

Toward more precise microwave ablation systems

by

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AN ABSTRACT OF A DISSERTATION

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DOCTOR OF PHILOSOPHY

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Abstract

Thermal ablation procedures aim to eradicate targeted tissue by heating to temperatures exceeding 55-60 °C, where cell death occurs through coagulative necrosis. In the context of tumor ablation, the goal of the procedure is to have the ablation zone encompass the pathological lesion and a surrounding 5-10 mm margin of normal tissue. Microwave ablation (MWA) is an image-guided, energy-based technology, typically operating at 915 MHz or 2.45 GHz, that is widely used for treating various solid tumors, including those in the liver, kidney, and lung. During an MWA treatment, monitoring the temperature and estimating the attributed to resultant thermal damage can provide valuable insights for clinicians. The absence of a widely available, reliable, low-cost, real-time imaging system is a recognized unmet clinical need, posing a barrier to wider clinical adoption of microwave thermal ablation procedures.

This dissertation presents an electromagnetic transmission coefficient-based method for monitoring MWA procedures where the intended target is bracketed by two or more applicators. The electromagnetic transmission signal between the applicators depends on the geometry between the applicators and the medium between them. During ablation, the latter changes, and since the tissue dielectric properties change, this signal varies accordingly. A custom experimental ablation platform was developed to facilitate periodic switching between "heating mode," during which power from the generator was coupled to the applicators, and "monitoring mode," during which the applicators were connected to a network analyzer for broadband transmission coefficient (s_{21}) measurements.

The initial aim was to assess the feasibility of monitoring the transient spread of thermal ablation zones using the microwave transmission coefficient-based technique in *ex vivo* tissue. MWA was performed on *ex vivo* bovine liver using a pair of custom 2.45 GHz directional

applicators. Experiments were conducted with applied powers ranging from 30 to 50 W per applicator for durations ranging between 53 and 1219 s. The transient s_{21} spectra collected throughout the ablations were analyzed to evaluate the feasibility of predicting the extent of ablation zones, and predictions were then compared against ground truth assessments derived from images of sectioned tissue. A linear regression-based mapping between the processed transmission data and the ground truth measurements was derived to predict the extent of ablation. The normalized average transmission coefficient initially decreased rapidly and then increased before asymptotically approaching a steady state. The transition time ranged from 53 s at 45 W to 109 s at 30 W. Analysis of the ground truth ablation zone images indicated that the time to complete ablation ranged from 230 to 350 s. The relative prediction error for the time to complete ablation, derived from the s_{21} data, was between 1.6% and 2.3% compared to the ground truth.

Next, an experimental study was designed to determine the feasibility of distinguishing between contiguous and discontinuous ablation zones using broadband transmission signals from a pair of omnidirectional-directional MWA applicators in an *in vivo* large animal model. Custom-built hardware facilitated the measurement of transmission signals during dual-applicator MWA at predetermined 46 s intervals. A multimodal ground truth was established using contrast-enhanced computed tomography (CECT) of ablation zones, cross-sectional and transversal gross pathologic assessments, and histopathologic evaluations of thermal injury. The study included 15 experiments on the livers of four domestic swine, with ablation durations of either 200 s or 600 s. Statistical analysis, correlation assessments, and exploratory data analysis were employed to assess the system's capability to distinguish between contiguous and discontinuous ablation zones.

Results showed clearly distinctive transmission signal datasets describing contiguous and discontinuous ablation zones. Spatiotemporal spread of ablation appears to be strongly correlated with measured and processed transmission signals (Spearman correlation coefficient 0.87, $p < 0.0001$). Based on processed transmission signal, a threshold value of 53% was determined as optimal for indicating ablation evolution through ROC analysis (AUC 0.84, $p = 0.02$, permutation test, 100,000 permutations).

To summarize, the feasibility of monitoring the spatiotemporal spread of thermal ablation zones using broadband microwave transmission coefficient measurements in *ex vivo* tissue, as well as effectively distinguishing between contiguous and discontinuous ablation zones in MWA procedures in *in vivo* tissue, were demonstrated. The presented technique holds potential to address the clinical need for a reliable method to monitor the spread of thermal ablation zones in real-time, potentially improving the precision and effectiveness of ablation therapies.

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The initial aim was to assess the feasibility of monitoring the transient spread of thermal ablation zones using the microwave transmission coefficient-based technique in *ex vivo* tissue. MWA was performed on *ex vivo* bovine liver using a pair of custom 2.45 GHz directional

applicators. Experiments were conducted with applied powers ranging from 30 to 50 W per applicator for durations ranging between 53 and 1219 s. The transient s_{21} spectra collected throughout the ablations were analyzed to evaluate the feasibility of predicting the extent of ablation zones, and predictions were then compared against ground truth assessments derived from images of sectioned tissue. A linear regression-based mapping between the processed transmission data and the ground truth measurements was derived to predict the extent of ablation. The normalized average transmission coefficient initially decreased rapidly and then increased before asymptotically approaching a steady state. The transition time ranged from 53 s at 45 W to 109 s at 30 W. Analysis of the ground truth ablation zone images indicated that the time to complete ablation ranged from 230 to 350 s. The relative prediction error for the time to complete ablation, derived from the s_{21} data, was between 1.6% and 2.3% compared to the ground truth.

Next, an experimental study was designed to determine the feasibility of distinguishing between contiguous and discontinuous ablation zones using broadband transmission signals from a pair of omnidirectional-directional MWA applicators in an *in vivo* large animal model. Custom-built hardware facilitated the measurement of transmission signals during dual-applicator MWA at predetermined 46 s intervals. A multimodal ground truth was established using contrast-enhanced computed tomography (CECT) of ablation zones, cross-sectional and transversal gross pathologic assessments, and histopathologic evaluations of thermal injury. The study included 15 experiments on the livers of four domestic swine, with ablation durations of either 200 s or 600 s. Statistical analysis, correlation assessments, and exploratory data analysis were employed to assess the system's capability to distinguish between contiguous and discontinuous ablation zones.

Results showed clearly distinctive transmission signal datasets describing contiguous and discontinuous ablation zones. Spatiotemporal spread of ablation appears to be strongly correlated with measured and processed transmission signals (Spearman correlation coefficient 0.87, $p < 0.0001$). Based on processed transmission signal, a threshold value of 53% was determined as optimal for indicating ablation evolution through ROC analysis (AUC 0.84, $p = 0.02$, permutation test, 100,000 permutations).

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Lastly, but certainly not least, my deepest thanks go to my family for their constant support.

Sincerely,

Nooshin Zeinali

Dedication

To the warriors battling cancer, whose strength and resilience inspired me.

Chapter 1 - Introduction

1.1 Microwave Ablation

Microwave ablation (MWA) is a minimally invasive technique primarily utilized for the treatment of tumors in organs such as the liver, lung, kidney, bone, prostate, and brain [1], [2]. The process involves transferring microwave power from an external generator to tissue through a thin, applicator inserted into the target tissue. The applicator includes an antenna and thermal management elements, and can be designed as: a rigid needle-type device for percutaneous placement guided by imaging or under surgical guidance; a flexible catheter-based device suitable for endoscopic deployment; and/or devices suitable for endocavity delivery [2], [3]. Within tissue, microwaves cause rapid oscillations of water and other polar molecules, generating friction and heat that ultimately cause cellular damage and tumor destruction. At temperatures exceeding ~55- 60 °C, cell death by coagulative necrosis is induced [4].

MWA is particularly advantageous for its rapid heating to elevated temperatures, typically requiring shorter treatment times compared to other ablation techniques like radiofrequency ablation (RFA) [5]. Because microwave propagation through tissue is not impeded by the formation of char at high temperatures, MWA offers the theoretical possibility for creating larger ablation zones than other modalities, making it effective even in highly perfused organs like the liver, where heat sink effects might diminish the efficacy of other techniques. MWA's ability to deliver high-energy doses rapidly is pertinent for effective treatment of larger tumors, offering a viable option for patients who are not candidates for conventional surgery. Beyond its oncological applications, MWA is also employed in treating a variety of non-cancerous conditions, including cardiac arrhythmias [6] and menorrhagia [7]

among others. The primary focus of this dissertation will be with reference to the use of MWA for treating tumors.

1.2 Components of MWA

MWA systems are designed to transmit energy from an external microwave generator to the specific area of targeted tissue for treatment. The energy is channeled through an applicator (with diameter in order of a few mm), which is inserted into the tissue. This applicator is connected to the generator through a specially designed cable that optimizes both power efficiency and usability (low loss cable). The applicator itself includes a transmission line (often a coaxial cable) and a radiating antenna, engineered to focus the energy on the target area and minimize any reflected power. Due to losses within the transmission line, practical MWA systems need to incorporate mechanisms for thermal management to regulate peak temperatures and thereby maintain structural integrity and performance of components, typically employing active cooling methods that utilize coolants such as water or gas and/or using pulsed power

delivery techniques. Key components of a MWA system are illustrated in Figure 1.1 and Figure 1.2.

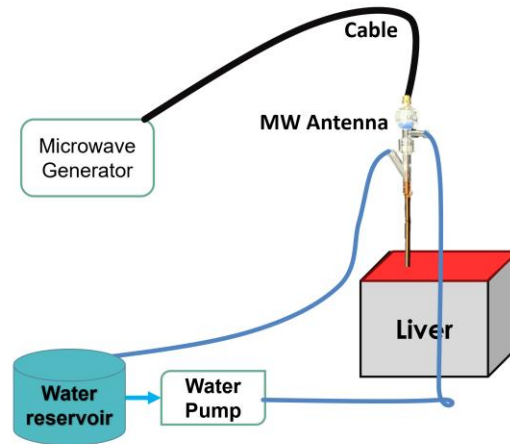


Figure 1.1. Key components of a microwave ablation system. Power is transferred from the microwave generator through a low-loss transmission line to an applicator. The applicator is connected to a peristaltic pump, responsible for cooling the applicator's shaft.

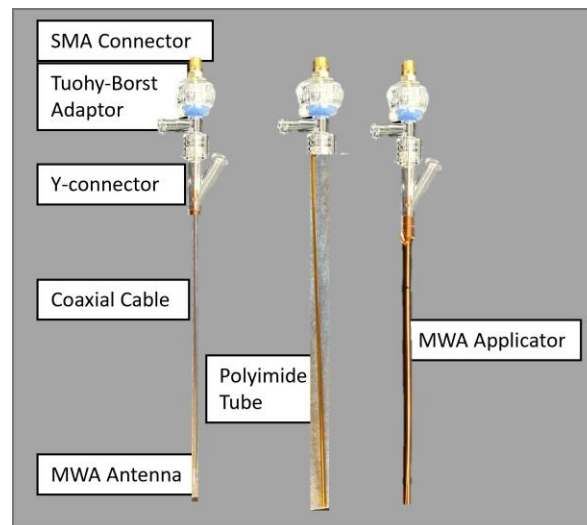


Figure 1.2. Components for fabrication of a water-cooled MWA applicator.

Most MWA systems in clinical use operate at frequencies of 915 MHz or 2.45 GHz, and systems operating at 5.8 GHz have also been proposed. These frequencies are chosen since they have been allocated for industrial, scientific, and medical (ISM) use, and favorable interactions

with tissue [8]. The typical power level used is 60-100 W for about 5-15 minutes, depending on the size of the tumor to be treated [9]. Commercial systems provide coagulation performance data based on experiments conducted either *ex vivo* or *in vivo* on animals [10]. Clinicians use this data to plan the treatment by deciding on the power level and duration of irradiation required for a specific outcome. Additionally, software tools have recently been developed to assist in determining the optimal insertion trajectory for the applicator and assessing the ablation zone after the procedure.

1.3 Goal of MWA

The primary objective of MWA is to eradicate targeted tumors while preserving the surrounding normal tissue. To achieve this, the treatment typically includes a margin of 5-10 mm of normal tissue around the tumor to reduce the risk of local tumor progression [11]. This approach aims to achieve an effective therapeutic effect, while minimizing collateral thermal damage to non-targeted tissue.

