{\omega\epsilon} \right) \mathbf{E} = 0 \quad (3.1)$$

$$\rho C_p \frac{\partial T}{\partial t} = \nabla \cdot (k \nabla T) + \frac{1}{2} \sigma \mathbf{E}^2 + \rho_b C_b \omega_b (T_b - T) \quad (3.2)$$

In (1), μ_r is the relative permeability ratio which is unity for all of the materials in this model, $\mathbf{E}$ [V m⁻¹] is the electric field, k_0 is the propagation constant in free-space, ϵ_r is relative permittivity ratio, σ [S m⁻¹] is electrical conductivity, ϵ_0 [F/m] is the permittivity of free-space, and ω [rad s⁻¹] is angular frequency. In (2), ρ [kg m⁻³] is the density, C_p [J kg⁻¹ °C⁻¹] is the heat capacity at constant pressure for the tissue, T [°C] is the temperature, k [W m⁻¹ °C⁻¹] is the thermal conductivity, ρ_b is the density of the

blood, C_b is the heat capacity at constant pressure for the blood, ω_b [s^{-1}] is the perfusion rate, and T_b is the temperature of blood.

Boundary Conditions and their Significance

A 2D rotationally-symmetric model was employed in this study (see Figure 3.1). A thermal insulating boundary condition and a first-order electromagnetic scattering boundary condition were applied at the outer edges of the model shown in Figure 3.1.

Figure 3.1. Illustration of the model geometry for simulating MWA with the Perseon ST applicator.

The electrical properties of all parts of the applicator were specified in the model, including the highly conductive metallic regions of the applicator (i.e., no perfect electrical conductor regions were assumed). Our measurements indicated approximately 1/3 of the generator power is dissipated within the cables connecting the microwave generator to the antenna. The input power was specified at the antenna port shown at the top of Figure 3.1, allowing for this attenuation. A thermal insulation boundary condition was applied at the outer surface of the model.

To approximate saline cooling of the proximal end of the antenna, the inside metal shaft of the applicator was assigned a fixed temperature boundary condition of

40 °C. Table 3.1 shows a compiled list of the electrical and thermal properties used in the simulation as well as their nominal values at approximately 37 °C.

Table 3.1. Material properties used within FEM simulations

Symbol	Quantity	Nominal Value (37 °C)		
		Liver	Plastic	Metal
<i>Electric Properties</i>				
ϵ_r	dielectric constant	46.8	2.2	1.0
σ	electrical conductivity [S/m]	0.86	0	5.96×10^7
<i>Thermal Properties</i>				
κ	thermal conductivity [W m ⁻¹ °C ⁻¹]	0.52	0.3	400
C_p	specific heat capacity [J kg ⁻¹ °C ⁻¹]	4187	1000	400
ρ	Density [kg m ⁻³]	1000	2200	8900
<i>Perfusion</i>				
ω_b	Perfusion rate [s ⁻¹]	0.0036	N/A	N/A
ρ_b	Blood density [kg m ⁻³]	1025	N/A	N/A
C_b	Blood specific heat [J kg ⁻¹ °C ⁻¹]	N/A	N/A	

Material Property Characterization

We make the approximation that, at any point in time, the material properties of the liver depend only upon the instantaneous temperature. The change in the properties caused by heating is due to chemical reactions including pyrolysis as well as water loss by the tissues¹⁹. Since the simulations do not continue after the microwave power is turned off, the temperature increases monotonically with time.

Several groups have reported experimental measurements of the dielectric properties of liver at 2.45 GHz changing as a result of water loss at elevated temperatures during microwave ablation^{17,18,19}, data are not available at 915 MHz. Ji and Brace¹⁷ employed a best-fit sigmoid of their data to approximate the electrical conductivity and dielectric constant of liver at 2.45 GHz as a function of the local temperature during ablation. We have followed and extend their efforts in this study. Our expression for the electrical conductivity of liver at 915 MHz is a first

approximation to include the effects of the chemical changes in an ablation which cause char and other products at high temperatures where little data for these properties is available. Equations 3.3 and 3.4 show the parameterization for electrical conductivity and relative permittivity used in our simulations. These expressions are approximately a sigmoid, similar to that employed by Ji and Brace¹⁷, with our estimates of the values at the higher temperatures.

$$\sigma(T) = 0.557 - \frac{0.454(T - 82.5)}{88.76} \quad (3.3)$$

$$\varepsilon_r(T) = 26.9 + 23.8 \times \left(1 - \frac{T - 79.5}{9 + |T - 79.5|} \right) \quad (3.4)$$

The parameterization for approximation of the thermal conductivity is also temperature dependent. Thermal conductivity was defined as: 0.526 W m⁻¹ °C⁻¹ at 20 °C, 0.52 W m⁻¹ °C⁻¹ at 50 °C, 0.48 W m⁻¹ °C⁻¹ at 80 °C to, 0.4 W m⁻¹ °C⁻¹ at 100 °C, .37 W m⁻¹ °C⁻¹ at 130 °C, with linear interpolation used to determine values at intermediate temperatures, and 0.36 W m⁻¹ °C⁻¹ at 200 °C allow for the presence of char. This parameterization captures the initial roll-off in the thermal conductivity of liver followed by a plateau caused by the formation of char at high temperatures. Equation 3.5 shows the temperature-dependency of the specific heat capacity used in our simulation. A Gaussian function centered at the boiling point of water is used to simulate the added heat sink associated with tissue water evaporation²¹.

$$C_p(T) = 2500 \left(1 - \frac{1}{1 + e^{0.18 \times (100 - T)}} \right) + 200 + 131576 \left(\frac{e^{-(T - 102)^2}}{50} \right) \quad (3.5)$$

To approximate the effects of microvascular stasis at elevated temperatures, the blood perfusion term was gradually reduced to zero at ablative temperatures²². This approximation was done over a temperature range; where at $T_{low}=50\text{ }^{\circ}\text{C}$, $\omega_b=0.016\text{ s}^{-1}$; at $T = 60\text{ }^{\circ}\text{C}$, $\omega_b = .0157\text{ s}^{-1}$; at $T_{hi}>65\text{ }^{\circ}\text{C}$, $\omega_b = 0$. Linear interpolation with constant extrapolation was used in these simulations.

Ablation Zone Evaluation

The Arrhenius tissue damage model was used to estimate extents of the ablation zone (frequency factor $A = 3.18 \times 10^{55}\text{ s}^{-1}$ and an activation energy $\Delta E = 3.513 \times 10^5\text{ J mol}^{-1}$)^{29, 30}. For the 10-15 min ablation durations considered in this study, ablation zone extents derived from the 50 °C isotherm were compared to calculations using the Arrhenius equation with a frequency factor^{31,32}. The Arrhenius equation was only used as *a posteriori*, and not in determining changes in the electrical and thermal properties of the tissue.

Model Validation and Measurements

Fresh bovine liver was acquired from a local abattoir and transferred to the lab in sealed plastic bags placed on ice. The liver was then warmed to ~37 °C in sealed plastic bags placed within a temperature-controlled bath. Once the liver sample was warmed, the tip of the applicator was precisely inserted 6 cm proximal to the liver surface. Temperature probes (Neoptix, RFX-04-1, Canada) were placed 5 mm, 10 mm, 15 mm and 20 mm radially away from the antenna at 6 cm depth from the proximal liver surface. MWA experiments were performed for 10 and 15 minutes, at applied power levels of 30 and 60 W, respectively. Temperature measurements were recorded for the duration of all ablation experiments.

The peak temperature during microwave ablation (i.e. immediately adjacent to the ablation applicator) is difficult to measure. Most experimental studies report temperature measurements at distances greater than 5 mm radially from the applicator surface^{17,18]}. Temperatures in excess of 120 °C have been experimentally reported²³. Due to the steep electric field gradients in proximity to the antenna, it is not unreasonable to expect temperatures in excess of 200 °C immediately adjacent to the antenna. Nevertheless, to test the hypothesis of maximum temperatures exceeding 200 °C during MWA, we performed experiments in which pieces of solder (with melting points up to 220 °C) were placed in proximity to the MWA antenna during 60 W ablations. The results of this would provide more insight into maximum temperatures reached during MWA and aid simulations.

Post ablation, a fine cut was made axially down the center off the ablated region using the antenna as a guide. Measurement of the ablation zone transverse and axial diameters were recorded from the cut liver samples. In addition, measurements of tissue dielectric properties post ablation were performed at different tissue locations using a high-temperature dielectric measurement probe (HP 85070A) and a vector network analyzer (HP 8753D). Each measurement location represented a region of specific discoloration of the tissue caused by the ablation, including “charred” , “brown”, and “pink”, as well as the “outside region” of non-ablated tissue. In addition, a pre-ablation measurement was taken on the liver surface as a control. For these measurements, the dielectric measurement probe was pressed at the surface of the measurement site. The probe surface was wiped clean with an alcohol wipe, and allowed to dry, in between each dielectric measurement taken in the discussed ablation

regions. Electrical conductivity and permittivity measurements at 915 MHz and 2.45 GHz are reported.

Results

Figure 3.2 shows simulated temperature maps following 60 W ablation for a duration of 5, 10, and 15 min. Figure 3.3 depicts the ablation zone following a 60 W 15 minute experiment in ex vivo bovine liver. Measurements of the ablation zone axial and transverse diameters after 60 W 15 minute ablation experiments and 30 W 10 minute ablation experiments are shown in Table 3.2.

Figure 3.2 Temperature maps(from in vivo simulations) and ablation extents for 60 W ablations at (A) 5 min, (B) 10 min, and (C) 15 min

Figure 3.3 Axial cut of a 60 W 15 ablation on an *ex vivo* liver sample.

Figure 3.4 is a simulation and *ex vivo* experiment comparison plot of the temperature change during ablation at various radial position form the applicator during 15 min, 60 W ablation experiments. The simulated transverse and axial diameters are presented in Table 3.2, as well as the difference from the simulated axial and transverse ablation extents.

Figure 3.4. Temperature rise during in *ex vivo* liver vs radial position at (a) 1 min, (b) 4 min, (c) 8 min, and (d) 15 min, during a 60 W experiment.

Table 3.2. Measurements of the ablation zone axial and transverse diameters after 60 W 15 minute ablation experiments and 30 W 10 minute ablation experiments. The simulated transverse and axial diameters are presented, as well as the percent difference from the simulated axial and transverse ablation extents is shown.

Experiment #	60W 15 min		30 W 10 min	
	<i>Transv. (cm)</i>	<i>Axial (cm)</i>	<i>Transv (cm)</i>	<i>Axial (cm)</i>
1	3.5	4.3	2.4	3.4
2	3.9	4.1	2.8	3.1
3	3.7	4.5	2.3	3.4
4	3.25	3.9	2.5	3.6
5	3.4	4.6	-	-
6	3.4	3.9	-	-
7	3.2	4.0	-	-
8	3.6	4.0	-	-
Average	3.53	4.22	2.5	3.5
Simulation	3.54	4.82	2.58	3.52
%Diff from Experiment	0.43	15.15	3.15	0.57

Figure 3.5. Post ablation position of dielectric measurements. Each region represents discoloration of tissue that occurs during ablation experiments, signifying a chemical change (charred region, brown, pink, and outside)

The average and standard deviation of the measured dielectric constant and electrical conductivity of ablation zone regions depicted in Figure 3.5 are shown in Table 3.3. The results of the maximum MWA temperature experiments showed that pieces of solder with melting points up to 220 °C that were placed in proximity to the device were melted during the course of an ablation. Figure 3.6 shows a log-log plot of the volumetric power absorbed (Q) within liver tissue and radial electric field (E_r) as a

function of radial distance. Figure 3.7 shows the simulated spatial distribution of temperature from simulations made using dynamic (temperature-dependent) tissue properties vs. static properties. Here the 50 °C temperature contour is also shown as an approximation to the extent of the ablation.

Table 3.3. Measurements of the dielectric constant and electrical conductivity of various ablation zone regions at 915 MHz and 2.45 GHz.

Region of excised Liver	915 MHz		2450 MHz	
	ϵ_r	σ [S/m]	ϵ_r	σ [S/m]
Liver Surface (Pre-Ablation)	36.96 ± 3.20	0.78 ± 0.06	35.37 ± 3.36	1.13 ± 0.07
Outside Region	34.41 ± 1.28	0.80 ± 0.05	32.50 ± 1.43	1.17 ± 0.12
Pink	27.94 ± 1.28	0.68 ± 0.05	26.32 ± 2.03	0.98 ± 0.13
Brown	16.47 ± 11.31	0.36 ± 6.06	15.83 ± 10.52	0.53 ± 0.46
Charred	1.58 ± 0.44	0.01 ± 0.01	1.58 ± 0.36	0.02 ± 0.01

Figure 3.6. Radial plots of (A) Q and (B) E_r at the onset of the treatment, 5 min, 10 min, and 15 min on logarithmic axes. These data were gathered from an in vivo simulation.

Figure 3.7. Simulations of 60W 15 minute treatments of perfused liver using shot-tip applicator. Simulated spatial temperature outputs from the model using(a) dynamic properties and (b) static properties, with 50 °C temperature contour overlaid to approximate the extent of ablation zone.

Discussion

The objective of this study was to formulate, develop, and experimentally verify a computational modeling platform for simulating MWA with a clinical 915 MHz ablation system. To accomplish this, the impact of dynamic changes in tissue electrical and thermal properties on transient temperature profiles and predicted ablation volume outcome were investigated. Results from computational models were compared with data from experiments in *ex vivo* tissue. Modeling results were used to analyze evolution of the energy deposition profile and ablation zone during heating.

The *in vivo* 60 W simulation ablation extents, depicted in Figure 3.2 by the 50 °C isothermal contour, show agreement with the estimates of the ablation zone made using the Arrhenius thermal damage model. Other studies have made similar comparisons between simulation and experimentally observed ablation extents in the temperature range of 50 – 52 °C which are also in agreement with thermal dose metrics for several tissue types^{32, 33, 34}. The measurements of the ablation zones for the

60 W 15 minute and 30 W 10 minute *ex vivo* experiments reported in Table 3.2 show good agreement with the simulated ablation extent. Specifically, 30 W simulated axial length and transverse ablation diameter were both within 1 mm when compared to the experimentally measured ablation extents. Furthermore, the 60 W simulation axial length and transverse ablation diameter were within 2.5 mm and 1 mm respectively when compared to the measurements. It is important to note that for all *ex vivo* experiments the sharp cut off in the charring along the central axis, due to the applicator cooling system seen in Fig 3.2, is also seen in the associated simulation. As expected, the *in-vivo* simulation shown in Figure 3.2 has a smaller ablation zone when compared to the *ex vivo* simulation because of heat dissipation via perfusion. These results suggest that simplified computational models, such as the one used in this study, have potential for predicting ablation zone dimensions.

Figure 3.4 depicts temperature change from the starting temperature measured by fiber optic probes placed at 5, 10, 15, and 20 mm from the antenna, compared to the simulated temperature change at the same radial positions. In general, the experimentally measured radial temperature profiles (i.e. temperature slope in the radial direction) are in agreement with simulated profiles (within 2-8 °C) although the numerical values do not align. We hypothesize that this discrepancy may be due to: (1) unknown tissue material properties and inter-sample variations, and (2) uncertainty in the position of the temperature sensor over the course of the ablation duration. Moreover, these curves illustrate that the change in slope of temperature for a particular radial position is more pronounced at time points at the beginning of

ablation, and has much less of an influence on the temperature slope at the end of ablation.

The hypothesis that it is not unreasonable to expect temperatures in excess of 200 °C immediately adjacent to the antenna was confirmed by the solder experiments. This result suggests that peak temperatures on the order of 240 °C (as seen in our simulations) may not be unreasonable. While we believe such high temperatures may not be unreasonable, more accurate temperature measurements in proximity to the ablation device need to be performed to increase simulation accuracy.

Table 3.3 provides a list of experimentally measured dielectric properties at 915 MHz and 2.45 GHz in different regions of the ablation zone. Previous studies have made similar measurements on liver tissue 2.45 GHz (necrotic, cirrhotic, and malignant liver samples), however, the variation of dielectric measurements across the regions of the ablation zones are not captured at 2.45 GHz^{35, 36}. From Table 3.3, the general trend of the measured electrical conductivity and permittivity decreasing as the point of measurement gets closer to the applicator axis is in agreement with their study. Similar to the measurements made by Lopresto et al.¹⁸, our data shows a decrease of both relative permittivity and electric conductivity in regions in which the temperature increased to over 60 °C (pink and brown region), with a dramatic drop within regions that reached temperatures exceeding 100 °C (char region). This trend captured is also in agreement with measurements reported in a pilot study by Brac. in the same frequency range³⁷. In that study the measured electrical conductivity of regions close to the applicator (char region) approaches 0 S/m, and this is reflected in Table 3.3 for both frequencies³⁷. Although more data is needed to accurately model

these types of biophysical tissue changes during MWA, the data presented can better inform ablation simulations in this context.

The fall-off of the electric field and heat deposition with radial distance from the applicator feedpoint is shown in Fig. 3.6. This figure shows that over 90% of the power is deposited within 2 mm of the applicator^{38,39}. Moreover, Figure 3.6 illustrates that there is a change in the electric field and heat deposition patterns. Initially, there is deeper electric field penetration at later time points during the ablation at 1-2 mm radially from the antenna. However, this pattern changes beyond 2 mm depicting that electric field penetrates tissue deeper at the onset of the ablation.

Using our expressions for the electrical properties of liver and the parts of the applicator, we find that a 20% change in the electrical conductivity of liver causes only a 5% change in the diameter of an ablation. This may be understood because, while (1) increasing the electrical conductivity σ reduces the electric field within the tissue, (2) the power dissipated per unit volume is proportional to σ multiplied by the square of the electric field, so these two effects may partially cancel.

The two plots in Figure 3.7 show the temperature distribution in simulations of 60 W 15 minute *in vivo* ablations using Person's ST applicator with dynamic temperature dependence of all properties, and the static properties at 37 °C. The transverse ablation diameter estimates are similar in both graphs, however the axial ablation diameter for the static property case is larger than the dynamic property simulation. This indicates modeling MWA treatments within liver tissue is very sensitive to the dynamic nature of dielectric properties during these procedures. Note that the static property model produces ablation extent estimations within 1/10th of the

time scale of models that incorporate dynamic properties (4 minutes compared to 40 minutes respectively), but provides an erroneous pattern by neglecting the dynamic effects of the multiphysics. In developing a modeling platform that is clinically useful several factors must be considered including model accuracy and solution time. Although computational models afford the flexibility for of introducing many levels of dynamic intricacy, a balance between model complexity, accuracy, and required computational resources must be struck for practical clinical application.

Biophysical models of tissue heating have been extensively employed for guiding the design and optimization of thermal ablation devices and treatment parameters (e.g. applied power levels, treatment time, single vs. multiple applicators)⁴⁰. Although the literature offers some approaches for ablation modeling, most of these methods are for ablation modalities such as RFA, laser, etc. Fuentes et al. used FEM with medical imaging datasets to compute current density and transient temperature profiles for RFA planning⁴¹. Several platforms have been proposed for device evaluation and predictive planning MWA procedures^{42, 43}. For example, Zhai *et al.* proposed a platform for preoperative surgery planning for percutaneous hepatic MWA in which they used iterative framework for necrosis field simulation and 3D necrosis zone reconstruction⁴³. Nevertheless, these systems were focused on pre-operative planning of MWA procedure at 2450 MHz. The current literature does not provide enough data for accurate modeling at this frequency. The model discussed in this study will provide further insight into the physical and biochemical dynamics of ablation treatments, thereby improving device design and predictive planning capabilities for 915 MHz MWA systems.

Conclusion

The objective of this study was to formulate, develop, and experimentally verify a computational modeling platform for simulating MWA with the 915 MHz Perseon ST applicator. In summary, the model's accuracy was confirmed by showing the agreement between simulated and measured ablation extents and radial temperature slope for 60 W and 30 W. Therefore, the dielectric and thermal liver tissue parameterizations used in this study may be good approximations for modeling the dynamic changes that occur during MWA at 915 MHz. Furthermore, the reported variation of dielectric measurements across the regions of the ablation zones will lead to more accurate parameterization of tissue dynamics to inform MWA simulations. Overall, the results of this study will lead to a better understanding of the dynamics of ablation, especially in the context of 915 MHz clinical systems.