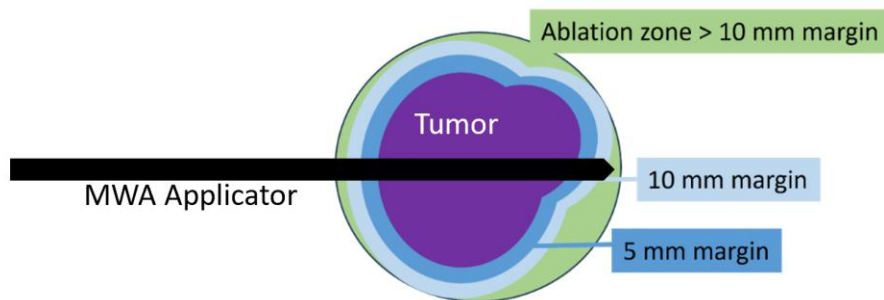


Figure 1.3. Schematic of a tumor (purple) with surrounding 5 mm (dark blue) and 10 mm (light blue) margins, and a given spherical ablation zone (green) area are illustrated.

1.4 Clinical Steps Involved in MWA

There are four typical steps involved in the clinical use of MWA [12]:

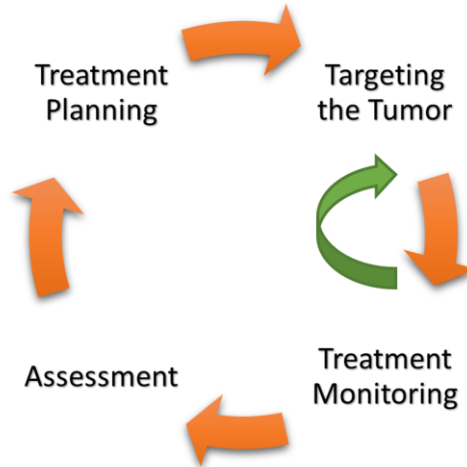


Figure 1.4. Workflow of a microwave ablation procedure.

1. Pre-procedure Planning:

Biopsy results and diagnostic images are used to define the type, location, size, and proximity of the tumor to vital structures, as well as any constraints related to the general health of the patient. This information aids in planning the approach, determining the trajectory of the applicators, and assessing the feasibility of safely delivering ablation[13], [14].

2. Ablation Procedure:

Depending on the complexity and location of the tumor, either local or general anesthesia is administered. Image guidance techniques such as Ultrasound (US) [15] or Computed Tomography (CT) [16] facilitate the precise insertion of the MWA applicator into the tumor. The applicator is typically percutaneously inserted following the path outlined in the imaging studies; in some settings, MWA may also be performed under open surgery or laparoscopy [17]. Depending on the size and complexity of the tumor, one or more applicators may be placed to target the tumor effectively, or a single applicator may be

used sequentially to cover the targeted area [18]. Once in position, the microwave generator is activated, emitting microwave energy that creates heat to ablate the tumor.

3. Treatment Monitoring:

The goal of monitoring is to observe the transient spatiotemporal spread of the ablation zone in 3D, to prevent undertreatment and reduce the risk of recurrence, as well as to prevent overtreatment and avoid damage to non-target tissue. Thermal damage is a function of time and temperature [19], [20], and therefore, the goal of monitoring would ideally involve measuring temperature profiles over time, although this is challenging to accomplish in the clinical setting.

4. Post-procedure Care and Outcome Assessment, Further Treatment:

Immediately post-procedure, a contrast-enhanced CT scan is performed to compare achieved ablation zone extents with the position of target. In case of non-overlapping regions between ablation and target, additional treatment sessions may be planned, or alternative therapies may be considered. Due to the local physiological effects of the ablation procedure, like hemorrhage, local hyperthermia, and tissue irritation, ablation zone as seen on CT scans can further evolve for up to several days after procedure, which is dependent on specific organs. Therefore, follow-up monitoring usually 14-30 days is performed to verify clinical success and to discover potential recurrence.

1.5 Limitations of Current MWA Practices and the Need for Real-time Monitoring

Although MWA procedures have been shown to be effective for tumors < 3 cm in maximum diameter [17], [21], there is a lack of a widely-available treatment monitoring method

to observe the spread of the ablation zone and to inform the physicians when to terminate the ablation. This may affect treatment outcomes, potentially leading to either incomplete ablation which increase the chance of local progression and tumor recurrence, or damage to surrounding normal tissue due to inadequate monitoring capabilities. To avoid leaving portions of the tumor untreated, depending on the size and complexity of the tumor, one or more applicators can be strategically placed to target the tumor, or a single applicator may be used sequentially to cover the entire targeted area [22].

Although there are treatment planning methods to mitigate complications during procedures, the most common approach involves using reference tables provided by applicator manufacturers. These tables are predominantly derived from *ex vivo* experiments under ideal conditions to produce repeatable ablation zones [23]. However, in clinical settings, accurately positioning applicators at the center of the targeted tissue is challenging, and the actual ablation zone may extend unpredictably to the organ's surface due to variations in tissue properties. Furthermore, these reference tables assume tissue homogeneity, while in reality, tumors can disrupt tissue uniformity, leading to deviations from expected ablation outcomes [24]. Consequently, relying solely on these tables has limitations. Physicians' experience becomes invaluable as they adapt to variances encountered in practice [25], [26], [27].

Additionally, the evaluation of treatment effectiveness typically occurs 3-4 weeks after the procedure, making it difficult to make immediate adjustments if the initial ablation was incomplete. Another challenge is image registration, which can be problematic when comparing pre- and post-treatment scans, further complicating the assessment of ablation success [28]. Therefore, there is a pressing need for a reliable real-time monitoring system to enhance the precision and efficacy of MWA treatments.

1.6 Proposal of a New Real-time Monitoring Method

This dissertation reports on the development and evaluation of a method for monitoring dual-applicator MWA procedures using the antennas within the applicators. Utilizing a dual-applicator setup during treatment, this system measures the broadband, complex-valued transmission signal (S_{21}) transmitted between antennas. It was hypothesized that variations in this signal correspond to changes in the tissue state throughout the ablation process, given the known temperature dependency of tissue dielectric properties. By quantifying these transient changes in transmission between antennas, the system has potential to provide a real-time indication of the tissue state ranging from non-ablated to fully ablated, thereby offering critical insights during the procedure.

To test this hypothesis, a platform capable of sequentially measuring the broadband, complex-valued transmission coefficient between a pair of water-cooled MWA antennas during ablation procedures was designed and developed. Additionally, the feasibility of this system under various experimental scenarios, *ex vivo* with a pair of directional applicators [29], [30], *ex vivo* with a pair of omnidirectional applicators [31], *in vivo* with a combination of omnidirectional and directional applicators were assessed. Throughout each experiment, the applicators were periodically switched between a connection to a microwave generator ("heating mode") and a vector network analyzer ("monitoring mode"). To evaluate the accuracy of this signal in predicting the extent of the ablation zone, ground truth data were systematically collected throughout the studies and compared with the signal's temporal changes.

1.7 Contributions

1. Design, Development, and *Ex Vivo* Evaluation:

- I proposed and executed the design and development of an ablation monitoring platform capable of sequentially measuring the broadband, complex-valued transmission coefficient between a pair of water-cooled MWA applicators. This platform was tested under various *ex vivo* conditions, including experiments with both directional and omnidirectional applicators. This comprehensive testing was critical to refining the system's capabilities and ensuring its accuracy and reliability in a controlled environment before advancing to *in vivo* applications. The details of this investigation are summarized in Chapter 3 of this dissertation.
- Furthermore, findings and developed methodologies have been disseminated through the following publications and presentations:

N. Zeinali, et al, "Electromagnetic transmission coefficient-based assessment of tissue state during microwave ablation," in *Frontiers in Biomedical Devices*, vol. 84815, V001T02A004, 2022/4/11, American Society of Mechanical Engineers.

N. Zeinali, et al, "Abstract No. 332 A Transmission Coefficient-Based Approach for Real-Time Monitoring of Multiple-applicator Microwave Ablation: Experimental Studies in *Ex Vivo* Liver Tissue," *Journal of Vascular and Interventional Radiology*, vol. 35, no. 3, p. S147, Mar. 2024, Elsevier.

N. Zeinali, et al, "Transmission Coefficient-based Monitoring of Microwave Ablation: Development and Experimental Evaluation in *ex vivo* Tissue," *IEEE Transactions on Biomedical Engineering*, Nov. 9, 2023, IEEE.

N. Zeinali, et al, "Feedback controlled microwave ablation: Preliminary experimental studies," presented at *Society for Thermal Medicine annual scientific meeting*, virtual meeting, 2022

N. Zeinali, et al, "Feedback controlled microwave ablation: Simulation-based validation of experiments in *ex vivo* liver tissue," in *Proc. National Radio Science Meeting*, Jan. 2023.

2. ***In vivo* Evaluation:**

- Following successful *ex vivo* testing, I designed and conducted *in vivo* study to assess the monitoring system's performance in living tissue with presence of heat sink effect of local blood flow, respiration-pulsation artifacts, unintended misalignment of the applicators, etc. Nevertheless, even this scenario still missed the presence of tumor. These studies involved the use of the system with a combination of omnidirectional and directional applicators, allowing us to evaluate its effectiveness and adaptability in a dynamic biological setting. The in-depth details of the *in vivo* study are thoroughly discussed in Chapter 4 of this dissertation.
- Furthermore, the findings and methodologies from this portion of the research have been documented and disseminated through a publication and an abstract:

N. Zeinali, et al, "Multi-applicator microwave ablation with directional and omni-directional antennas: Feasibility study in normal porcine liver *in vivo*,"

presented at *Society for Thermal Medicine annual scientific meeting*, Houston, TX, 2024

N. Zeinali, et al, "Microwave Transmission-Based Monitoring of Dual Applicator - Microwave Ablation: Experimental Assessment in an *In vivo* Porcine Liver Model," in preparation for submission to a peer-reviewed journal

Chapter 2 – Background

To understand the underlying physics of the interactions between biological tissues and microwaves during ablation procedures, it is informative to review the biophysics of electromagnetic-thermal interactions with tissue. This section is intended to provide a foundation for the proposed microwave transmission-based monitoring system.

2.1 Dielectric properties of tissue

The electrical characteristics of tissues over a wide range of frequencies can be described by the material properties relative permittivity (i.e., dielectric constant), ϵ_r' and effective electrical conductivity, σ . From both of these, the relative complex permittivity, ϵ_r^* , can be defined by the equation:

Equation 2.1

$$\epsilon_r^*(\omega) = \epsilon_r'(\omega) - j\epsilon_r''(\omega)$$

where ϵ_r' is the real part of the relative complex permittivity, ϵ_r'' is the imaginary part, and ω is the angular frequency of the external electromagnetic field. The dielectric loss represented by the imaginary part is linked to the effective electrical conductivity, and can be written as:

Equation 2.2

$$\epsilon_r'' = \frac{\sigma}{2\pi f \epsilon_0}$$

where f represents frequency [Hz] and ϵ_0 is the permittivity of free space [F/m] ($\epsilon_0 = 8.854 \times 10^{-12}$ F/m). These dielectric properties (ϵ_r' , and ϵ_r'') are tissue-, frequency-, and temperature dependent.[32], [33], [34].

Relative permittivity ϵ_r' : primarily affects how an electric field is stored within a material, impacting capacitive properties and the propagation of electromagnetic waves within the medium.

Dielectric loss ϵ_r'' : describes how freely charges can move through the material, which affects the material's ability to conduct electric current and dissipate energy when subjected to an alternating electric field.

Both properties are crucial in describing a material's response to microwave fields. During ablative heating, temperatures can rise from physiologic temperature ($\sim 37^\circ\text{C}$) to temperatures above $\sim 100^\circ\text{C}$. At these elevated temperatures, biophysical properties undergo significant changes due to water vaporization and desiccation, leading to irreversible alterations in tissue properties, as illustrated in Figure 2.1. Notably, when temperatures exceed approximately 90°C , both dielectric properties exhibit a significant decrease [35]. The interplay between these properties determines the penetration depth, absorption characteristics, and phase velocity of electromagnetic waves in the material, all of which are essential for designing effective electromagnetic-based medical devices. The dielectric properties of target tissues are key inputs for computational models of electromagnetic-thermal interactions with tissue, widely used for device design and optimization, and device characterization.

Several studies have reported the dielectric properties of tissues across microwave frequencies, including temperature dependencies [33], [36], [37], [38], [39], [40]. For *ex vivo* bovine liver, a commonly used tissue medium for evaluating ablation devices, based on the equations provided in [40], two plots were created: one showing changes in relative permittivity and the other in electrical conductivity, both across a wide range of temperatures and frequencies pertinent to MWA.