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CHAPTER 4

Manuscript-II

PHYSICAL MODELING OF MICROAWE ABLATION ZONE CLINICAL MARGIN VARIANCE

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Introduction

Thermal ablation has emerged as a minimally invasive modality for treatment of tumors in the liver, lung, kidney, bone and other organs. Ablation is also in clinical use for treatment of malignant and benign disease in prostate and uterine tissue, and for treatment of cardiac arrhythmias¹. Typically, treatments involve the clinician percutaneously inserting an ablation applicator during surgery into the region of interest, and applying energy to this region to induce necrosis. Ablation may also be performed laparoscopically or under open surgery. The most frequently used energy sources for thermal ablation include radiofrequency current or microwaves, lasers, focused ultrasound, and cooled, thermally conductive applicators with RF and MW as the dominant tumor ablation modalities^{2,3}. Microwave ablation (MWA) procedures have played an increasingly important role in cancer treatment for patients not eligible for chemotherapy, radiotherapy or surgical resection. Compared to other ablation modalities, advantages of microwave energy include: the potential to produce faster heating over a larger volume of tissue even in the presence of heat sinks; effectiveness in tissues with relatively high electrical impedance such as lung or charred tissue; effective utilization of multiple applicators; and treatments that do not require ancillary components⁴. MWA procedures are typically performed with image guidance to help localize the disease, inform device placement, and facilitate post-ablation confirmation of the treated zone. Ultrasound and X-ray computed tomography (CT) are the most commonly used imaging modalities for guiding ablation procedures. Image-guided ablation treatments have been shown to have relatively low complication rates compared to surgical resection⁵. This makes ablation therapy a

preferred treatment for high-risk patient populations that are not ideal candidates for other more physically taxing and invasive procedures^{5,6}. The attempted clinical goal for most MWA procedures is to ablate the entire tumor with an additional 5-10 mm margin along the entire circumference of the tumor to account for any residual cancerous cells that cannot be detected via imaging^{7,8}.

Ablation volume and tumor size are important factors that have been shown to correlate with adequate, local control^{9,10}. Residual disease left behind after percutaneous ablation treatment may be due to the result of failing to achieve a lethal thermal dose throughout the target volume^{11,12}. Moreover, such residual disease may be exacerbated by remnant tumor potentiating effects^{13,14,15}. The number of variables that affect the size and shape of the ablation zone relative to the tumor present a major challenge in accurately predicting the ablation treatment zone margin. For small tumors (less than 2 cm diameter) it is likely that complete ablation will be achieved. However, for larger tumors ablation zone outcomes have a higher local failure rate¹⁶. Consequently, it has been hypothesized that poor outcomes are due to inadequate heating throughout the target volume and that larger tumors may be biologically more likely to have spread systemically^{17,18}. Currently, planning for MWA is done with vendor specification diagrams that provide estimates of expected ablation treatment region size as derived from experimental measurements in non-perfused animal tissue. This approach ignores the effects of tissue perfusion, tumor type and location, and the influence of surrounding anatomy present in actual clinical procedures. Furthermore, the use of 2D ablation zone predictions on 3D anatomy places a considerable burden on the physician's spatial treatment planning skill, and treatment accuracy may be

skewed by physician experience. Predictive patient-specific planning and visualization tools derived from imaging data, similar to the tools used for guiding delivery of ionizing radiation as a cancer treatment, have the potential to improve the reliability of thermal ablation procedures.

Biophysical models of tissue heating have been extensively employed for guiding the design and optimization of thermal ablation devices and treatment parameters (e.g. applied power levels, treatment time, single vs. multiple applicators)¹⁹. These modeling approaches have been extended and adapted for planning ablation procedures. Fuentes et al. used finite element models (FEM) informed by magnetic resonance imaging (MRI) datasets to compute current density and transient temperature profiles for radiofrequency ablation (RFA) planning²⁰. Their study used a range of physically realistic blood perfusion parameters in a computer simulation to predict ablation lesions measured *in vitro* in perfused bovine liver models. Zhai et al. proposed a platform for preoperative surgery planning for percutaneous hepatic MWA that uses an iterative framework for necrosis field simulation and 3D necrosis zone reconstruction²¹. Challenges with the use of biophysical models for treatment planning include lack of knowledge of patient-specific tissue biophysical properties and clinical impracticality due to computational time constraints.

Imaging data that is collected prior to and during ablation treatments has strong potential to inform biophysical models for treatment planning. Computational models guided by imaging data offer the ability to determine the impact of tissue heterogeneity, blood perfusion, antenna positioning relative to the target, vascular

cooling, and other parameters that can affect the size and shape of the treatment effect region. Specifically, segmented imaging datasets may be used to inform the assignment of tissue material properties for computational models. Past studies have demonstrated the viability of estimating dielectric properties for radiofrequency hyperthermia treatment planning based on CT and MRI data^{22,23}. Functional dynamic perfusion measurements via CT or MRI have been presented and used by groups for the diagnosis and treatment efficacy of liver cancer^{24,25}. Anatomical image datasets annotated with such biothermal properties could provide more accurate insight into ablation margin assessment prior to treatment²⁶.

While computational models can afford the flexibility for including detailed tissue anatomy and heterogeneity, a balance between model complexity, accuracy, and required computational resources must be struck for practical clinical application. Investigating the contributing factors to ablation variance is therefore important because they provide guidelines for the level of detail needed for patient-specific modeling of microwave ablation procedures. Other groups have investigated the effects of changes in tissue properties on tumor ablation zones, however these sensitivity studies focused on RFA and did not discuss other possible clinical sources of variability^{27,28,29}. This paper focuses on measuring MWA variability related to: (1) tumor vs. normal tissue heterogeneity, (2) applicator tip position relative to tumor, and (3) discrete vessel cooling. The results of this study identify the tissue biophysical properties that have the greatest impact on predicted ablation zone outcome.

Methods

Our approach was to simulate electromagnetic energy deposition and bioheat transfer during MWA using a two-compartment model that mimics a tumor embedded within background liver tissue. Varying tissue properties were assigned to each compartment to assess the impact of anatomic heterogeneity on treatment outcome. Input parameters for the dielectric and thermal properties considered in this study were based on previously reported measurements for healthy and malignant (primary and/or metastatic) liver tissue.

Figure 4.1 shows the geometry of the multi-compartmental model for these simulations. Compartment 1 (C1) represents liver and compartment 2 (C2) represents a primary hepatocellular carcinoma (HCC) tumor sample embedded within C1. The antenna modeled in this study was the 915 MHz Short-Tip (ST) applicator from Perseon Medical (Salt Lake City, UT). Figure 4.1 does not illustrate the modeled antenna, and we cannot provide detailed information regarding the antenna geometry due to a non-disclosure agreement with Perseon Medical. To allow for reproducibility we conducted an additional set of simulations using an insulated 915 MHz dipole antenna. These simulations employed the same parameter variance that will be discussed later in detail. The geometry of the dipole antenna as well as simulation results are reported as additional supplementary data for this study⁷³.

Two tumor sizes were simulated, one with 1.5 cm radius, which is representative of the average sized tumors treated for single-antenna cases in our clinic, and one with 1.0 cm radius to study the effect of smaller tumor size on treatment zone. Typically, viability for single-antenna treatment is determined based on the intended ablation

margin desired by the clinician, and for most cases a 10 mm circumferential margin is ideal. For both tumors, the simulated treatment time was 15 minutes with 60 W of power at the generator. Due to attenuation within the power cable, the average power at the applicator feed point was approximately 70% of the power at the generator. This was accounted for in all simulations. The generator power, treatment duration, and tumor sizes were chosen based on review of 10 single-antenna MWA treatments performed using the Perseon device at our institution.

Figure 4.1: Two-compartmental geometry with (A) 2 cm length x 1.5 cm width and (B) 1.5 cm length x 1 cm width

Biophysical Model of Microwave Ablation

The dominant physical processes during microwave ablation are the electric fields radiated into tissue by the applicator, absorption of the electric field leading to heating, and distribution of thermal energy by thermal conduction and blood perfusion^{30,31}. Biophysical models of MWA aim to simulate these processes with the objective of predicting the transient temperature profile during a procedure. The electric fields radiated into tissue by a particular antenna may be approximated with analytical expressions, estimated from experimental measurements, or computed

numerically. In this study, the radiated electric field was computed with the Helmholtz electromagnetic equation (Equation 4.1):

$$\nabla \times \mu_r^{-1}(\nabla \times \mathbf{E}) - k_0^2 \left(\varepsilon_r - \frac{j\sigma}{\omega\varepsilon_0} \right) \mathbf{E} = 0 \quad (4.1)$$

Where $\mathbf{E}$ [V m⁻¹] is generated electric field, k_0 [m⁻¹] is propagation constant in free space, μ_r is the relative permeability ratio, ε_r is the relative permittivity ratio, σ [S m⁻¹] is the electrical conductivity, ε_0 is the permittivity of free-space, and ω is the frequency [rad s⁻¹]. Transient temperature profiles in tissue were computed using the Pennes bio-heat transfer equation (Equation 4.2)^{32,33}:

$$\rho c \frac{\partial T}{\partial t} = \nabla \cdot k \nabla T + Q_{mv} - m_{bl} c_{bl} (T - T_{bl}) \quad (4.2)$$

where ρ [kg m⁻³] is tissue density, c [J kg⁻¹ K⁻¹] is tissue specific heat capacity, T [K] is temperature, k [W m⁻¹ K⁻¹] is tissue thermal conductivity, Q_{mv} [W m⁻³] is microwave power deposited, m_{bl} [kg m⁻³ s⁻¹] is blood mass perfusion rate, c_{bl} [J kg⁻¹ K⁻¹] is specific heat capacity of blood and T_{bl} [K] is temperature of inflowing arterial blood. For MWA sources, the electromagnetic power loss within tissue is given by (Equation 4.3)³⁴:

$$Q_{mv} = \frac{1}{2} \sigma \mathbf{E}^2 \quad (4.3)$$

Table 1 provides a compiled list of the variables used in these equations along with liver nominal values (at 37 °C). The temperature dependence of tissue properties used in our simulation is described in the following sections.

Table 4.1. Physical parameters of liver and their nominal values(at 37 °C) used in biothermal computational models

Parameter	Nominal Values	Units	
<i>Electrical Properties</i>			
Relative permittivity, ϵ_r	49.03	1	29
Electrical conductivity, σ	0.86	S m ⁻¹	29
<i>Thermal properties</i>			
Thermal conductivity, k	0.51	W m ⁻¹ K ⁻¹	32-35
Specific heat capacity, c_p	3400	J kg ⁻¹ K ⁻¹	36
Density, ρ	1050	kg m ⁻³	50
Nominal blood perfusion rate, m_{bl}	18	kg m ⁻³ s ⁻¹	44,45

The FEM model was implemented in COMSOL Multiphysics v4.4 (Burlington, MA) and all post-processing was performed with MATLAB (The Mathworks, Inc., Natick, MA). Initial tissue temperature for all models was 37 °C (T_{bl}). Boundary conditions on the edges of the modeled tissue (12 cm $\times$ 10 cm) were set to a fixed temperature 37 °C respectively. A fixed temperature boundary condition ($T = 20$ °C), was applied at the inner applicator wall to simulate the room-temperature saline circulating through the applicator. A high resolution triangular Lagrangian element mesh was used throughout all simulation regions, including the boundaries of the tumor, applicator, and surrounding liver to discretize the solution space. Specifically, the mesh resolution had a maximum element edge length of 0.0024 mm and minimum

element size of 4.8 μm . An implicit solver with a maximum time step of 5 s ($0.001 < \Delta t < 5$ s) was used to solve the transient bioheat equation for 15 min ablations³⁴. Spatial temperature profiles were used to update values of tissue physical properties at each time step, as described in the following sections. It is important to note that model accuracy was assessed by comparing the simulated ablation zone extents within ex vivo tissue to standards provided by the vendor³⁵.

Table 2 describes the temperature dependent dielectric properties used in our simulations. While it is known that tissue dielectric properties change substantially during heating to ablative temperatures, detailed measurements of dielectric properties at 915 MHz for temperatures above 60 °C are not currently available in the literature³⁶. In contrast to this, temperature dependent dielectric properties of tissue at 2.45 GHz have been reported by multiple groups^{32,37}. The simplified expressions listed in Table 4.2 were obtained by fitting linear equations to experimental data reported in a pilot study by Brace³⁶.

Table 4.2. Liver dielectric property parameterization used in models

$\epsilon_r(T)$	$\sigma(T)$	$T(^{\circ}\text{C})$
$0.0172 \times T(^{\circ}\text{C}) + 48.64$	$0.00897 \times T(^{\circ}\text{C}) + 0.528$	0-95
$-3.40 \times T(^{\circ}\text{C}) + 3700$	$-0.112 \times T(^{\circ}\text{C}) + 12.02$	95-100
30	0.82	>100

For thermal conductivity, a linear approximation was used (Equation 4.3) where k_0 is the thermal conductivity at the reference temperature, k_1 is a temperature coefficient, and T and T_0 are the transient and reference temperatures^{38,39}. Determination of k_0 (.503 W m⁻¹ K⁻¹) and k_1 (.092 %°C⁻¹) was based on experimental data previously reported for experiments performed on human and porcine liver^{40,41}. Temperature dependent specific heat capacity of tissue was implemented using the parameterization reported by Yang et al.⁴². The steep drop at temperatures above 90 °C corresponds to the loss of tissue water.

$$\begin{cases} k(T) = k_0(1 + k_1(T - T_0)) & T < 100 \text{ }^\circ\text{C} \\ k(T) = k_0(1 + k_1(100 - T_0)) & T > 100 \text{ }^\circ\text{C} \end{cases} \quad (4.3)$$

The simulated blood perfusion parameterization is outlined in equation 4. This expression indicates that below 60 °C the perfusion rate is m_{bl} (kg/m³/s), and 0 at higher temperatures. Another method for modeling perfusion within liver is simulating this process as a function of thermal dose/damage⁴³. Nevertheless, the parameterization described in equation 4.4 (perfusion as a step function of temperature, with a 60 °C threshold for the transition) has been used by several groups to simulate perfusion during MWA^{44,45}.

$$\rho c \frac{\partial T}{\partial t} = \nabla \cdot k \nabla T + Q_{mv} - m_{bl} c_{bl} (T - T_{bl}) \quad (4.4)$$

$$\begin{cases} m_{bl} = m_{bl} & T \leq 60 \text{ }^\circ\text{C} \\ m_{bl} = 0 & T > 60 \text{ }^\circ\text{C} \end{cases}$$

Two Compartmental Model

Stauffer et al. measured the dielectric properties of malignant and normal *ex vivo* human liver tissue⁴⁶. They reported that, on average, the relative permittivity of freshly excised human liver tumor at 915 MHz was 12% higher when compared to normal

liver and that electrical conductivity was 24% higher than normal liver tissue⁴⁶. A study performed by O'Rourke et al. reported that relative permittivity of tumor can have mean values of 7% higher than normal with the largest statistically relevant difference being 19% at 915 MHz (one standard deviation away from the mean between normal and malignant)⁴⁷. O'Rourke et al. also reported that tumor electrical conductivity was 16% higher than normal liver on average with the largest statistically relevant difference being 44% higher (one standard deviation away from the mean from normal and malignant) at 915 MHz⁴⁷. We compared the largest difference between tumor and normal tissue within one standard deviation for the dielectric properties. As such, when comparing dielectric property variations, C2 (HCC tumor) was assigned a 19% higher permittivity and a 44% higher electrical conductivity than the surrounding normal liver (C1).

Studies have reported thermal conductivity values of core and peripheral tumors resected from humans and animal models to be as much as 20% higher than healthy liver tissue^{48,49,50}. Moreover, it has been reported that patients with hepatic steatosis (fatty liver disease) have approximately 50% lower thermal conductivity when compared to healthy liver²⁹. Considering both situations is important because it is becoming increasingly common that patients with colon liver metastatic disease also have fatty liver disease secondary to systemic chemotherapy administration⁵¹. As such, this study includes simulating scenarios of fatty liver disease and evaluates its clinical relevance in planning MWA procedures for this patient population. To consider the variance in these conditions we performed one simulation in which C2 had 20% higher thermal conductance than healthy liver, and another simulation in

which C2 remained 20% higher, but C1 had 50% lower thermal conductance than normal healthy liver.

Previously reported blood perfusion data for cirrhotic, normal and malignant liver tissue was used to evaluate the impact that perfusion has on the ablation zone treatment effect region. Previous studies by Zhou et al. and Hashimoto et al. used a contrast enhanced triphasic acquisition (arterial, portal venous, and equilibrium phase) technique to measure normal hepatic blood flow. In this study normal liver perfusion averages of approximately $18 \text{ kg/m}^3/\text{s}$ were measured^{52,53}. Other studies have reported average hepatic blood flow ranges slightly higher and lower ($14 \text{ kg/m}^3/\text{s}$ - $21 \text{ kg/m}^3/\text{s}$). However, the variance in these studies makes it difficult to explore a clinically significant range. In this study we also wanted to simulate cirrhotic liver tissue perfusion. A study done by Schutt et al. modeled variation in RFA zone estimates with varying perfusion rates using data measured in humans⁵³. That data reported cirrhotic liver perfusion values to be approximately 36% lower than healthy liver tissue²⁴. Consequently, $11 \text{ kg/m}^3/\text{s}$ was chosen as the cirrhotic liver perfusion parameter. It is important to note that lower perfusion values have been reported for severe cirrhosis (e.g. Child-Pugh class C); but these values were not used in this study. Ablation is typically contra-indicated for patients with this type of severe cirrhosis since they usually undergo transplantation or die of their liver disease, but not of their liver cancer²⁴. For this set of models, a blood perfusion parameter was added to both C1 and C2, with C2 having the tumor perfusion parameter and C1 having either healthy or cirrhotic perfusion flow rate. The tumor perfusion input values for C2 included: 3, 7, 10, 14, 21, and $24 \text{ kg/m}^3/\text{s}$. The hypo-perfused cases were chosen to incorporate the

25th-75th percentile ranges reported in two previous studies that measured HCC blood flow rate^{54,55}. The last hyper-perfused tumor case was modeled because several groups have reported tumors that had relatively higher hepatic blood flow rates than their surrounding parenchyma⁵⁶. To see how the combination of these properties affected the ablation zone margin, the largest variance of all properties discussed was modeled and compared to the baseline homogeneous healthy liver model.

Ablation Zone Margin Comparison

The 52 °C isothermal contour at the end of the 60 W 15 minute simulations for all models was used as the comparison metric. In a previous study, the 52 °C isothermal contour was in agreement with the Arrhenius thermal damage and CEM₄₃=240 thermal dose metrics⁵⁷. Therefore, for this study used the 52 °C as a metric for comparing ablation zone boundaries predicted by simulations. Figure 4.2 illustrates the comparisons that are made for each of the simulations discussed.

Figure 4.2: Illustration of the isothermal comparisons made in this study. For each simulation, the 52 °C isotherm contour lines were evaluated to make transverse and

radial axis measurements and volume comparisons between tumor electrical and thermal property variance simulations.

Applicator Position

Ablation treatments are typically performed under image guidance, which allows the clinician to deliver treatments more precisely. Although treatment accuracy is improved using medical imaging, challenges such as guiding the applicator through surrounding anatomy (e.g. rib cage and large blood vessels) coincident with patient respiratory motion can lead to imprecise positioning. A clinical study done by Zhang et al. showed significant asymmetry in the ablation zone as a result of shifts in RFA needles (approximately 2-5 cm)⁵⁸. A translatable analysis of applicator placement in the context of MWA would provide more insight into their impact on MWA outcomes. Therefore, to evaluate the sensitivity of MWA antenna position we simulated all tumor perfusion models previously discussed with the antenna moved 5 mm anteriorly (+5 mm) and posteriorly (-5 mm). Comparisons of the reference position ablation margin and thermal profile were made to these antenna displacement simulations.

Large Vessel Cooling

The liver is an intricately perfused organ that circulates blood from the hepatic artery and the portal vein. Portal and hepatic veins of different sizes are found throughout the liver. Several studies have shown that during thermal ablation, large blood vessels may induce considerable tissue cooling and thereby limit the size of the coagulation zone^{59,60,61}. To investigate the impact of discrete vessels adjacent to the desired target, we considered variably sized blood vessels positioned at varying distances from the tumor. Since this study employed axially symmetric mode

geometry, incorporating a circular cross-section vessel would correspond to a “donut shaped” vessel in 3D, i.e. a vessel encircling the tumor and applicator. Although such a vessel is physically unrealistic, it affords comparative evaluation of the heat sink offered by vessels placed at varying distances from the target volume. The heat-sink offered by the discrete vessels was modeled using a convective heat flux boundary condition as in a study done by Haemmerich et al.⁶². Equation 4.5 shows the convective cooling boundary conditional parameterization used for these simulations, where h is the heat transfer coefficient, N_{u_D} is the Nusselt number that is proportional to vessel length and flow rate, and D is vessel diameter. A previous study used a similar boundary condition for vessel sizes between 3 mm and 18 mm. Each vessel was simulated to have a vessel wall thickness of 1 mm and length of 70 mm, the typical length of the portal vein⁶³.

$$h = N_{u_D} k_b / D \quad (4.5)$$

Blood vessels of 7 mm, 10 mm, and 15 mm diameter were simulated at distances of 2 mm, 5 mm and 10 mm from the tumor. The agreement between the simulated baseline (S) and vessel-cooled (S with boundary volume, S_{BV}) treatment effect regions is summarized with a Dice coefficient (Equation 4.6).

$$Q_s = \frac{2|S_{BV} \cap S|}{|S_{BV}| + |S|} \quad (4.6)$$

This comparison was performed for multiple simulations using models with normal and HCC blood flow rates with and without with a nearby vessel.