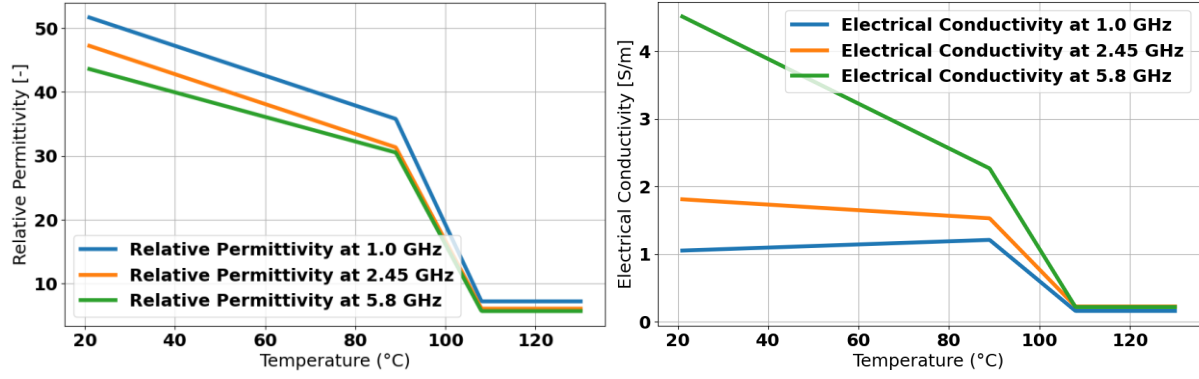


Figure 2.1. Relative permittivity and electrical conductivity spanning the ablative temperature range for three different frequencies pertinent to microwave ablation (curves generated from parametric models of temperature and frequency dependent dielectric properties presented in [40]).

The Pennes bioheat equation, commonly used to model heat transfer within biological tissues, is given by:

Equation 2.3

$$\rho c \frac{\partial T}{\partial t} = \nabla \cdot k \nabla T - \rho c \omega_{bl} (T - T_{bl}) + Q_{src}$$

where ρ is the tissue density, c is the specific heat, T is the temperature, k is the thermal conductivity, ω_{bl} is the blood perfusion rate, and T_{bl} is blood temperature. The term Q_{src} represents the heat generated by external sources, which can be linked to the electric field vector in tissue, $\mathbf{E}$, as:

Equation 2.4

$$Q_s = \frac{1}{2} \sigma |\mathbf{E}|^2$$

where σ is the electrical conductivity of the tissue [41]. The transient temperature profile from solution of Equation 2.3 can then be used to estimate the extents of thermal damage.

2.2 Real-time Monitoring Methods of Microwave ablation

The currently available methods for planning MWA procedures are primarily based on manufacturer-provided reference tables of ablation zone extents based on idealized conditions in homogeneous *ex vivo* tissue. While these tables facilitate repeatable outcomes in controlled

environments, they are not well suited to predicting ablation zones in clinical practice where tissue heterogeneity, the presence of variable and unknown blood perfusion, and imperfect antenna placement influence the predictability of ablation zones [23], [42]. Additional CT scans during the procedure increase patient exposure to radiation, and while they provide extra information about tissue changes, these may not necessarily represent ablation boundaries. These limitations underscore the need for more effective real-time monitoring techniques in MWA. In this section, existing methods for monitoring thermal ablation procedures are reviewed, including approaches that have been employed in the clinical setting, and emerging methods. Existing methods can be categorized into two main types: temperature change-based and tissue state change-based methods [43]. Below, the mechanisms and relative strengths of each method are presented and comparatively assessed.

Extent of ablation zone during the ablation is a function of time-temperature history during heating. Though, thermal dosimetry provides continuous insight into the level of thermal damage experienced by tissue during exposure, quantization of the thermal damage can be beneficial for monitoring purposes [19]. There exist thermal damage estimation methods like Arrhenius model to demonstrate the relationship between temperature and rate constant of a chemical reaction:

Equation 2.5

$$k = Ae^{-\frac{E_a}{R_g T}}$$

Where k is the chemical reaction rate constant [1/s], A represents frequency factor [1/s], E_a is the activation energy barrier [J/mol], R_g is the universal gas constant [1.987×10^{-3} Kcal/mol/K], and T is the temperature [K]. Lower activation energies and higher temperatures

increase the rate constant of a given reaction. This first-order rate process model can quantify the damage using a single parameter (Ω), which is time-dependent:

Equation 2.6

$$\ln \left(\frac{C(0)}{C(t)} \right) = A \int_0^t e^{-\frac{E_a}{R_g T(t)}} dt = \Omega(t)$$

where $C(0)$ is the concentration of viable cells before the procedure and $C(t)$ is the concentration at time t . The fraction of surviving cells can be computed by:

Equation 2.7

$$C(t) = 100 e^{-\Omega} (\%)$$

In practice, the kinetic parameters (A and E_a) must be determined experimentally by exposing cells to (near) isothermal heating conditions, and assessment of the corresponding changes in cell survival. A threshold value of $\Omega = 1$ (corresponding to 63.2% of the thermal damage process being complete, or analogously 36.8% of cells remaining viable) is often employed for estimating the extent of the ablation zone [20], [44], [45], [46].

Temperature increase can be monitored directly, or the effect of temperature on tissue can be observed. If the method directly measures temperature changes, it is classified as a temperature change-based monitoring method, as discussed in the following section. Conversely, if the monitoring method is based on the impact of temperature on tissue and the resulting changes in its state, it is considered a tissue state change-based monitoring method.

2.2.1 Temperature Change-Based Monitoring Methods

These methods quantify temperature changes in tissue during ablation to provide a direct assessment of treatment effects.

2.2.1.1 Temperature Sensors

Temperature Sensors (Electrical and Optical Fiber Probes)

Temperature sensors, such as electrical (thermocouples and thermistors) and optical fiber probes (Fluoroptic or fiber bragg grating sensors, FBG), are inserted directly into the target tissue for thermal ablation procedures. These sensors enable precise monitoring of localized temperature changes, crucial for tracking ablation progress and determining when to adjust or halt energy delivery. However, when these sensors are not integrated within the ablation applicator, their insertion introduces additional invasiveness, complicating the procedure, and potentially increasing patient risk. The localized measurements provided by these sensors capture temperature changes at specific points, which may not accurately reflect broader thermal dynamics within the ablation zone [47], [48]. Additionally, sensors employing metallic components (such as thermocouples or thermistors) are susceptible to electromagnetic interference.

To improve the utility of probe-based temperature sensors, a multipoint temperature sensing strategy may be implemented. This method involves deploying several sensors positioned along a single needle/catheter to gather a more comprehensive dataset on temperature fluctuations within tissue exposed to the ablation field [49], [50]. Coupled with computational models, multipoint temperature sensors can offer real-time tracking of ablation progress, facilitating more precise control over the procedure.

2.2.1.2 Imaging-based thermometry methods

Ultrasound Thermometry

Ultrasound thermometry estimates temperature changes by detecting variations in the speed of sound and thermal expansion within tissues. During ultrasound imaging, a high-frequency sound wave is transmitted into the human body using a mechanical transducer. The

ultrasound image is created from echoes produced by the reflection of these waves. The depth of the examined tissue can be determined by the time it takes for the wave to travel to the tissue and back to the transducer [49]. This time delay can be calculated using the following equation:

Equation 2.8

$$t(T_0) = \frac{2z}{c_0(T_0)}$$

where $t(T_0)$ represents the time delay of reflected wave measured at depth z and temperature T_0 , c_0 is the known speed of sound in the tissue at the reference temperature T_0 (usually at physiologic temperature, $\sim 37^\circ\text{C}$). A time shift can be detected due to the medium's thermal expansion and variation in sound speed when temperature changes. The temperature change can be computed by:

Equation 2.9

$$\Delta T \approx \frac{c_0}{2} \frac{1}{\alpha - \frac{1}{c_0} \frac{\partial c}{\partial T}} \frac{\partial}{\partial z} (\Delta t)$$

where ΔT is the temperature change, α is the thermal expansion coefficient, and speed of sound sensitivity to temperature is $\frac{\partial c}{\partial T} \approx -5 \text{ m/s}^\circ\text{C}$ [51].

However, its reliability is constrained because the speed of sound only increases with temperature up to approximately 50°C in non-fatty tissues, after which it begins to decrease. This method's accuracy is compromised by tissue-specific responses and nonlinear changes in acoustic properties caused by heating, which pose challenges in heterogeneous tissue environments. Additionally, the effectiveness of ultrasound thermometry is not well established at higher temperatures ($> 50^\circ\text{C}$), as transducers often encounter interference from a hyperechogenic cloud resulting from water vaporization at temperatures around 100°C [52], [53], [54], [55].

X-ray Computed Tomography Thermometry

Each pixel within a computed tomography (CT) scan corresponds to a measure of X-ray attenuation, expressed as a CT number (expressed in Hounsfield Unit, HU). This number serves as an indicator of tissue density, revealing the degree to which X-rays are absorbed or blocked by the tissue [49]. CT numbers can be computed using the following equation:

Equation 2.10

$$CT(x, y) = \frac{1000 \cdot [\mu(x, y) - \mu_w]}{\mu_w}$$

where μ_w represents the water linear attenuation coefficient and $\mu(x, y)$ represents the average linear attenuation coefficient in the (x, y) voxel. The linear attenuation coefficient is influenced by tissue-X-ray interactions, mainly due to the Compton effect (a process where X-rays are scattered by electrons, resulting in a change in the photon's direction and energy, and providing key evidence for the dual nature of light as both wave and particle), which is impacted by ρ tissue density, and inversely depends on temperature variation as given by:

Equation 2.11

$$\rho(T) = \frac{\rho(T_0)}{1 + \alpha \cdot \Delta T}$$

where ΔT represents the temperature variation, T_0 is the room temperature, α is the thermal expansion coefficient. By applying Taylor series linearization, temperature can be estimated from CT numbers. During thermal ablation procedures, by monitoring changes in CT numbers during an ablation procedure, there is an opportunity to indirectly observe the thermal effects

within the tissue, utilizing these variations as a proxy to assess the progression and extent of the ablation zone [49], [56], [57], [58].

The feasibility of this method was tested in studies within *ex vivo* tissue, showing good spatial resolution with a temperature precision of around 3°C. However, it has not been used clinically due additional X-ray exposure and tissue-type specificity.

Magnetic Resonance Thermometry

MRI thermometry, using the Proton Resonance Frequency (PRF) shift method, is a non-invasive approach for monitoring thermal changes during MWA. The PRF method exploits the linear correlation between temperature and the frequency shift of protons. The frequency shift is determined by measuring the difference in phase acquired by two gradient-echo scans [49]. The change in temperature between the scans (ΔT) is given by:

Equation 2.12

$$\Delta T = \frac{\varphi - \varphi_{ref}}{\gamma \cdot \alpha \cdot B_0 \cdot TE}$$

where α is the PRF change coefficient, TE is the time to echo of a gradient echo pulse sequence, φ , and φ_{ref} are the image phases at temperature T and T_0 , respectively, γ is the gyromagnetic ratio, and B_0 is the magnetic field strength of the MR scanner.

However, the technique has notable limitations. Its effectiveness is reduced in tissues like fat and bone due to poor sensitivity, and it is highly susceptible to motion artifacts caused by cardiac, respiratory, or patient movements, which can significantly distort temperature readings [59], [60], [61], [62].

To improve accuracy, a reference less approach has been introduced, which obtains the reference phase from an area outside the thermotherapy zone. While this enhances precision, it does not entirely resolve motion sensitivity issues. Furthermore, the standard practice of setting a

reference temperature, typically at 37°C, can lead to underestimations of the actual damage zone, as residual heat may raise the baseline temperature [60].

MRI thermometry is also incompatible with ferromagnetic materials, requiring the use of applicators made from non-ferromagnetic materials and microwave generators need to be carefully designed [62]. Additionally, the method's spatial averaging can lead to recorded temperatures being up to 30% lower than the true peak values within a voxel, which may underestimate the true extent of the thermal spread [60]. Moreover, MRI thermometry does not capture cavitation, and the cost and speed of scans pose further challenges.

Despite these challenges, PRF shift thermometry is valued for its high spatial and temporal resolution, which are critical for effectively monitoring the ablation process. Research continues to advance this technology, including the development of volumetric thermometry for three-dimensional monitoring, aiming to enhance its application in clinical settings.

Microwave Thermometry

The basic principle of microwave imaging-based monitoring of ablation involves probing the treated region with an array of external antennas and recording the spatial-temporal spread of the back-scattered electromagnetic field during treatment. While the ablation treatment is taking place, a limited number of antennas are positioned above the tissue sample. These antennas record the evolution of the scattered field, which is then processed to obtain a spatial map of the complex permittivity variation as the tissue is ablated. Variations in the recorded data over time are processed using an inverse scattering algorithm, generating an image that depicts changes in the electromagnetic properties of the treated area. Recent research has demonstrated significant alterations in the dielectric permittivity and electrical conductivity of tissues exposed to very high temperatures (up to 120 °C) during MWA procedures. By analyzing these data, a spatial

map of complex permittivity variations can be reconstructed, solving an inverse problem to accurately image the thermal effects on tissues [63], [64], [65].

However, a notable challenge in microwave tomography is penetration depth, as the antenna arrays are positioned externally to the patient's body, and currently, imaging is carried out at a single frequency. This method is still in the exploratory phase, aiming to overcome such limitations and enhance its potential in the clinical setting.

2.2.2 Tissue State Change-Based Monitoring Methods

These methods quantify changes in tissue state—whether mechanical, optical, or electrical—during ablation to assess treatment effects. Below is a review of mechanical and electrical methods, including their mechanisms and performance assessment.

2.2.2.1 Mechanical Property-Based Techniques

Elastography techniques rely on basic relations governing tissue displacement and motion to estimate changes in tissue mechanical properties [66]. In ultrasound elastography for monitoring thermal ablation, the key concept is to measure tissue stiffness, which changes as a function of temperature. Various elastography imaging methods, rely on monitoring the changes in tissue properties during thermal ablation.

Shear Wave Elastography

Shear Wave Elastography (SWE) is ultrasound imaging technique used to measure the stiffness of tissues by observing the propagation of mechanically induced shear waves within them. This method involves the use of focused ultrasound beams to generate transient shear

waves in the tissue. As these shear waves propagate perpendicular to the direction of the ultrasound beam, they create displacements within the tissue.

The ultrasound system captures the velocity of these waves as they move through the tissue. Since the speed of shear waves is directly related to the mechanical stiffness of the tissue, and tissue stiffness increases with temperature, this measurement can be used to infer the elasticity or stiffness of the area being examined. The stiffer the tissue, the faster the shear waves travel through it [67], [68].

Strain Elastography

Strain elastography, a technique introduced by Ophir et al. in 1991 [69], measures tissue stiffness by utilizing mechanical perturbations to induce tissue displacements (one dimensional). This method applies a mechanical force, either externally or internally [70], tracks the resulting displacements, and calculates strain. The strain data are then used to generate a map displaying relative differences in tissue stiffness, providing non-invasive insights into the mechanical properties of tissue under stress. Elastography can apply forces that range from quasi-static to dynamic and impulse deformations [66], [71], [72], [73], [74], allowing for detailed evaluations under various mechanical stresses.

While promising *in vivo*, clinical application of strain elastography faces challenges. During thermal ablation, temperature rise can cause bubble formation, reducing ultrasound signal-to-noise ratio (SNR) and complicating imaging. Large ablation zones may suffer from non-uniform transducer compression, affecting image quality. To address these issues, approaches like electrode displacement elastography (EDE) use the ablation electrode to induce

strain directly at the ablation site, enhancing accuracy and reliability. *In vivo* studies and clinical trials have demonstrated EDE's efficacy in delineating ablated regions with superior image contrast compared to B-mode [75] or radiation force imaging [76].

Acoustic Radiation Force Impulse

Acoustic radiation force impulse (ARFI) imaging is an elastographic technique that leverages radiation pressure, similar to shear wave elastography, to generate images based on tissue displacement caused by focused ultrasound pulses [77]. This noninvasive method allows for the creation of 2D images by sweeping the ultrasound's focal point across a designated region of interest, thereby eliminating the need for manual compression typically required in other forms of elastography. In soft tissue, the primary cause of attenuation is absorption. F represents the magnitude of radiation force from a focused ultrasound pulse in a specific spatial location which is shown by α the absorption, c speed of sound of the tissue, and I represents the local temporal average intensity of the acoustic beam [78]:

Equation 2.13

$$F = \frac{2\alpha I}{c}$$

The absorption of acoustic energy generates heat within the tissue. For a single pulse, by neglecting heat loss due to perfusion and thermal conduction, the temperature rise in the tissue can be estimated by:

Equation 2.14

$$\Delta T = \frac{q_v}{c_v} t = \frac{2\alpha I}{c_v} t$$

where q_v represents the rate of heat production per unit volume generated from absorption of acoustic energy, and c_v is the heat capacity per unit volume of the tissue. ARFI has been particularly noted for its efficacy in differentiating pre-ablation and post-ablation states of malignant tumors, providing superior boundary delineation when compared to traditional B-mode ultrasound imaging [79], [80]. Similar to SE method, the rise in temperature can lead to bubble formation within the tissue, which reduces ultrasound signal-to-noise ratio (SNR) and in general, framerate of creating 2D images are moderate.

Harmonic Motion

Harmonic Motion Imaging (HMI) employs focused ultrasound (FUS) to generate localized, low-frequency mechanical vibrations within target tissues. By directing ultrasound energy to a precise location, the tissue at this focal point begins to oscillate due to the radiation force exerted by the ultrasound. As the tissue vibrates, either the same ultrasound system or an additional imaging transducer monitors these oscillations (oscillatory deformations), tracking how the tissue responds over time.

The response of the tissue, influenced by its mechanical properties, varies with its stiffness; stiffer tissues exhibit smaller displacements and potentially higher resonance frequencies, while softer tissues show larger displacements under the same conditions. [81], [82].

Magnetic Resonance Elastography

MR Elastography measures tissue mechanical properties by observing the propagation of shear waves induced within the tissue. These waves can be generated through several methods: an external driver on the skin, a percutaneous ablation probe, or an acoustic pulse via Acoustic

Radiation Force Impulse (ARFI) imaging. MRI technology then captures how these waves travel through the tissue, allowing for the analysis of tissue stiffness by examining the waves' speed and displacement patterns.

Although MRE can measure all three spatial components of induced tissue displacement, making it ideal for quantitative elastography, it encounters challenges such as the high costs associated with MRI and the requirement for MRI-compatible ablation probes. It also suffers from longer scan times and larger voxel sizes than ultrasound elastography, which hinders its ability to provide real-time monitoring and precise boundary delineation of ablation zones. Ongoing research aims to overcome some of the limitations by integrating MRE with MRI thermometry (MRT) [83], [84].

2.2.2.2 Electrical Property-Based Techniques

There are several studies that have explored electrical property changes over the course of ablations. As an example, Besler et al. [85] utilized a device-based approach that combined electrode impedance measurements with machine learning to predict ablation depth during radiofrequency ablation. They employed a hardware setup to simultaneously perform the ablation and collect impedance data. Various machine learning algorithms were tested to predict the ablation depth in three dimensions based on the collected data. Temperature was measured at different distances, interpolated, and classified binarily to determine whether the tissue volume at the specified face and depth was ablated. This classification served as the target value for the training dataset and was used to evaluate the predicted depth estimation based on complex electrical impedance. The complex impedance data, measured at 100 kHz, was collected by the same RFA device performing the ablation, thus eliminating the need for additional measurement

equipment and avoiding complexity in the patient setup. The study demonstrated general trends in complex electrical impedance as the ablation lesion at a particular face grew deeper, estimating the ablation depth to be around 2 cm from the RFA applicator.

To exploit the dielectric boundary between two domains (e.g., tumor or ablation zone and normal tissue) of tissue, Wang et al [86] utilized the same microwave applicator used for ablative treatment. They measured time-domain signal reflections in ultrawideband (UWB) from the interface between tumors and the liver, providing information about the tumor boundary in both radial and axial directions. By measuring the response from the tumor embedded in the liver, they obtained a signal containing reflections from both the antenna–tissue interface and the tumor–liver interface, denoted as total reflection. They demonstrated that a hypothetical reflection could be produced from the antenna inserted into an all-tumor homogeneous medium through simulation or phantom experiments. By subtracting the two signals, the interface response can be acquired. Based on the signal peak delay time, the distance from the antenna feed point to the tumor/liver interface can be estimated, determining the tumor radius.

Some other examples of exploiting the electrical properties of tissue include monitoring the reflection coefficient of the antenna during MWA. As the tissue heats and vaporizes, its dielectric properties change, creating an impedance mismatch between the antenna and the tissue. This mismatch causes an increase in reflected microwave energy. Monitoring the reflected power can indicate tissue vaporization and the extent of thermal damage. Based on insights from the reflected power, the procedure can be stopped, and the antenna can be moved to another location (e.g., thyroid nodules)[87]. Adjusting the operating frequency during the procedure can achieve efficient power transfer to the tissue [88], [89].

To leverage electrical conductivity and relative permittivity, a monitoring method for MWA utilizing two or more antennas was introduced to measure complex broadband transmission signals traveling between them. These signals, representing a fraction of what is emitted by the transmitting antenna and received by another, dynamically shift in response to changes in tissue properties throughout the ablation process. This method has been demonstrated as an effective tool for assessing the extent of the ablation zone between pairs of directional and omnidirectional antennas in both *ex vivo* bovine liver and *in vivo* porcine liver. While this monitoring system does not provide a 3D image, it offers a real-time assessment of ablation completion between a pair of antennas. One significant advantage is that it integrates seamlessly with the existing MWA setup without requiring additional devices, utilizing the MWA antennas themselves as the monitoring apparatus.

Chapter 3 – Transmission Coefficient-Based Monitoring of Microwave Ablation: Development and Experimental Evaluation in *Ex Vivo* Tissue¹

3.1 Introduction

Microwave ablation (MWA) is a clinically accepted minimally invasive procedure for treating tumors in the liver, lung, kidney, bone, and other tissues [90], [91], [92], [93]. During MWA, one or more ablation applicator(s) are placed into the intended location/s within or adjacent to the target tumor under image guidance. After confirming appropriate positioning, the applicator(s) couple microwave power from an external power source (microwave generator) to the target tissue. A variety of microwave ablation applicator designs have been developed, with the vast majority of those in clinical use creating ablation patterns largely cylindrically symmetric about the applicator shaft, whereas applicators with directional heating patterns have also been proposed and are under development [3], [10]. In current clinical practice, X-ray Computed Tomography (CT) and ultrasound (US) imaging are the most widely used modalities for guiding device placement and are also used to assess the technical success of the procedure [94], [95]. One of the current challenges with MWA is a lack of established techniques for intra-

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procedural monitoring to determine treatment endpoint, and this remains an area of active investigation [43].

The objective of a thermal ablation procedure is to fully encompass the tumor and a 5–10 mm circumferential margin of normal tissue with an ablative thermal dose [95], [96] while limiting the thermal damage to surrounding non-target tissues [41], [97]. Achieving an adequate treatment margin decreases the likelihood of local tumor progression, while constraining non-target heating may decrease the risk of adverse events [98]. While thermal damage in tissue is a function of the time–temperature history during heating, at temperatures in excess of approximately 60 °C tissue can be considered fully ablated.

Accurate applicator positioning relative to the target, and selection of applied energy delivery settings, are recognized as key factors in achieving technical success. The development of robotic systems for percutaneous applicator placement [99], [100] and ablation treatment planning tools [101], [102] are anticipated to contribute to the reliable delivery of ablation procedures. Moreover, intra-procedural real-time monitoring of ablation zone growth has the potential to substantially enhance the efficacy and safety of MWA by providing feedback to the clinician on when to terminate applied power; by considering the extent of target ablation coverage and risk to surrounding tissues. MRI offers the capability for real-time volumetric monitoring of temperature profiles, such as with the proton resonance frequency shift technique [62]. Wide adoption of MRI thermometry is, however, currently limited by the requirement of developing MRI-conditional ablation systems, the high costs of procedures in the MRI suite, and the need for specially trained personnel. Volumetric thermometry with X-ray CT and ultrasound has also been investigated, though these are not in current routine clinical practice [51], [58], [103], [104].