Results

Initial model accuracy was assessed by comparing the simulated ablation zone extents to the vendor provided ablation size guidelines. Results from experiments in

ex vivo tissue provided by the vendor indicated ablation zone dimensions of 2.6 cm x 3.2 cm for 60 W, 5 min, and 3.1 cm x 3.7 cm for 60 W, 10 min; simulations run mimicking these experimental conditions yielded ablation zone dimensions of 2.70 cm x 3.50 cm, and 3.5 cm x 4.2 cm, respectively³⁵. The final ablation zones for the two-compartmental simulations are summarized in Table 4.3 and Table 4.4. Table 4.3 shows the results of the two-compartmental model simulating the 1.5 cm length x 1.0 cm width tumor (C2) within surrounding normal liver tissue (C1). Table 4.4 shows the results of the two-compartmental model simulating the 2.0 cm length x 1.5 cm width tumor (C2) within surrounding normal liver tissue (C1). The dielectric and thermal property variations and their subsequent transverse and axial ablation diameter measurements of the ablation treatment effect region are shown. In addition, the tables show the total volume for each ablation simulation (as implied by radial symmetry), as well as a volumetric comparison (percent difference) to an ablation simulated in a normal homogenous liver. Table 4.5 shows a comparison of MWA zone variance across normal liver perfusion range. Figure 4.3 shows the final ablation zone dimension from a two-compartmental model that simulates the worst-case combination across the values studied for all parameters in both tumor sizes. Comparison of the transverse and axial ablation zone diameters for all of the 2.0 cm x 1.5 cm perfusion variance simulation was performed with the antenna shifted 5 mm anteriorly and posteriorly respectively. The results of this antenna placement sensitivity analysis showed that there was less than a 1.5 mm radial difference in the size of the ablation zone as a result of this shift. Figure 4.4 shows the change in clinical ablation margin after displacing the antenna 5mm anteriorly (A) and

posteriorly (B) from the 2.0 cm x 1.5 cm tumor. The next set of simulations modeled the change in ablation zone dimension due to hepatic vessels near the region of interest. Three blood vessel diameters were simulated (7 mm, 10 mm, 15 mm) at 2 mm, 5 mm, and 10 mm distances from the tumor edge. Figure 4.5 shows the results of the 15 mm diameter blood vessel at those distances. Table 4.6 shows the Dice coefficient comparison of ablation zone extents for all blood vessel simulations.

Table 4.3: Compiled variances from the two-compartmental simulations for 1.5 cm x1.0 cm tumor. * C1 for model had a multiplier of 0.5 to simulate tumor within surrounding fatty liver

Liver Tissue (C1)	Changed Parameter	Tumor(C2) Parameter Multiplier	Axial diameter (cm) [% Diff.]	Transverse diameter (cm) [%Diff.]	Volume (cm ³) [%Diff.]
Normal	No Change	No Tumor, Homogeneous (i.e C1=C2)	3.52	2.98	9.75
	<i>Electrical</i>				
Normal	$\epsilon_r(T), \sigma(T)$	(1.19,1.44)	3.43 [-2.30%]	3.00 [+0.67%]	9.65 [-1.03%]
	<i>Thermal</i>				
Normal	$k(T)$	(1.20)	3.52 [0%]	2.97 [-0.34%]	9.78[+0.31%]
Fatty* Liver	$k(T)$	(1.20)	4.02 [+13.30%]	3.18 [+6.49%]	12.78 [26.90%]
	<i>Perfusion</i>				
Cirrhotic	11(kg/m ³ /s)	No Tumor, Homogeneous (i.e C1=C2)	3.89 [+9.99%]	3.38 [+12.58%]	14.15 [+36.79%]
Normal	18 (kg/m ³ /s)	3 (kg/m ³ /s)	3.41 [-3.17%]	2.97 [-0.34%]	9.76 [+0.11%]
Cirrhotic	11 (kg/m ³ /s)	3 (kg/m ³ /s)	3.88 [+9.73%]	3.37 [+12.28%]	14.05 [+36.13%]
Normal	18 (kg/m ³ /s)	7 (kg/m ³ /s)	3.51 [-0.28%]	2.97 [-0.34%]	9.76 [+0.11%]
Cirrhotic	11 (kg/m ³ /s)	7 (kg/m ³ /s)	3.89 [+9.99%]	3.37 [12.28%]	14.05 [+36.13%]
Normal	18 (kg/m ³ /s)	10 (kg/m ³ /s)	3.51 [-0.28%]	2.97 [-0.34%]	9.74 [-0.12%]
Cirrhotic	11 (kg/m ³ /s)	10 (kg/m ³ /s)	3.89 [9.99%]	3.38 [15.58%]	14.10 [+36.50%]
Normal	18 (kg/m ³ /s)	14 (kg/m ³ /s)	3.52 [0%]	2.98 [0%]	9.91 [+1.60%]
Cirrhotic	11 (kg/m ³ /s)	14 (kg/m ³ /s)	3.89 [+9.99%]	3.40 [+13.17%]	14.35 [+38.16%]
Normal	18 (kg/m ³ /s)	21(kg/m ³ /s)	3.52 [0%]	2.98 [0%]	9.91 [+1.60%]
Cirrhotic	11 (kg/m ³ /s)	21(kg/m ³ /s)	3.88 [+9.73%]	3.38 [+12.32%]	14.05 [+36.13%]
Normal	18 (kg/m ³ /s)	24 (kg/m ³ /s)	3.51 [-0.28%]	2.77 [-7.30%]	4.91 [+1.60%]
Cirrhotic	11 (kg/m ³ /s)	24 (kg/m ³ /s)	3.89 [+9.99%]	3.38 [+12.58%]	14.10 [36.50%]

Table 4.4: Compiled variances from the two-compartmental simulations for 2.0 cm x1.5 cm tumor. * C1 for model had a multiplier of 0.5 to simulate tumor within surrounding fatty liver

Liver Tissue (C1)	Changed Parameter	Tumor(C2) Parameter Multiplier	Axial diameter (cm) [% Diff.]	Transverse diameter (cm) [%Diff.]	Volume (cm ³) [%Diff.]
Normal	No Change	No tumor, Homogenous (i.e. C1=C2)	3.52	2.98	9.75
<i>Electrical</i>					
Normal	$\epsilon_r(T), \sigma(T)$	(1.19,1.44)	3.43 [-2.59%]	3.04 [+1.99%]	10.08 [+3.33%]
<i>Thermal</i>					
Normal	$k(T)$	(1.20)	3.50 [-0.57%]	2.98 [0%]	9.66 [-0.93%]
Fatty* Liver	$k(T)$	(1.20)	3.99 [+12.52%]	3.19 [+6.81%]	12.95 [+28.19%]
<i>Perfusion</i>					
Cirrhotic	11(kg/m ³ /s)	No Tumor, Homogenous (i.e. C1=C2)	3.89 [+9.99%]	3.38 [+12.58%]	14.15 [+36.82%]
Normal	18 (kg/m ³ /s)	3 (kg/m ³ /s)	3.51 [-0.28%]	2.97 [-0.34%]	9.71 [-0.41%]
Cirrhotic	11 (kg/m ³ /s)	3 (kg/m ³ /s)	3.88 [+9.73%]	3.37 [+12.28%]	14.09 [+36.41%]
Normal	18 (kg/m ³ /s)	7 (kg/m ³ /s)	3.51 [-0.28%]	2.97 [-0.34%]	9.71 [-0.41%]
Cirrhotic	11 (kg/m ³ /s)	7 (kg/m ³ /s)	3.86 [+9.21%]	3.38 [+12.58%]	14.09 [+36.41%]
Normal	18 (kg/m ³ /s)	10 (kg/m ³ /s)	3.52 [0%]	2.95 [-1.01%]	9.70 [-0.51%]
Cirrhotic	11 (kg/m ³ /s)	10 (kg/m ³ /s)	3.88 [+9.73%]	3.37 [+12.28%]	14.09 [+36.41%]
Normal	18 (kg/m ³ /s)	14 (kg/m ³ /s)	3.51 [-0.28%]	2.97 [-0.34%]	9.72 [-0.31%]
Cirrhotic	11 (kg/m ³ /s)	14 (kg/m ³ /s)	3.88 [+9.73%]	3.37 [+12.28%]	14.05 [+36.31%]
Normal	18 (kg/m ³ /s)	21 (kg/m ³ /s)	3.51 [-0.28%]	2.97 [-0.34%]	9.71 [-0.41%]
Cirrhotic	11 (kg/m ³ /s)	21 (kg/m ³ /s)	3.88 [+9.73%]	3.37 [+12.28%]	14.09 [+36.41%]
Normal	18 (kg/m ³ /s)	24 (kg/m ³ /s)	3.52 [0%]	2.97 [-0.34%]	9.71 [-0.41%]
Cirrhotic	11 (kg/m ³ /s)	24 (kg/m ³ /s)	3.88 [9.73%]	3.37 [+12.28%]	14.09 [+36.41%]

Table 4.5: Comparison of MWA zone variance across normal liver perfusion range

Liver perfusion (kg/m³/s)	Axial Diameter (cm)	Transverse Diameter (cm)	Volume (cm³)
14	3.73	3.13	11.74
16	3.63	3.02	10.72
18	3.52	2.98	9.75
21	3.43	2.79	8.53

Figure 4.3: Isothermal comparison of the ablation zone for each tumor size model. The dashed lines represent the simulated ablation zone size when each tumor size had the worst-case combination of studied variability across physical parameters.

A

B

Figure 4.4: The change in ablation margin after displacing the antenna 5mm anteriorly (A) and posteriorly (B)

Figure 4.5: Simulation of vessel cooling by 15mm diameter blood vessel and its impact on the ablation zone. The baseline simulation without a vessel (A) was compared to simulated vessels a distance of 2mm (B), 5mm (C), and 10mm (D) away from the edge of the tumor and had a connective cooling condition that was proportional to the length and diameter of the vessel.