Besides image-based methods for real-time monitoring of the ablation zone, methods exploiting changes in physical properties of tissue during heating – electrical, optical, mechanical, and/or thermal – using measurements made with the ablation device(s) have also been explored as a means for monitoring time-dependent growth of the ablation zone. Besler et al. studied such a device-based approach using electrode impedance measurements coupled with a machine learning approach to predict the ablation depth during radiofrequency ablation [85], [105]. Employing multipoint temperature sensors within the ablation field, coupled with computational models, has the potential to provide real-time tracking of the ablation progress, at the expense of increased invasiveness [106].

The dielectric properties of tissue within the microwave frequency range are known to vary with temperature, with considerable changes in dielectric property values between ablated and non-ablated tissue (Figure. 3.1(a)) [37], [38], [39]. Some studies have investigated the use of externally positioned microwave antennas and employed a microwave imaging approach to assess temperature-induced changes in tissue dielectric properties, from which the extent of ablation zone is inferred [107]. Others have investigated using the ablation antenna to transmit a broadband pulse and, the same antenna to receive the associated scattered/reflected signal at the ablation zone boundary to estimate the depth of the ablation zone [86], [108]. The use of applicators with directional (“side-firing”) radiation patterns offers the opportunity for ablating targets with two or more applicators positioned on the target periphery and directing power toward the center of the target (Figure. 3.1(b)). Such an approach may allow for defining the extent of the treatment margin by applicator positioning. Further, as proposed in our earlier preliminary experimental studies [29], such an approach offers the potential for estimating the

spread of the ablation zone from the complex-valued electromagnetic transmission coefficient between the applicators, as illustrated in Figure. 3.1(c).

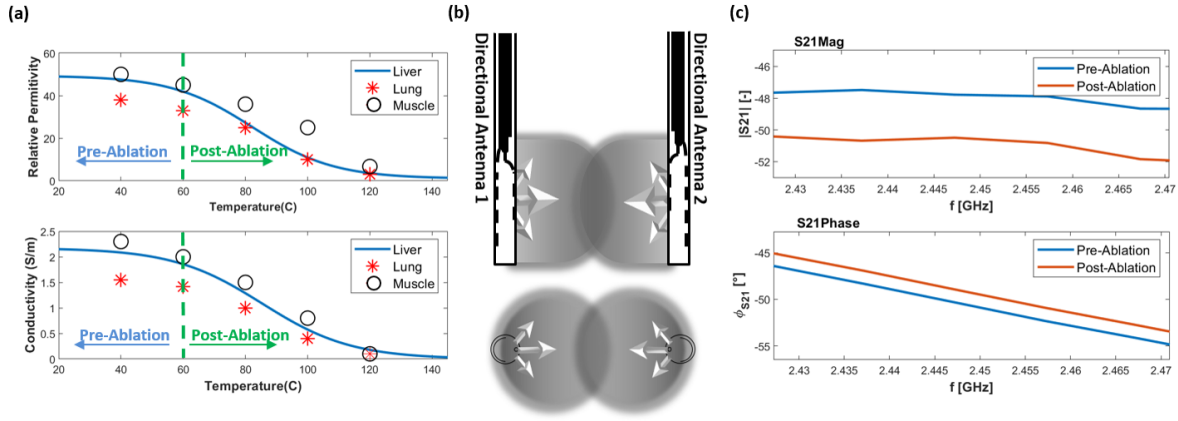


Figure 3.1. (a) Temperature-dependent permittivity and conductivity of liver, lung, and muscle tissue at 2.45 GHz decrease at ablative temperatures (temperatures in excess of 60 °C tissue can be considered fully ablated). (b) Illustration of microwave ablation of tissue with a pair of directional applicators positioned at the target periphery and directing power towards the center. (c) Changes in the magnitude and phase of the transmission coefficient (s_{21}) between a pair of directional applicators before and after ablation over the frequency range.

The complex valued transmission coefficient at frequency f , $s_{21}(f)$, between a pair of antennas is given by:

Equation 3.1

$$s_{21}(f) = 20 * \log_{10} \left(\frac{v_2(f)}{v_1(f)} \right)$$

where $v_2(f)$ is the voltage phasor on antenna 2 (receiving antenna) and $v_1(f)$ is the voltage phasor on antenna 1 (transmitting antenna) [109]. The voltage $v_2(f)$ depends on the radiation pattern of both antennas, the distance between the antennas, and the dielectric properties of the medium between the antennas. In the context of dual-antenna microwave ablation, the antenna spacing is fixed, the radiation pattern of both antennas is known and changes in the $s_{21}(f)$ can be attributed to changes in the dielectric properties of the tissue between the antennas.

The objective of this study was to assess the technical feasibility of predicting the extent of tissue ablated between a pair of directional MWA applicators based on time-dependent changes in the microwave transmission coefficient between the antennas, demonstrated in Figure 3.2. A custom apparatus was developed to enable dual-antenna MWA and intermittent measurement of the transmission coefficient (s_{21}) between the antennas with a vector network analyzer. We present experimental data and signal analysis approaches demonstrating the feasibility of tracking the growth of microwave ablation zones in *ex vivo* bovine liver.

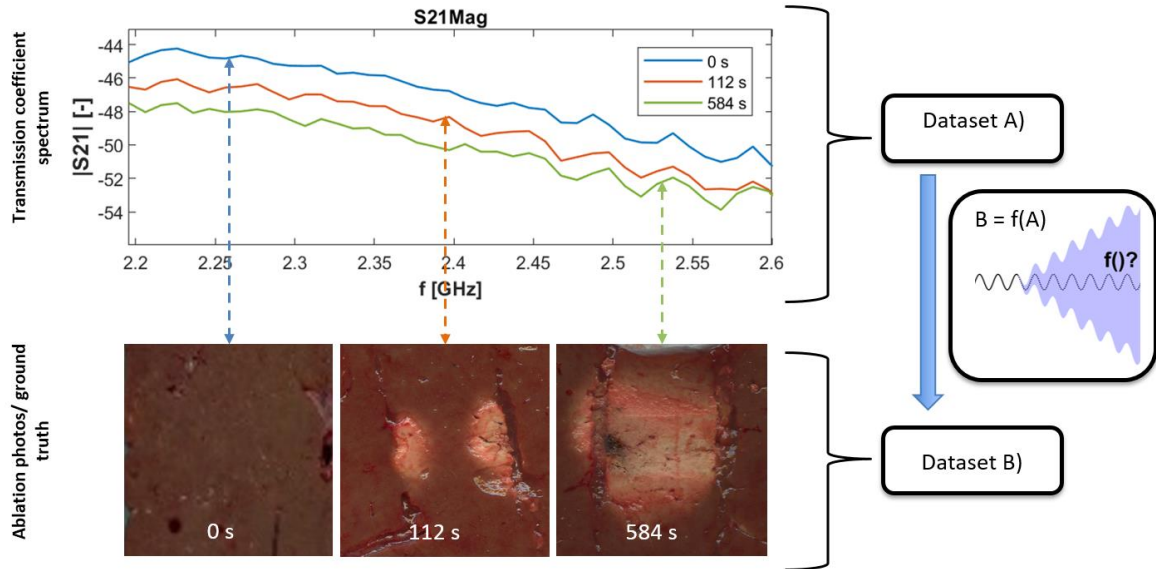


Figure 3.2. Overview of analysis of s_{21} transmission coefficient for predicting the extent of ablation completeness between a pair of directional antennas, and corresponding ablation zone cross-sectional assessment of ablation (images of tissue discoloration).

We anticipate the proposed method would offer complementary information to imaging. For example, in current practice, after ablation for the specified duration of time is complete, a post-treatment ablation scan with contrast is performed [110]. Successful development and translation of the proposed monitoring approach could inform when to stop the ablation and acquire the post-treatment scan. The monitoring approach offers the advantage of no added

ionizing radiation exposure and may potentially reduce the use of contrast agents by identifying a time for post-treatment scans when the ablation is likely to be complete. Additionally, the presented monitoring approach operates in real-time and does not require repositioning the patient in an imaging scanner.

3.2 Materials and Methods

We performed a total of 53 ablations in fresh *ex vivo* bovine liver tissue using a pair of directional microwave ablation antennas positioned 2.5 cm apart. The fresh bovine liver tissue samples were obtained from a nearby slaughterhouse and immediately placed in a plastic bag on ice for transportation to our laboratory. The tissue was then sliced into approximately $6 \times 6 \times 6$ cm³ samples, placed in sealed Ziploc bags, and kept on ice in a cooler. The experiments were conducted within approximately 3 to 24 hours post-mortem. Experiments were performed at three distinct input power levels – 30 W, 36 W, and 45 W as estimated at the radiating tip per applicator – for ablation durations ranging between 53–1219 s. As detailed in the following sections, a custom apparatus was developed to allow for transmission coefficients between the antenna to be intermittently measured during ablation experiments. Following each experiment, the tissue sample was sectioned in a plane parallel to both of the applicator shafts and optically scanned to obtain an image of the ablation zone, as assessed by the extent of visibly discolored tissue.

3.2.1 Microwave Ablation Experiments in *Ex Vivo* Tissue

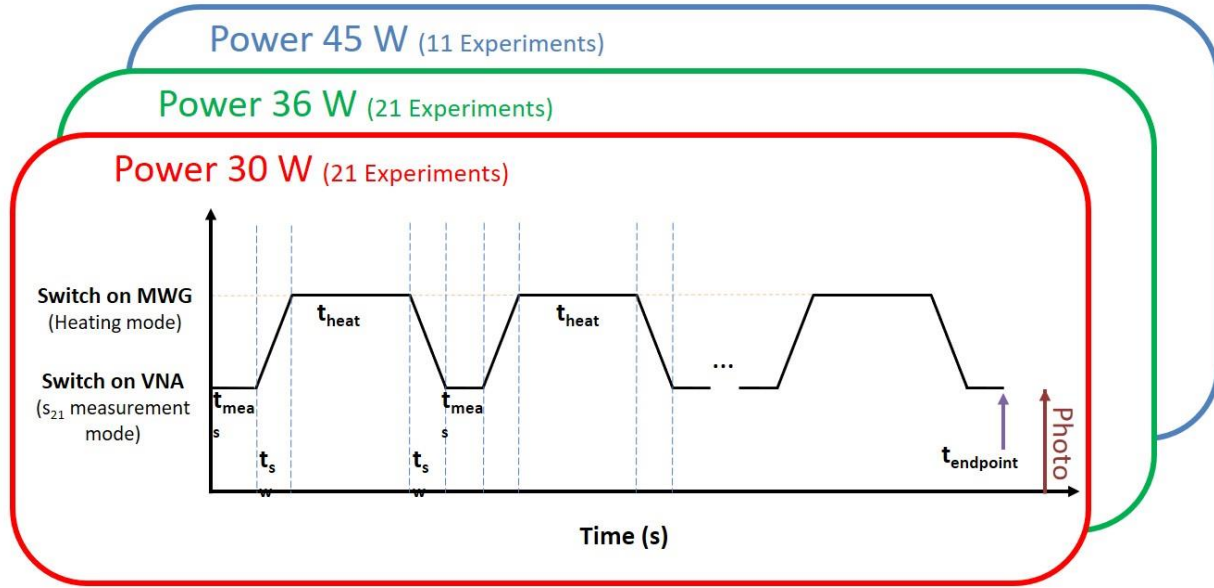


Figure 3.3. Illustration of the interleaved pattern for microwave heating and s_{21} measurement, and time point at which ground truth images of the ablation zone were acquired. MWG represents the microwave generator, and VNA stands for Vector Network Analyzer.

Table 3.1. Number of experimental datapoints ($s_{21}(f_k, t_i, j)$) and ground truth images of the ablation zone gathered for each applied power level.

Set 1, Distance 2.5 cm, Power at each applicator 30 W									
$t_{\text{heat}} = 40 \text{ s}$, $t_{\text{meas}} = 13 \text{ s}$, $t_{\text{sw}} = 2 \text{ s}$									
Time t_i [s]	0	53	159	212	318	371	636	901	1219
Number of $s_{21}(f_k, t_i, j)$	21	21	18	15	12	9	6	3	2
Number of photos *	-	3	3	3	3	3	3	1	2
Number of Experiments J	21								
Set 2, Distance 2.5 cm, Power at each applicator 36 W									
$t_{\text{heat}} = 40 \text{ s}$, $t_{\text{meas}} = 13 \text{ s}$, $t_{\text{sw}} = 2 \text{ s}$									
Time t_i [s]	0	106	212	318	371	424	636	901	

Number of $s_{21}(f_k, t_i, j)$	21	21	18	15	12	9	6	3
Number of photos *	-	3	3	3	3	3	3	3
Number of Experiments J	21							
Set 3, Distance 2.5 cm, Power at each antenna 45 W								
$t_{\text{heat}} = 50 \text{ s}, t_{\text{meas}} = 7 \text{ s}, t_{\text{sw}} = 2 \text{ s}$								
Time t_i [s]	0	112	230	348	584			
Number of $s_{21}(f_k, t_i, j)$	11	11	8	5	2			
Number of photos *	-	3	3	3	2			
Number of Experiments J	11							

* These numbers also denote; how many ablation experiments were terminated at this specific time-point t_i .

From each individual ablation experiment at given power level, we gathered A.) complex-valued electromagnetic transmission coefficients $s_{21}(f_k, t_i, j)$ at multiple frequencies ($f_k, k = 1, 2, \dots, K$), and at multiple time points ($t_i, i = 1, 2, \dots, N_j$) where N_j is the total number of time points for given experiment $j(j = 1, 2, \dots, J)$, during the course of ablation and B.) an ablation zone cross-sectional assessment of the ablation profile between the applicators right after terminating heating at time t_{N_j} . J represents the number of experiments performed at each considered power level.

Each ablation experiment was divided into N_j cycles. During the first part of the cycle (t_{heat} [s]), microwave power was passed from the generator to both applicators simultaneously via a power splitter. In the remaining part of the cycle (t_{meas} [s]), the applicator input ports were electronically switched to couple to a Vector Network Analyzer (VNA) (Fieldfox N9923 A, Keysight) to measure the transmission coefficient $s_{21}(f_k, t_i, j)$ between the applicators (transmission coefficients based on (1) can be measured with a VNA as described in [109], [111]). The s_{21} data were captured over 201 linearly spaced frequencies $f \in \langle 0.5, 6 \rangle$ GHz. The t_{heat} and t_{meas} phases were separated by a period of $t_{sw} = 2$ s to ensure adequate time for switching.

The structure of the experiments and number of data points collected are summarized in Figure 3.3 and Table 3.1. To capture the temporal progression of ablation extent, we repeated the ablation for each power level M times to sample M distinct time endpoints ranging between 0 s and 1219 s (Time t_i represents time endpoints in Table 3.1). Table 3.1 presents the number of $s_{21}(f_k, t_i, j)$ collected at specific time endpoints. For instance, when the time endpoint was 53 s, $s_{21}(f_k, t_i, j)$ were measured at 0 s and 53 s. Similarly, for experiments with a time endpoint of 159 s, $s_{21}(f_k, t_i, j)$ were collected at 0 s, 53 s, 106 s, and 159 s. This explains the decreasing trend in the number of $s_{21}(f_k, t_i, j)$ samples starting from 0 s and continuing until reaching 1219 s. For the majority of applied power/time combinations, ablations were repeated $n = 3$ times; the 30 W/applicator experiments for 901 s and 1219 s, and the 45 W/applicator experiments for 584 s were not repeated in triplicate as these were pilot experiments. The t_{meas} parameter varies between set 1 and set 2 compared to set 3 due to the initial analysis of data from set 1 and set 2, which led us to concentrate specifically on the trend of completion ablation rather than the number of samples. Therefore, set 3 has a distinct t_{meas} parameter value.

3.2.2 System Setup

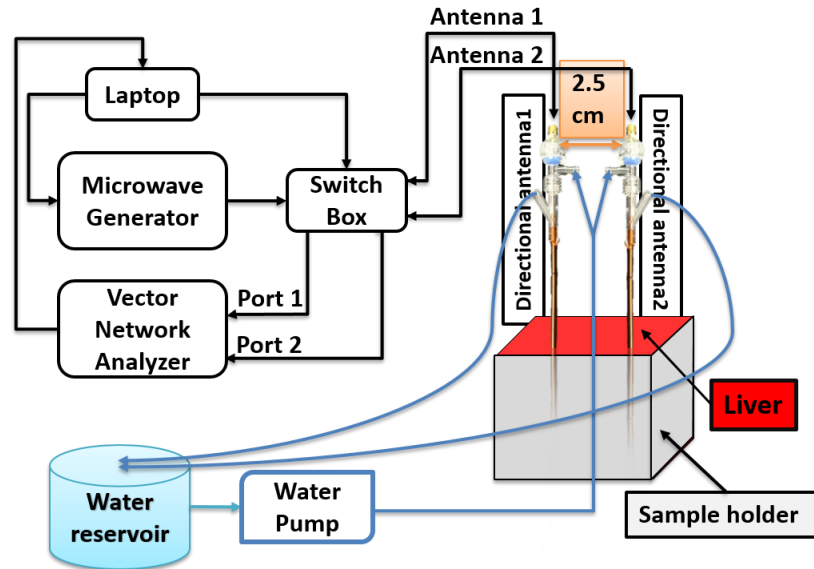


Figure 3.4. Block diagram of experimental setup illustrating the microwave applicators positioned within the tissue sample, microwave generator, vector network analyzer, and switch box.

We developed a custom computer-controlled switching apparatus to periodically switch the antennas from ablation mode (i.e. coupled to the generator) to monitoring mode (i.e. coupled to the Vector Network Analyzer (VNA)) was developed, as illustrated in Figure 3.4. Microwave power is passed from the microwave generator (SAIREM GMS 200 W) through a 3 ft-long RG393 coaxial cable (Pasternak Inc., 0.918 attenuation at 2.45 GHz) to a power meter (Bird Technologies 7022 Statistical). The output of the power meter is connected through another 3 ft-long RG393 cable to the custom-made switch box. The main purpose of the switch box is to implement the heat/measurement cycles of ablation experiment as shown in Figure 3.4. During the heating part of the cycle, power through power meter is distributed by power splitter (MECA

Electronics R2N-1.900-M01, insertion attenuation 0.912) through dedicated microwave cold switches (Teledyne Relays Coaxial Switches, CCR-33S30) to two identical cables (PE-C240, Pasternak Inc., attenuation 0.8197), which transfer the microwave power to the SMA connectors of the microwave applicators. Based on the attenuation of all cables and components in the path between the power meter and applicators, we estimate that 34.3% of power as seen at the power meter reaches the SMA connector of each applicator.

During the measurement part of the cycle, the switches disconnect power splitter outputs from MWA applicators and connect ports of the VNA (Fieldfox N9923 A, Keysight) through low-loss coaxial cables (PE-C100 LSZH, Pasternak Inc., attenuation 0.58) to the MWA applicators. The VNA then measures the complex-valued transmission coefficient $s_{21}(f_k, t_i, j)$ over the frequency range 0.5–6 GHz.

Since the switches employed in this study require “cold switching”, it is essential to turn off the power from the generator before switching, and correspondingly, when switching back to heating mode, switching must take place before the generator is turned on. Therefore, we incorporated an interval t_{sw} between intervals t_{heat} and t_{meas} as depicted in Figure 3.3. A custom control program (implemented with MATLAB R2020a, The Mathworks Inc., Natick, MA) was written to control the generator, and switches, and to send measurement requests to VNA during measurement part of each cycle. The MWA applicators used in our experiments were water-cooled 2.45 GHz directional applicators, as previously described [112], [113]. A peristaltic water pump (Cole Parmer Masterflex economy drive 7015-20) was used to circulate chilled water (2–6 °C) from a reservoir through the applicator in a closed-loop manner.

The experimental setup incorporated custom 3D printed plastic fixtures which were constructed for holding the *ex vivo* liver tissue samples (approximately $6 \times 6 \times 6 \text{ cm}^3$),

maintaining the position of the applicators within the liver over the course of the experiment, and limiting distortion of the ablation zone while cutting the tissue.

3.2.3 Data Analysis

To study the relation between the measured scattering coefficients $s_{21}(f_k, t_i, j)$ and the ablation zone cross-sectional ablation progression in tissue (as captured on ablation images), we transformed both of these datasets to come up with an estimated curve of ablation completion. In this study, we define the term “ablation completion” as the event when the ablation zone first fully encompasses the area between the two applicators such that no perpendicular line between the radiating end of each applicator axes contains non-ablated tissue. The hypothesis is, that if the estimated ablation completion curves from ablation images and $s_{21}(f_k, t_i, j)$ coefficients are closely related, then, the change of microwave transmission coefficients is indicative of ablation progression.

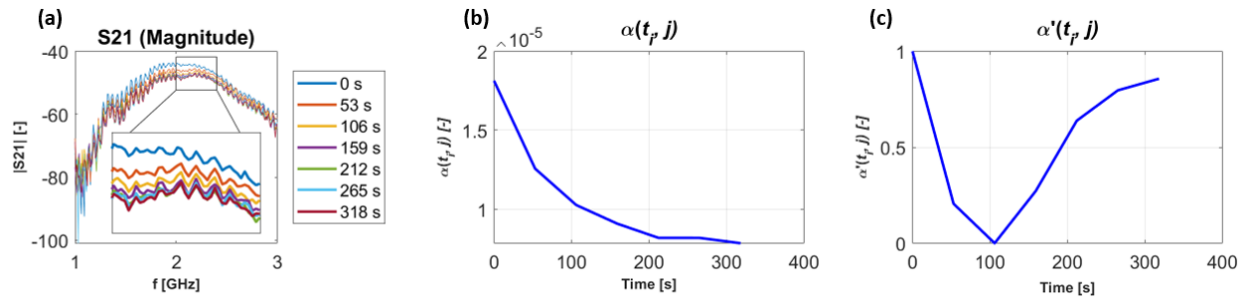


Figure 3.5. Example (a) magnitude of $s_{21}(f_k, t_i, j)$ for $j - th$ experiment with total time 318 s and 45 W input power. Also shown are (b) average transmission coefficient $\alpha(t_i, j)$ and (c) applicator feedback $\alpha'(t_i, j)$.

1) Processing of Transmission Coefficients: The example of the collected magnitude of transmission coefficients $s_{21}(f_k, t_i, j)$ is shown in Figure 3.5(a) over the frequency range 1–3 GHz (we initially acquired $s_{21}(f_k, t_i, j)$ data over the frequency range 0.5–6 GHz to observe the broadband transmission coefficient profile). On inspection of the $s_{21}(f_k, t_i, j)$ spectrum, it was

evident that $s_{21}(f_k, t_i, j)$ levels fell below -50 dB at frequencies below 1 GHz and above 3 GHz. Thus, we restricted our analysis to the frequency range 1-3 GHz. The shown data show convergence of magnitude curves as time progresses, which suggests the potential to exploit the trend of gradually decreasing rate of change of the broadband $s_{21}(f_k, t_i, j)$ to predict ablation completion. First, we determine the average of the magnitude of transmission coefficients over K frequencies between 1 and 3 GHz:

Equation 3.2

$$\alpha(t_i, j) = \frac{1}{K} \sum_{k=1}^K |s_{21}(f_k, t_i, j)|,$$

where $\alpha(t_i, j)$ is the average transmission coefficient from the $j - th$ experiment. Next, to assess the relative change in the average transmission coefficient, we determine the time difference magnitude $\Delta\alpha(t_i, j)$ from the average transmission coefficient $\alpha(t_i, j)$. The relative change ($\Delta\alpha(t_i, j)$) was computed as a fraction that describes the size of the absolute change in comparison to the reference value:

Equation 3.3

$$\Delta\alpha(t_i, j) = \alpha(t_i, j) - \alpha(t_{i-1}, j).$$

We further apply smoothing on $\Delta\alpha(t_i, j)$ and normalize it, such that the values of resulting time curve $\alpha'(t_i, j)$, further denoted as “applicator feedback”, always start at 1 and are restricted to the interval $\langle 0, 1 \rangle$

Equation 3.4

$$\alpha'(t_i, j) = 1 - \frac{|\Delta\tilde{\alpha}(t_i, j)|}{m_j},$$

where $\Delta\tilde{\alpha}(t_i, j)$ is smoothed $\Delta\alpha(t_i, j)$ according to:

Equation 3.5

$$\Delta\tilde{\alpha}(t_i, j) = \frac{1}{3} \sum_{l=0}^2 \Delta\alpha(t_{i-l}, j),$$

and m_j is an absolute maximum of smoothed difference magnitude found along the time axis according to

Equation 3.6

$$m_j = \max_{t_i} |(\Delta\alpha(t_i, j))|.$$

Figure 3.5(b), and (c) summarizes these transformations for magnitude of $s_{21}(f_k, t_i, j)$ from $j - th$ experiment.