Table: 4.6: Dice coefficient values for comparing ablation zone extents for all blood vessel simulations. The dice coefficient was evaluated by comparing the size of the ablation zone from all liver models containing a vessel with normal and HCC blood flow rates to a baseline simulation without a blood vessel

Vessel Diameter (mm)	Vessel Distance (mm)	Q_s (Normal Flow)	Q_s (HCC Flow)
7	2	0.936	0.935
10	2	0.917	0.918
15	2	0.891	0.891
7	5	0.950	0.950
10	5	0.938	0.938
15	5	0.921	0.921
7	10	0.998	0.998
10	10	0.998	0.998
15	10	0.990	0.990

Figure 4.6: Ablation zone comparison of ablation when simulating a 7mm, 10mm, and 15mm vessel at a distance of 2cm from the tumor. The desired clinical ablation margin is shown to compare the impact of the simulated vessel cooling.

Discussion

Table 4.33 and 4.4 show the results of the two compartmental modeling experiments with varying dielectric properties and thermal properties for each of the two tumor sizes discussed. When incorporating the coupled difference in relative permittivity and electrical conductivity between malignant and healthy liver tissue, these simulations showed slight variations in the axial or transverse diameter (less than 6 mm) in ablation zone size. In addition, the smaller ablation zone volume as a result of the higher tumor permittivity relative to background liver tissue is reflective of shallower microwave penetration⁶. However, this effect is less prominent when simulating heterogeneity for the larger tumor model. Moreover, higher electrical conductivity of the tumor relative to the background liver tissue may have enhanced heating in a small margin surrounding the tumor as reported by Sollazo et al.⁶⁴. The slight decrease in volume due to the dielectric heterogeneity for the smaller simulated tumor (approximately 0.10 cm^3) when compared to the homogeneous liver simulation reflects this result. However, it is not well understood whether this observation has relevant clinical impact. The results of our study provide insight into accounting for dielectric properties when modeling MWA procedures in liver. The results suggest that when using this antenna and power/time combination, treatment outcome is minimally impacted by dielectric heterogeneity in tumor or healthy tissue. Similarly, varying tumor size resulted in less than 4% volume difference across these scenarios. These results are important in anticipating patient-specific treatment modeling, in

which adequate modeling of heterogeneity must be weighed against increasing computational complexity and clinical time.

The variance of thermal conductivity showed a more clinically relevant impact, with a 27% increase in volume (more than 3 cm³) between simulated treatment effect regions in livers with fatty liver disease versus the baseline homogeneous normal liver simulation. This result suggests that it will be useful to identify specific kinds/stages of liver diseases (including fatty liver) when modeling patient-specific ablation treatment effect regions. This result is in agreement with Brace et al. which has explained that increases in thermal conductivity allow for potential increases in ablation margins⁶.

The impact of hepatic perfusion variance on ablation outcomes has been extensively discussed in the literature. In this study, we simulated several hypo-perfused and hyper-perfused tumors within normal and cirrhotic liver perfused liver and evaluated the resulting ablation zone sizes. The lower perfusion rate of cirrhotic tissue is of particular importance for tumor ablation because approximately 90% of patients with primary liver cancer (HCC) suffer from cirrhosis⁶⁵. Our results suggest that ablation zone volume could increase by 36% or more ($> 4 \text{ cm}^3$) in patients with cirrhotic liver tissue surrounding the tumor. Schutt and Haemmerich have similarly reported that lower perfusion rates in cirrhotic patients resulted in larger ablation zones than in those with normal liver tissue for RFA²⁴. Furthermore, the results reported in Table 4.5 indicate that there is a significant change in ablation zone extents within the normal hepatic perfusion range. This result also suggests that it will be useful to distinguish cirrhotic versus healthy tissue when modeling patient-specific

ablation treatment effects. Moreover, the variance effects reported in Table 4.5 suggests that accurate quantification of hepatic perfusion even among healthy patients may be essential for pre-operative planning for MWA. The hyper-perfused and hypo-perfused tumor simulations within surrounding normal liver tissue showed minimal variation in volume (less than 2%) when compared to simulations in which the surrounding tissue was cirrhotic. These results indicate that although perfusion may be the most important parameter to incorporate in a patient-specific manner, the relative difference in blood perfusion of the tumor itself when compared to surrounding tissue may only play a small role in modeling ablation zone outcomes. Figure 3 further supports this claim by showing minimal change in ablation zone extents when the homogeneous normal liver baseline simulation is compared to a simulation of a cirrhotic liver. This model simulated the worst-case combination of thermal and electrical properties variations. There are clinical tools and protocols used to parameterize perfusion^{22,25,54,55}. These tools employ techniques, such as correlating HU change with volumetric blood flow by measuring the flow of contrast over several different arterial and venous liver phases via CT or MR to quantify perfusion for diagnosis and possible treatment modalities^{22,25,52,53}. The discussed results advocate using such tools and approaches to quantify perfusion parameters as inputs into patient specific modeling strategies.

It is important to note that these results are reflective only of cases with small tumors that can be treated effectively with a single antenna (less than 2 cm diameter). In a similar study previously done by our group using a dipole antenna on a larger hepatocellular carcinoma, there was substantially more variation in ablation zone size

given similar hyper-perfused and hypo-perfused tumor parameters to those used here⁵⁷. This is less clinically relevant for single antenna treatments, but warrants further investigation as we anticipate multiple antenna simulations.

The results of the antenna displacement model scenarios indicate that the absolute difference in axial and transverse ablation diameter are insensitive to applicator position (< 1.5 mm difference). However, when considering the overlap between the ablation zone and the ideal clinical margin when the antenna was displaced 5 mm anteriorly and posteriorly, there was approximately a 6 mm gap between the margins as depicted by Figure 4.4. Additionally, a recent study simulating ablation zone variation when multiple antennas were displaced in a non-parallel fashion showed that this type of perturbation could result in substantial differences in power deposition⁶⁶. This suggests that proper treatment planning approaches need to be developed to account for accurate needle placement.

Table 4.6 shows Dice coefficient measurements for the blood vessel simulations. As expected, the 15mm diameter blood vessel showed the largest impact on the ablation treatment effect region. The predicted ablation for the model scenario that simulated a 15 mm blood vessel 2 mm away from the tumor was approximately 11% smaller than the baseline according to Dice statistics. This is depicted in Figure 4.5 as the ablation zone radius being approximately 5 mm smaller in transverse radius (10 mm in diameter) when compared to the ablation zone simulation without the blood vessel. The difference in ablation zone extent was 8-9% smaller as the blood vessel distance from the tumor increased to 5 mm and 10 mm. A similar trend was seen in the other blood vessel sizes with distance from the tumor. This result is consistent with

previously reported data that suggests significant heat-sink effects caused by hepatic veins as far as 8 mm away⁶⁷. In relation to blood vessel size, the effect of convective cooling by the blood vessel seemed to increase with blood vessel diameter, as illustrated by Figure 4.6. The findings in Lu et al. and Pillai et al. support this claim by reporting that heat-sink effect is significantly dependent on hepatic vein size, especially when discussing vessels greater than 3 mm in diameter^{68,69}. At a distance of 10 mm or greater our data suggests that blood vessels less than 10 mm in diameter do not cause much variation in the ablation zone outcome. However, blood vessels larger than 10 mm potentially may have an effect on ablation treatment outcomes. Typical diameters of the main and first order portal vein and hepatic veins are 0.8 – 27 mm and 5-15 mm⁷⁰. Nevertheless, it is rare to encounter a vessel greater than 10 mm peripherally. Clinically, it is more common to encounter a vessel diameter of that size centrally within the liver.

The model employed in this study does not account for tissue shrinkage due to steam transport which may affect the growth of the ablation zone. Moreover, this study estimated the ablation zone with the 52 °C isotherm contour, rather than thermal dose or thermal damage. Although cell death due to thermal damage is a complex function of the time-temperature history during heating, using an isotherm for estimating the extent of the ablation zone is a reasonable approximation when comparing ablations over the same treatment duration⁵⁷. In our models, the blood perfusion rate is adjusted only as a function of temperature, rather than temperature and time. In addition, although the peak temperatures reported by our simulations appear to be high (~240 C), there remains a lack of research showing accurate

measurement of peak tissue temperature immediately adjacent to an ablation applicator (i.e. these high simulated temperatures can neither be corroborated or discredited)⁴³. Lastly, all models considered for this variance study apply to smaller tumor sizes, thus further investigation may be warranted when considering MWA margin variance among larger tumors.

The objective of this study is to identify what level of heterogeneity needs to be captured for ablation modeling for patient-specific applications. The results of the simulated scenarios suggest that varying perfusion within the liver (cirrhotic vs normal) has significant impact on ablation zone extent variability and should be carefully measured and incorporated in patient-specific planning for MWA. The significant variability in ablation extents when comparing simulations of normal liver and fatty liver (thermal conductivity variance) also suggests careful quantification for patient-specific applications. Moreover, in the context of MWA margin assessment antenna placement and vasculature within the vicinity of 10 mm should also be carefully analyzed and incorporated in predictive planning. The results suggest that heterogeneity between tumor and surrounding liver dielectric properties (electrical conductivity and permittivity) does not provide significant changes during MWA, and therefore may be approximated as homogeneous for patient-specific planning. Nevertheless, in order to evaluate the discussed parameters in the context of assigning patient-specific values for model improvement, another study is needed to evaluate combinatory effects of these parameters. The presented results is a first step towards accomplishing this task, but a follow-up study is warranted using statistical techniques

for evaluating which biophysical tissue properties cause the most impact on thermal margin.

Nevertheless, in order to evaluate the discussed parameters in the context of assigning patient-specific values for model improvement, another study is needed to evaluate combinatory effects of these parameters. The presented results is a first step towards accomplishing this task, but a follow-up study is warranted using statistical techniques for evaluating which biophysical tissue properties cause the most impact on thermal margin.

Future work will concentrate on further evaluation quantification of the ablation sensitivity to some of the discussed parameters via CT or MRI within the liver. Nevertheless, incorporating these types of imaging quantification techniques in the clinical workflow will be difficult, due to the amount of time and necessary steps to make precise and accurate measurements. For example, the presented results indicate hepatic perfusion may potentially be an important parameter to incorporate in a patient-specific manner; however, commonly used techniques involve measuring the flow of contrast over several different arterial and venous liver phases (via CT or MRI), which is taxing on the patient, can lead to additional patient radiation dose, and can take a considerable amount of time^{24,25}. In addition, the results suggest the potential need for accurate vessel reconstruction techniques. There are known techniques for accomplishing vascular reconstruction, such as vessel tree segmentation⁷¹. Moreover, this technique has been used with the intent for numerical simulation for RFA⁷².