Finally, we averaged applicator feedback time series $\alpha'(t_i, j)$ across J experiments and assembled non parametric average curve $\alpha'_{av}(t_i)$ as well as upper envelope $\alpha'_u(t_i)$, and lower envelope $\alpha'_l(t_i)$ of the confidence interval (Mean $\pm$ STD). Averaging as well as standard deviation (STD) computations were done at each time sample; accordingly, there are fewer $\alpha'(t_i, j)$ samples for averaging as time progresses, as summarized in Table 3.1. The resulting non-parametric curves were fit to a logistic function with the use of a nonlinear least squares' algorithm, yielding the fitted curves $\hat{\alpha}'_{av}(t_i)$, $\hat{\alpha}'_u(t_i)$, $\hat{\alpha}'_l(t_i)$ representing the average, upper, and lower envelopes of $\alpha'(t_i)$ respectively.

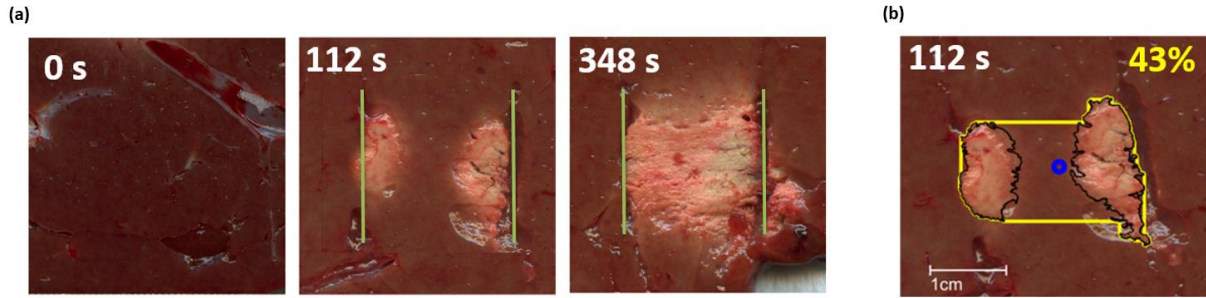


Figure 3.6. (a) Example images of sectioned liver tissue from experiments at 0 s, 112 s, and 348 s, the vertical lines show the position of microwave antennas. (b) The percentage of ablation completion is computed based on the ratio of two areas shown in the photo, two black contours (ablation zone) over the yellow contour (ablated zones extend to fill the distance between them).

2) Processing of Ablation Photos: Figure 3.6(a) shows three example images of tissue gathered at 0 s, 112 s, and 348 s, when there is no, partial, and complete ablation, respectively. In order to compute the estimate of ablation completion curve as a function of time, ablation areas in each image were segmented with the use of a two-step algorithm. The first step consists of k-means clustering with two centroids in the RGB space of the image, which separates the pixels of image into two clusters – ablated or unablated tissue. In the second step, mutually connected pixel groups are identified and those with areas smaller than 5% of the overall ablation area are removed. The black contour in Figure 3.6(b) shows an example of such segmented ablation zone. In order to get an estimate of ablation completion as a fraction between 0 and 1 (0 corresponding to no ablation, and 1 corresponding to fully ablated area between applicators) for each considered image, we also estimated the contour of the completed ablation shown as yellow contour in Figure 3.6(b) by horizontally connecting segmented ablation parts. This procedure assumes that the ablation can be considered complete when extents of the ablation from each applicator join together. We estimated the anticipated upper bound of the ablation zone with the yellow contour, by using a region-growing method to cover the area between the two antennas, where ablation could be expected. Although the actual ablation zone would seldom be expected

to be a straight line, this provided an estimate for comparing the actual ablation zone at a given time point vs. a theoretical/estimated complete (i.e. 100% ablation). The estimate of ablation completion $\beta(t_i, j)$ for the $j - th$ experiment, is a ratio of number of pixels within segmented area (black contour in Figure 3. 6(b)) and area of estimated finished ablation (yellow contour in Figure 3.6(b)).

At each time point we averaged ablation completion $\beta(t_i, j)$ across all experiments j to obtain $\beta_{av}(t_i)$, and its standard deviation. The non-parametric average curve and corresponding confidence interval (Mean $\pm$ STD) $\beta_{av}(t_i), \beta_u(t_i), \beta_l(t_i)$ are then assembled and fit to a logistic function with non-linear least squares procedure. The fitted curves are denoted as $\hat{\beta}_{av}(t_i), \hat{\beta}_u(t_i), \hat{\beta}_l(t_i)$, representing the average estimated ablation completion, upper envelope of confidence interval of estimated ablation completion, and lower envelope of confidence interval of estimated ablation completion respectively.

3) Comparison of Ablation Completion Estimates from Photos and Transmission

Coefficients: To test the prediction of ablation completion in tissue by transmission coefficient changes between applicators, we attempted to predict ablation completion estimate $\hat{\beta}_{av}(t_i)$ with the use of applicator feedback envelope $\hat{\alpha}_{av}(t_i)$ according to the regression model

Equation 3.7

$$\tilde{\beta}_{av}(t_i) = \sum_{m=1}^M c_m \cdot \hat{\alpha}'_{av}(t_i - \tau_m),$$

where $c_m, m = 1, 2, \dots, M$ are prediction coefficients, τ_m are corresponding time delays with $\tau_1 = 0$ s, and M is the number of chosen delays for prediction. Similar regression modeling was applied to the upper and lower envelopes of confidence intervals of ablation completion

estimates from the ground truth assessment of the ablation images $\hat{\beta}_u(t_i), \hat{\beta}_l(t_i)$ and applicator feedback $\hat{\alpha}'_u(t_i), \hat{\alpha}'_l(t_i)$.

3.3 Results

3.3.1 Analysis of Measured Electromagnetic Transmission

Coefficients

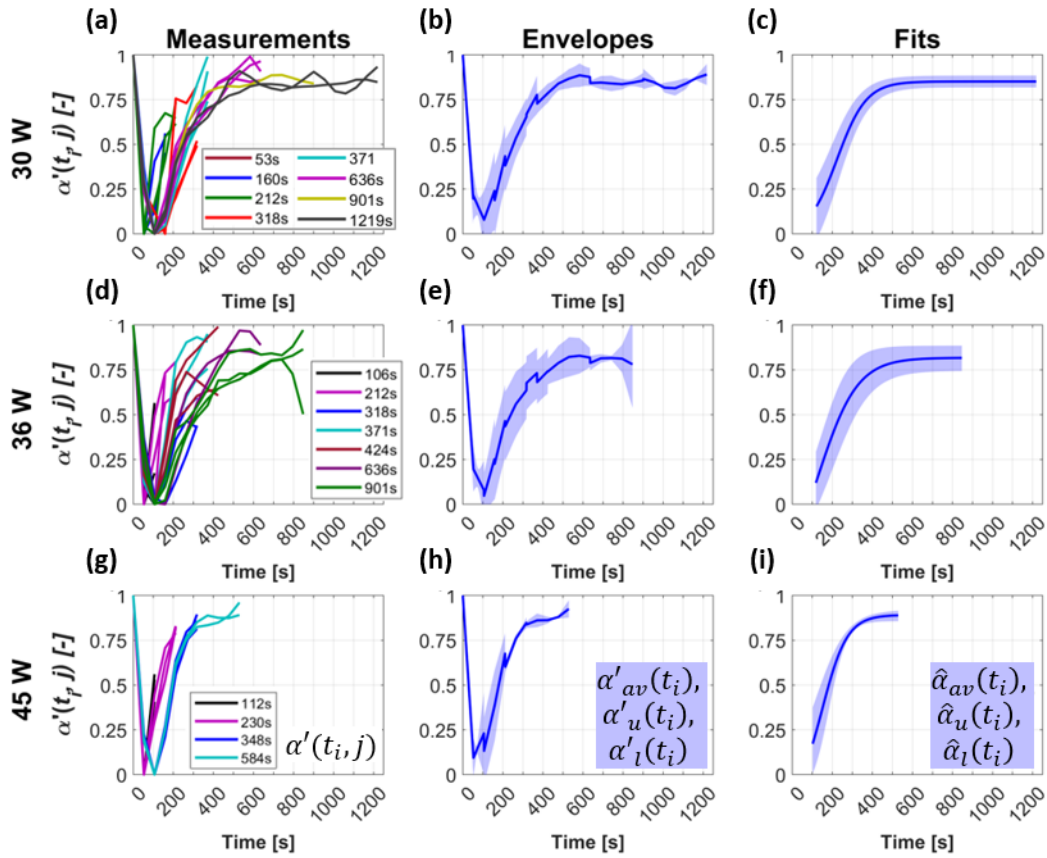


Figure 3.7. Applicator feedback time series $\alpha'(t_i, j)$ at various time endpoints for input power of (a) 30 W, (d) 36 W, and (g) 45 W per antenna. Also shown are average envelopes and confidence intervals for respective power levels in (b), (e), and (h) as well as their logistic fits in (c), (f), and (i).

Figure 3.7 shows the collected applicator feedback time series $\alpha'(t_i, j)$ from all experiments $j = 1, 2, \dots, J$ as well as computed average envelopes $\alpha'_{av}(t_i)$, confidence intervals $\alpha'_u(t_i) - \alpha'_l(t_i)$, and resulting logistic fits $\hat{\alpha}'_{av}(t_i)$, $\hat{\alpha}'_u(t_i)$, $\hat{\alpha}'_l(t_i)$. for all three power levels 30 W, 36 W, and 45 W per applicator.

The data presented in Figure 3.7 exhibit a temporal trend that is largely consistent across all three considered power levels. The first part of the $\alpha'(t_i, j)$ curve is monotonically decreasing until the global minimum at value 0 is reached. The second part of the $\alpha'(t_i, j)$ curve can be characterized by monotonic increase with sigmoidal trend eventually converging to zero slope. This generally observed shape of applicator feedback is important for our subsequent analysis.

Figure 3.7(b), (e), and (h) provide average applicator feedback across all experiments as well as upper and lower envelopes of confidence interval. From the average envelope, we observed the time, when global minimum takes place, to be 109 s, 106 s, and 53 s for 30 W, 36 W, and 45 W per applicator respectively, suggesting that this inflection point might play important role in monitoring ablation progression in time. is no surprise that for higher power values, when ablation growth is faster, we observe this inflection point sooner. The root means square error (RMSE) between the raw data and fitted values were low – 1.9%, 1.4%, and 1.1% for the 30 W, 36 W, and 45 W per applicator average envelopes – suggesting that the data generally follow similar trends. Similar fitting errors were observed for the upper and lower envelopes.

3.3.2 Ablation Completion Time Series as Estimated from Ground Truth Ablation

Images

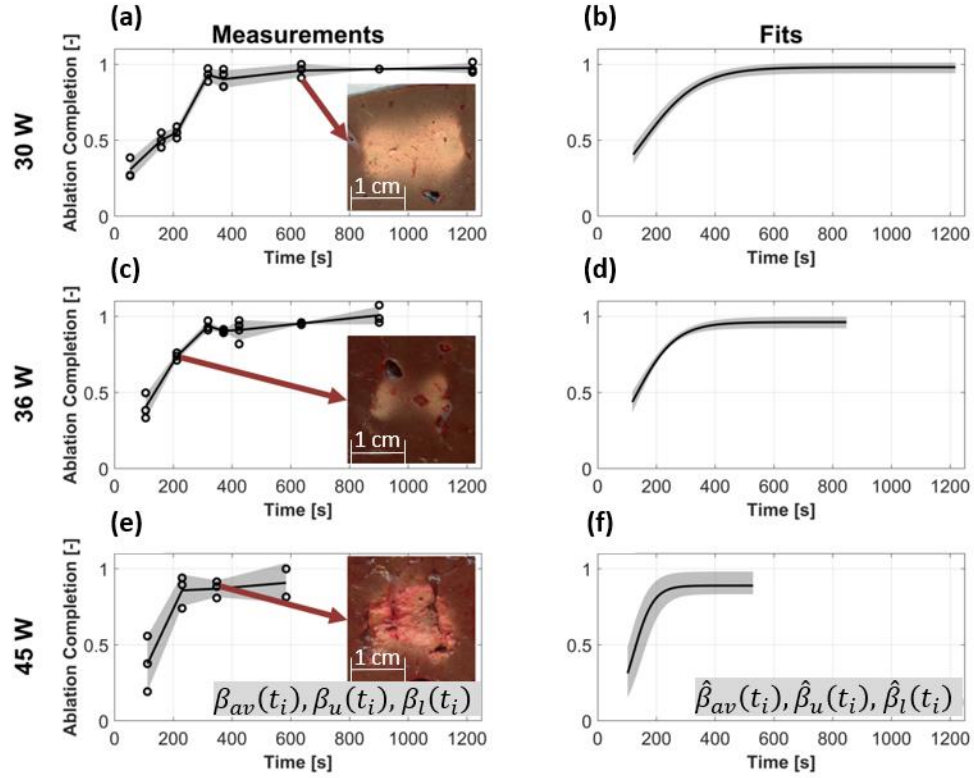


Figure 3.8. Estimated ablation completion values and the average, upper and lower envelopes $\beta_{av}(t_i), \beta_u(t_i), \beta_l(t_i)$ for (a) 30, (c) 36, and (e) 45 W per antenna. Plots (b), (d), and (f) show corresponding logistic fits $\hat{\beta}_{av}(t_i), \hat{\beta}_u(t_i), \hat{\beta}_l(t_i)$ of individual envelopes. An example image of sectioned liver tissue illustrating the ablation zone is shown for each power level with 1 cm scale bar.