Detailed 3D patient-specific segmentation and representative meshing within the simulation will most likely be needed in order to more accurately quantify the thermal effect. Clinically, attempts at applicator placement confirmation are performed via intra-operative imaging right before the procedure begins. However, pre-operative positioning errors and intra-operative patient motion increases the uncertainty applicator placement, and therefore allows for variation of the intended ablation margin. A MWA planning system that can provide an ideal applicator insertion position and trajectory while accounting the biophysical inputs and maintaining clinical feasibility would be ideal. Such a tool within the planning platform would need a highly sophisticated 3D imaging system that could be imported into simulations that uses modeling techniques (i.e. Monte Carlo) to generate the most likely applicator insertion.

Conclusion

The goal of this study was to identify the parameters that can be derived from imaging that will have the greatest impact on the shape and size of a MWA treatment effect region. The results from simulating treatment effects given variance in tissue thermal and electrical properties will help to better approximate MWA zone extents using biophysical modeling techniques. Moreover, these simulations help identify properties that we should concentrate on in patient-specific modeling, and which properties we can approximate with a certain level of confidence. Ultimately, this study will help understand and effectively predict the underlying bio-physical changes that occur over the duration of MWA procedures in order to make a more useful treatment planning system. Although, more data needs to be collected in order to

develop a clinically useful treatment planning simulation tool, the presented results will help in developing a potential platform for incorporating patient specific biophysical measurements for simulating MWA procedures.

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CHAPTER 5

Manuscript-III

EXPERIMENTAL MEASUREMENT OF MICROWAVE ABLATION HEATING PATTERN AND COMPARISON TO COMPUTER SIMULATION

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Introduction

Microwave ablation (MWA) procedures have been playing an increasingly important role in the treatment of cancer. Compared to radiofrequency ablation, MWA induces faster heating over a larger volume of tissue, is more effective near vasculature, is effective in tissues with relatively high electrical impedance (such as lung or charred tissue), has the advantage of utilization of multiple applicators, and does not require ground pads [1]. MWA procedures are typically performed with image guidance (X-ray Computed Tomography (CT) or Ultrasound) to help localize the disease, inform device placement, and facilitate post-ablation confirmation of the treated zone. Nevertheless, on a patient specific basis, MWA still has many unknowns with regard to the energy dissipation from the antenna, as well as biophysical effects in tissue adjacent to the antenna and at the treatment margin [2,3].

Pre-operative patient-specific planning and visualization tools have the potential to improve the reliability of MWA procedures as both a palliative and curative treatment modality. Predictive planning is becoming increasingly important for MWA procedures as clinicians move toward standardizing surgical approaches. The attempted clinical goal for most MWA procedures is to ablate the entire tumor with an additional margin (typically ~ 5-10 mm) along the target circumference to account for any residual cancerous cells that may not be detected via imaging [4,5]. Residual disease left behind after treatment may be the result of inadequate ablation margin [6,7].

The current standard for MWA planning is restricted to dimensions of ellipsoids parameterized from *ex vivo* tissue tests, with some new systems providing overlays of

these ellipsoids on pre-treatment imaging [8]. This approach ignores the effects of tissue perfusion, tumor type and location, and the influence of surrounding anatomy present in actual clinical procedures. Furthermore, the use of 2D ablation zone predictions on 3D anatomy places a considerable burden on the physician's spatial treatment planning skill, and treatment accuracy may be skewed by physician experience. To facilitate personalized treatment delivery and simplify planning for physicians, there has been renewed interest in the development of modeling and visualization techniques towards treatment planning of ablation treatments [9,10,11].

Mathematical models of the processes that occur during MWA have been employed during the design and optimization of devices for MWA [12,13,14,15,16]. These models use numerical techniques to solve the partial differential equations which govern electromagnetic propagation, power deposition, and bioheat transfer [17,18]. Such models may help physicians to choose the treatment parameters (e.g. number of antennas, applied power levels, antenna insertion paths) which maximize the likelihood of a desired treatment outcome. Predictive modeling tools are of particular clinical relevance due to the shortage of practical techniques for intra-operative monitoring of thermal damage. There are few proposed simulation platforms that have been adapted for planning ablation procedures in the context of ablation [10, 11, 19, 20]. Challenges with creating a treatment planning simulating framework for MWA include: limited patient-specific knowledge of tissue biophysical properties, integrating data from clinical imaging datasets with computational models, impracticality of lengthy computational times within the clinical workflow, and lack of knowledge of the applicator geometry.

Current MWA models often include multi-physics simulation techniques to compute the electric field and electromagnetic power absorption profile within tissue. Calculation of the electric field radiated by a particular applicator, requires knowledge of the antenna geometry, and applicator material properties. Furthermore, accurate patient-specific calculations require knowledge of tissue dielectric properties for individual patients. However, the proprietary design of applicators in current clinical use is usually unknown. Alternative simulation techniques that characterize the power absorption pattern during MWA without requiring knowledge of proprietary antenna design information may facilitate bioheat transfer modeling within clinical treatment planning.

Infrared thermographic SAR measurement, which has been in use for more than several decades [21], is well suited to interstitial measurements because of the high spatial resolution afforded by commercial thermal cameras, as well as the ability to image the temperature distribution of an entire plane in a single experiment. Some work has been done to investigate thermographic SAR measurements and minimizing associated measurement error under experimental conditions for external applicators [22]. A study involving measuring SAR for interstitial hyperthermia devices using an IR thermographic system was done by Gladman *et al.* [23]. They acquired serial thermographic IR temperature measurements that were made during multiple heating periods and cooling periods within a tissue equivalent phantom to determine errors caused by thermal conduction and convection when calculating SAR. In that study the phantom was layered so that the interstitial device was not exposed during heating ; temperature data acquisition was limited to the period immediately following heating.

Another study performed by Haemmerich *et al.* used thermocouples to acquire temperature data in a similar fashion to correct for thermal conduction errors during tissue heating [24].

The goal of the current study was to examine any differences between the SAR profile predicted by multi-physics simulations and SAR computed from experimentally measured temperature profiles with an infrared camera. This study employed commercially available antennas in clinical use (Perseon Medical Short Tip and Long Tip antennas) with known geometry. This will serve as experimental validation of the multi-physics model, and the experimental SAR data may allow an alternate modelling strategy where experimentally measured SAR data are used in a computer model to allow simulation of MWA procedures in absence of knowledge of the antenna geometry.

Methods

Experimental Setup

We used the experimental setup illustrated in Figure 5.1 to measure SAR in fresh *ex vivo* porcine liver tissue. We performed a total of 9 studies to measure the change in SAR during ablation with either of two clinically employed 915 MHz MWA antennas: Perseon short-tip (ST) antenna ($n=3$), or long-tip (LT) antenna ($n=6$). Liver tissue samples were placed in 0.9% saline until tissue temperature was completely equilibrated with water bath temperature (21 °C). The MW antenna was placed in firm contact on top of a tissue sample. An infrared camera (Mikron M7500) was positioned above the sample and additional thermocouples were placed on the tissue surface to calibrate temperature values derived from the IR camera. We assumed tissue emissivity of 0.9 [25]. The tissue surface temperature was recorded via IR camera (~3.3 fps, 320x240 resolution) and stored on a PC for later image analysis. Microwave power (20 W) was applied to the antenna for a total of 6 minutes, and antenna cooling by room temperature water was initiated just before power was turned on. Power was interrupted for ~5 seconds every 20 seconds (0-2 minutes), or every 30 seconds (2-6

minutes). At the end of each study, a photographic image was taken to visualize the coagulation zone.

The initial rate of temperature rise was calculated for each pixel from the IR imaging data (Fig. 1. B,C). In addition, slope of temperature rise/fall was calculated just before, and just after each time power was turned off (t_{off}^- , t_{off}^+). Similar to a prior study, SAR was calculated during heating from these two slopes [24] as specified in equations 1 and 2. In both equations c is the specific heat of the tissue sample, k is the thermal conductivity of the tissue sample, and ρ is the tissue density. Since the tissue temperature is equal immediately before (t_{off}^-), and immediately after (t_{off}^+) the power is turned off, the heat conduction term (first right-hand term in equations 5.1 and 5.2) also has to be identical as it depends on the temperature gradient; however, SAR=0 right after power is switched off (t_{off}^+), leaving only the thermal conduction term in equation (5.2).

$$c \frac{\partial T}{\partial t} \Big|_{t_{\text{off}}^-} = \frac{\nabla \cdot k \nabla T}{\rho} + SAR \quad (5.1)$$

$$c \frac{\partial T}{\partial t} \Big|_{t_{\text{off}}^+} = \frac{\nabla \cdot k \nabla T}{\rho} \quad (5.2)$$

SAR during MW heating can then be calculated by subtraction of equation (5.2) from equation (5.1), i.e. by subtraction of the two temperature slopes before and after power is turned off (equation 5.3):

$$SAR = c \left(\frac{\partial T}{\partial t} \Big|_{t_{\text{off}}^-} - \frac{\partial T}{\partial t} \Big|_{t_{\text{off}}^+} \right) \quad (5.3)$$

Figure 5.2: Example point temperature change at during an ablation experiment in which the power was intermittently turned off to correct for thermal conduction.

Thus, we were able to calculate SAR at the beginning of each experiment, as well as each time power was transiently turned off, every 20 s (0-2 minutes), or every 30 s (2-6 minutes) as illustrated in Figure 5.2.

Data Analysis of Experiments

Experimental infrared temperature measurements and subsequent transient SAR spatial profiles were post processed using MATLAB (The Mathworks, Inc., Natick, MA). The spatial temperature changes captured by the infrared camera were compared to a previously validated simulation model using the Perseon ST antenna [9] that mimicked the same experimental setup (discussed in the next section). The initial and transient SAR profiles were compared to the simulation as well. The simulated ablation zone and SAR profile (S_{sim}) were compared to the experimentally measured ablation zone and SAR profile (S_{exp}) using a Dice coefficient (Equation 5.4).

$$DSC = \frac{2|S_{exp} \cap S_{sim}|}{|S_{exp}| + |S_{sim}|} \quad (5.4)$$

Simulation Framework

A 3D model was employed in this study as illustrated in Figure 5.3. The simulation geometry illustrated is similar to the experimental setup previously discussed in which half of the antenna was immersed within liver tissue sample and half was exposed to air. The FEM model was implemented in COMSOL Multiphysics v4.4 (Burlington, MA) to simulate the described experiment. The model used to simulate the ablation experiments for this study was used in a previous study to quantify clinical margin variability during MWA treatments with the Perseon ablation system [9].

Figure 5.3: Simulation geometry of the MWA antenna at an air-liver boundary that was compared to the experimental SAR data. Note that the ablation zone is on the surface of the liver (not in air).

Table 5.1 presents the temperature dependent dielectric and thermal properties used in our simulations within liver. The parameterizations of the liver permittivity and electrical conductivity was also employed in a prior investigation for modeling MWA procedures within liver at 915 MHz [9]. Moreover, a similar linear approximation for thermal conductivity was used, where k_0 is the thermal conductivity

at the reference temperature, k_1 is a temperature coefficient, and T and T_0 are the transient and reference temperatures [26,27]. Determination of k_0 and k_1 was based on experimental data previously reported for experiments performed on human and porcine liver [28,29]. In addition, we used a temperature dependent specific heat capacity parameterization in our simulation. A Gaussian function centered at the boiling point of water is used to simulate the added heat sink associated with tissue water evaporation [30].

Table 5.1. Temperature dependent liver dielectric and thermal property parameterization used in models

$\epsilon_r(T)$	$\sigma(T)$	$\kappa(T)$	$T(^{\circ}\text{C})$
$0.0172 \times T(^{\circ}\text{C}) + 48.64$	$0.00897 \times T(^{\circ}\text{C}) + 0.528$	$k(T) = k_0(1 + k_1(T - T_0))$	0-95
$-3.40 \times T(^{\circ}\text{C}) + 3700$	$-0.112 \times T(^{\circ}\text{C}) + 12.02$	$k(T) = k_0(1 + k_1(T - T_0))$	95-100
30	0.82	$k(T) = k_0(1 + k_1(100 - T_0))$	>100

Results

The spatial profiles of SAR and temperature at several time points during the ablation experiment for the short-tip and long-tip Perseon applicators are illustrated in Figure 5.4 and Figure 5.5. For both figures the thermal conduction correction was applied for SAR calculations. Figure 5.4 and figure 5.5 also illustrate simulated temperature and SAR spatial profiles during the course of an ablation for the short-tip and long-tip applicators. Figure 5.6 is a photo of the ablation zone following a 15 W, 6 minute ablation using the short-tip applicator and long-tip applicator. Figure 5.7 is a comparison ablation zone dimensions between simulation and experiment of a short-tip applicator. The 60 °C isothermal contour was used to compare the extent of the

ablation zone of simulation vs. experiment. The simulated and average experimentally measured transverse and axial ablation zone diameters were 1.28 cm and 1.30 cm (+/- 0.0327cm) and 2.10 cm and 2.66cm (+/-0.223cm) after 5 minutes of heating. Moreover dice coefficient comparison shows an average of 0.832 (+/- 0.025), demonstrating good agreement. Figure 5.8 is a comparison of transient SAR profile between experiment and simulation, for a 15 W ablation with a short-tip antenna. Table 5.2 contains Dice coefficient comparison of the SAR profiles for the ex vivo ablation experiments to the simulated transient profile at various time points.

Figure 5.4: (a) Temperature (top) and SAR (bottom) spatial profiles during the course of an ablation experiment using the short-tip applicator. (b) Temperature (top) and SAR (bottom) spatial profiles during the course of an ablation simulation using the short-tip applicator.

Figure 5.5: (a) Temperature (top) and SAR (bottom) spatial profiles during the course of an ablation experiment using the long-tip applicator. (b) Temperature (top) and SAR (bottom) spatial profiles during the course of an ablation simulation using the long-tip applicator.

Figure 5.6: Axial view of a 15 W 6 minute ablation on an *exvivo* liver sample using the short-tip applicator (left) and long-tip applicator (right).

Figure 5.7: Comparison of simulation and experiment for a 15 W ablation (half liver-half air) using the short-tip applicator. The 60 °C isothermal contour was used to compare the extent of the ablation zone of simulation vs. experiment (n=3) at 1 minute (DSC agreement = 0.788 ± 0.0655), 3 minutes (DSC agreement = 0.832 ± 0.0248) and 6 minutes (DSC agreement = 0.845 ± 0.0252). Temperature maps are shown from simulation.

Figure 5.8: Comparison of simulated transient SAR profile to experimentally measured SAR profile during ablation

Table 5.2: Dice coefficient comparison of the SAR profiles between *ex vivo* experiments and simulation at various time points.

Applicator	0 sec DSC	20 s DSC	60 s DSC	150 s DSC	210 s DSC	330 s DSC
1000 W/kg iso-SAR						
Short-tip	0.740+/-0.045	0.738 +/-0.043	0.715+/-0.031	0.753+/-0.032	0.759+/-0.023	0.738+/-0.01
Long-tip	0.773+/-0.028	0.749+/-0.060	0.748+/-0.020	0.742+/-0.010	0.716+/-0.010	0.766+/-0.033
500 W/kg iso-SAR						
Short-tip	0.832+/-0.011	0.803+/-0.026	0.760+/-0.050	0.771+/-0.049	0.766+/-0.032	0.816+/-0.043
Long-tip	0.769+/-0.013	0.746+/-0.012	0.774+/-0.015	0.755+/-0.013	0.768+/-0.010	0.759+/-0.010

Discussion

Infrared cameras have been employed in prior studies to evaluate tissue or phantom heating for thermal therapy devices [21,22,23]. Here, we used infrared camera measurements on *ex vivo* liver tissue to quantify temperature and SAR of two clinically employed MWA antennas. By intermittently turning power off, we were able to correct for thermal conduction (equations 5.1, 5.2, 5.3) and thus calculate SAR both initially and during ablation, to characterize changes in SAR. We used the results of these experimental measurements to validate a prior multi-physics MWA model [9]. There was reasonable agreement in shape and dimension of the ablation zone (defined by the 60 °C isotherm), with deviations of 0.3 cm (transverse diameter) and 0.4 cm (axial diameter) (Figures 5.6, 5.7). There was however a considerable change in SAR observed during the experiments, which was not apparent in the computer models. For both short-tip and long-tip applicator experimental studies, hot spots were apparent during the first 150 seconds but disappeared later (Figures 5.4 (a), 5.5(a)). A similar change in SAR was not apparent in the computer simulations (Figures 5.4(b), 5.5(b)) suggesting that the temperature dependence of tissue properties – particularly that of dielectric properties – is not adequately captured in the simulation. This may be in part due to the difficulty of direct measurement of temperature dependence of dielectric properties, particularly at high temperatures (> 100 °C). While there are reports of temperature dependent tissue dielectric properties at 915 MHz, measurements at 2.45 GHz suggest values of tissue electrical conductivity and permittivity drop considerably at temperatures in excess of ~ 80 C [31,32], attributed to loss of tissue water. A similar trend at 915 MHz would suggest reductions in SAR

at tissue temperature in excess of 100 °C , which was not observed in experiments for $t < 50$ s. Our results suggest that the greatest changes in SAR occur once tissue temperature exceeds 100 °C (see Figures 4, 5, $t=360$ s).

Differences were also observed in the temperature profile, with more uniform temperature surrounding the antenna in experimental studies, and larger gradients in the computer simulations –a result from the differences in SAR pattern.

In addition, comparison of simulated SAR profile to experimentally measured SAR profile for a 15 W, 6 minute ablation with the short-tip applicator at different time points is illustrated in Figure 8. Table 5.1 shows approximately 78 % agreement between the simulated and experimentally measured transient SAR profiles. The 18-20% discrepancy between simulation and experiment depicted in Table 1 and Figure 5.8, is in part likely because the simulated ablation captured the SAR along the shaft of the antenna.

We experimentally demonstrated considerable change in SAR during ablation, which is not adequately captured in the computer simulation, likely due to inaccuracies in temperature dependence of dielectric properties. Nevertheless, the ablation zone dimensions between simulation and experiment agreed reasonably well suggesting that the impact of this change in SAR during heating is somewhat limited.

In future work we will examine an alternate modeling approach based on using these experimentally measured SAR data as direct input into the simulation framework to simulate ablation zone extents. Such a simulation approach does not require knowledge of the specific antenna design, and is also computationally less demanding allowing shorter simulation times. While we employed infrared thermometry in this

study, the proposed technique to estimate SAR changes during heating may also be employed with magnetic resonance thermometry to facilitate 3D measurements.

Conclusion

The focus of this study was to experimentally characterize the transient power deposition pattern during MWA given a commercially available antenna with known geometry. The experimental results suggest significant changes in SAR during heating which were not present in simulation results, though ablation zone dimensions agreed well between model and experiment. The experimentally measured SAR data may potentially be used in computer simulations to predict ablation zone dimensions for MWA when the antenna geometry is unknown.

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CHAPTER 6

SUMMARY AND CLINICAL IMPACT

This manuscript in developing ablation treatment planning and guidance tools for accurate and precise treatment delivery. Chapter 3 focused on presenting methods and results for building and validating a model for simulating MWA procedures for a Person Medical's MWA applicators (a clinically used system. In summary, the model's accuracy was confirmed by showing the agreement between simulated and measured ablation extents and radial temperature slope for 60 W and 30 W. Therefore, the dielectric and thermal liver tissue parameterizations used in this study may be good approximations for modeling the dynamic changes that occur during MWA treatments at 915 MHz.

Chapter 4 presented data on investigating the variability in the physical parameters incorporated in MWA treatments. While computational models afford the flexibility for including detailed tissue anatomy and heterogeneity, a balance between model complexity, accuracy, and required computational resources must be struck for practical clinical application. This data presented in chapter 5 may potentially provide guidelines for the level of detail needed for patient-specific modeling of MWA procedures. The results from simulating treatment effects given variance in tissue thermal and electrical properties will help to better approximate MWA zone extents using biophysical modeling techniques. Moreover, these simulations help identify properties that clinicians and engineers should concentrate on in patient-specific modeling, and which properties we can approximate with a certain level of

confidence. Ultimately, this study will help understand and effectively predict the underlying bio-physical changes that occur over the duration of MWA procedures in order to make a more useful treatment planning system. Although, more data needs to be collected in order to develop a clinically useful treatment planning simulation tool, the presented results will help in developing a potential platform for incorporating patient specific biophysical measurements for simulating MWA procedures.

Chapter 5 discussed a methodology for potentially extend these simulation methods to other devices with unknown geometry by investigating alternative techniques for providing thermal spatial estimates during MWA procedure. It focused on experimentally characterize the transient power deposition pattern during MWA using the Person MWA applicator in with known geometry. The experimental results suggest significant changes in SAR during heating which were not present in simulation results, though ablation zone dimensions agreed well between model and experiment. The experimentally measured SAR data may potentially be used in computer simulations to predict ablation zone dimensions for MWA when the antenna geometry is unknown (most clinical situations).