From images of the ablated tissue, we estimated the ground truth ablation progression toward completion (Figure 3.8). Figure 3.8(a), (c), and (e) show ablation completion values as estimated from ablation photos $\beta(t_i, j)$ at measurement time points t_i as well as their average and lower and upper envelopes $\beta_{av}(t_i), \beta_u(t_i), \beta_l(t_i)$. All the data points in Figure 3.8(a), (c), and (e) have a corresponding image of the ablation zone; as an example, the corresponding image for

one data point is shown for each of the considered applied power levels. The corresponding logistic fits $\hat{\beta}_{av}(t_i)$, $\hat{\beta}_u(t_i)$, $\hat{\beta}_l(t_i)$ are shown in Figure 3.8(b), (d), and (f) respectively.

The calculated average, as well as upper and lower envelopes (Figure 3.8(a), (c), (e)), generally follow a sigmoid function starting at 0 (corresponding to 0% ablation) and reaching a value of 1 (corresponding to 100% of ablated tissue as defined by the term “ablation completion”). We were able to achieve good fits with the logistic function as shown in Figure 3.8(b), (d), and (f) with RMSE of 3.44%, 2.7%, and 1.25% of maximum value of average ablation completion for the 30 W, 36 W, and 45 W per applicator respectively. Similar RMSEs were observed for the fit of the upper and lower envelopes.

3.3.3 Prediction of Ablation Completion Based on Applicator Feedback

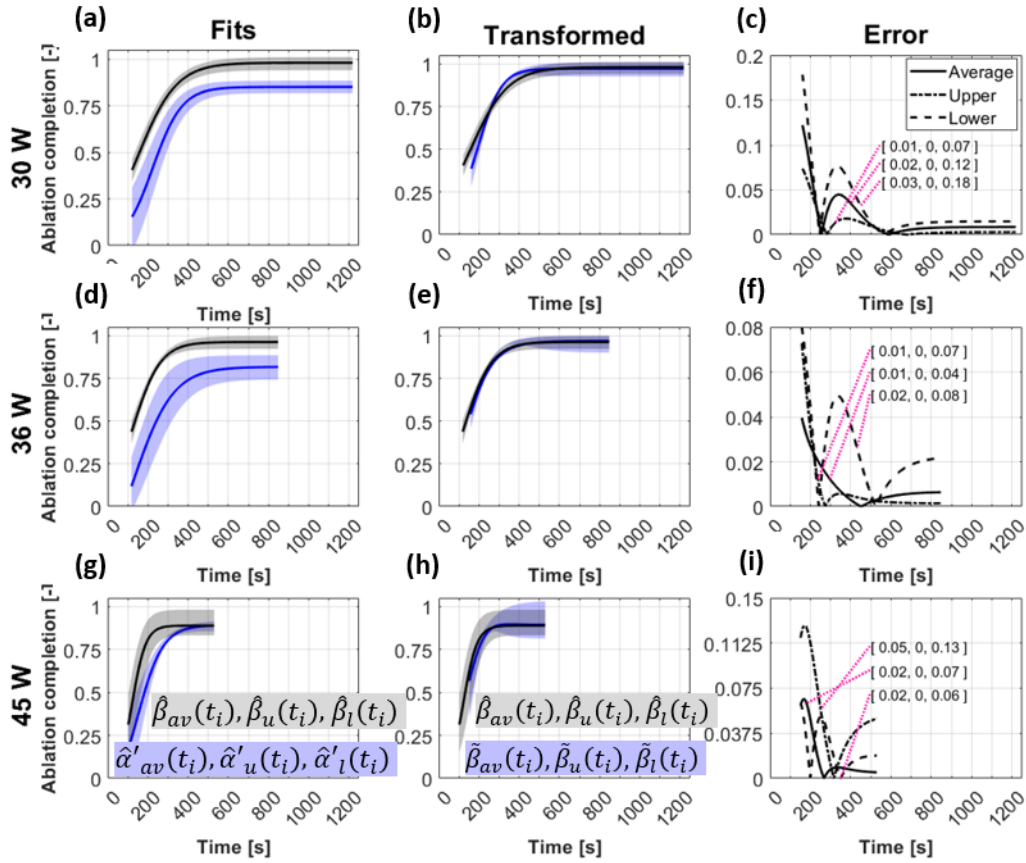


Figure 3.9. Comparison of confidence intervals of 1.) ablation completion as estimated from photos $\hat{\beta}_{av}(t_i), \hat{\beta}_u(t_i), \hat{\beta}_l(t_i)$ were represented by black lines and 2.) applicator feedback $\hat{\alpha}'_{av}(t_i), \hat{\alpha}'_u(t_i), \hat{\alpha}'_l(t_i)$ for (a) 30 W, (d) 36 W, and (g) 45 W per antenna by blue lines. Plots (b), (e), and (h) show comparison between envelopes $\hat{\beta}_{av}(t_i), \hat{\beta}_u(t_i), \hat{\beta}_l(t_i)$ black lines and predictions $\tilde{\beta}_{av}(t_i), \tilde{\beta}_u(t_i), \tilde{\beta}_l(t_i)$ blue lines. Errors between predictions and ablation estimate envelopes are shown in (c), (f), and (i) for power levels 30 W, 36 W, and 45 W respectively, annotations for each error curve provide average, minimum and maximum of mean absolute errors respectively.

Ablation completion estimates and their logistic fits from Figure 3. 8 show a similar monotonic shape as the second part of applicator feedback time series from Figure 3.7. Therefore, we applied a non-linear least squares fitting with logistic function to the second part of applicator feedback envelopes shown in Figure 3.7(c), (f), and (i). Due to the similar trends observed in the fits of estimated ablation completion and the second part of the applicator

feedback time series (shown in Figure 3.9(a), (d), and (g) for 30 W, 36 W, and 45 W per applicator respectively, with black lines representing estimated ablation completion and blue lines representing the second part of applicator feedback), we decided to demonstrate the possibility of ablation progression prediction with applicator feedback in the time interval of the second part of applicator feedback curves. Indeed, Figure 3. 9(b), (e), and (h) show the good quality of achieved predictions closely following ablation completion for average, upper, and lower envelopes. Figure 3.9 illustrates the prediction process of fitted estimated ablation completion envelopes $\hat{\beta}_{av}(t_i), \hat{\beta}_u(t_i), \hat{\beta}_l(t_i)$ by regression (4) of applicator feedback envelopes $\hat{\alpha}'_{av}(t_i), \hat{\alpha}'_u(t_i), \hat{\alpha}'_l(t_i)$ and resulting prediction errors.

Prediction errors are shown in Figure 3.9(c), (f), and (i) and are on average 2.3%, 1.6%, and 2.3% of ablation completion estimate for average, upper, and lower envelopes across all power levels. Table 3.2 provides estimated regression coefficients and time delays for the prediction of ablation completion from applicator feedback envelopes.

Table 3.2. Regression coefficients c_k and corresponding time delays τ_k from (Eq. 3.7) for prediction of ablation completion.

30 W	$c_1 [-]$	$c_2 [-]$	$\tau_1 [s]$	$\tau_2 [s]$
Envelope $\tilde{\beta}_{av}(t_i)$	2.4094	-1.2670	0	40
Envelope $\tilde{\beta}_u(t_i)$	1.5116	-0.3714	0	40
Envelope $\tilde{\beta}_l(t_i)$	3.1440	-2.0115	0	40
36 W	$c_1 [-]$	$c_2 [-]$	$\tau_1 [s]$	$\tau_2 [s]$
Envelope $\tilde{\beta}_{av}(t_i)$	2.9740	-1.7880	0	40
Envelope $\tilde{\beta}_u(t_i)$	1.6482	-0.5188	0	40

Envelope $\tilde{\beta}_l(t_i)$	4.7945	-3.5856	0	40
45 W	$c_1 [-]$	$c_2 [-]$	$\tau_1 [s]$	$\tau_2 [s]$
Envelope $\tilde{\beta}_{av}(t_i)$	1.9567	-0.9533	0	50
Envelope $\tilde{\beta}_u(t_i)$	1.5720	-0.4456	0	50
Envelope $\tilde{\beta}_l(t_i)$	1.8318	-0.8822	0	50

3.4 Discussion

Microwave ablation with directional antennas offers the potential opportunity to define the extent of the treatment margin by placement of the ablation applicators on the desired treatment boundary and directing energy towards the center of the targeted tumor [114]. We hypothesized that the use of multiple antennas around the tumors may offer a means to assess when the tissue between the antennas was adequately ablated by analyzing changes in the transmission coefficient between the antennas during the course of ablation. In the present study, we investigated the relationship between time-dependent changes in the complex-valued transmission coefficient between a pair of 2.45 GHz directional ablation antennas and extent of the ablation zone in the tissue region between the antennas.

The premise of this study was that changes in tissue dielectric properties during ablation would yield changes in transmission coefficient between antennas and that these measurements would be indicative of extent of ablation. While several papers [37], [38], [39] have reported on changes in tissue dielectric properties at ablative temperatures, the studies do not distinguish between reversible changes (i.e. due to temperature alone) and irreversible changes in dielectric properties that would remain even if tissue were subsequently cooled. The presented technique

similarly does not aim to distinguish between these changes, although this presents an important avenue for future study. Over some portion of the microwave frequency spectrum, changes in dielectric properties due to heating are primarily observed in the real part of the complex permittivity (i.e., ϵ'), whereas over other frequency ranges, substantial changes in electrical conductivity due to heating are observed. Further investigation of the mechanisms underpinning these temperatures induced dielectric property changes can inform the analysis of changes in complex-valued transmission coefficients between antennas during microwave ablation procedures.

We observe a progressive decrease in the $s_{21}(f_k, t_i, j)$ value over time, indicating a decline in the transmitted signal or power level. This decline suggested signal attenuation and losses in the transmission path (tissue) as the antenna geometry and distance remained constant. The focus of the analysis was on extracting the “applicator feedback” from the $s_{21}(f_k, t_i, j)$ value and examining the time it took for the “applicator feedback” to stabilize. During each experiment in *ex vivo* liver tissue with a pair of antennas spaced 2.5 cm apart, we observed that applicator feedback $\alpha'(t_i, j)$ initially decreased during the course of the ablation, before reaching a turning point, followed by an increase and eventually asymptotically towards a steady-state value (Figure 3. 7(a), (d), and (g)). While these curves exhibit some variability, they all follow similar trends. Notably, the turning point of average applicator feedback $\alpha'_{av}(t_i)$ appeared to occur sooner for increasing input power (53 s for 45 W vs 109 s for 30 W), suggesting that this parameter may be indicative of the rate of heating during ablation. The most informative part of the fitting curve, characterized by an increase followed by a steady state, was of primary interest in the present study. This part of the curve corresponded to an initial temperature rise within the first 90-100 seconds, followed by further temperature increases and changes in tissue state.

Extracting information about tissue state changes from the $s_{21}(f_k, t_i, j)$ data was the primary objective, providing valuable insights for the study.

To determine the relationship between applicator feedback $\alpha'(t_i, j)$ and when the tissue between the two antennas was completely ablated, we conducted ablation experiments in *ex vivo* tissue for time periods ranging between 53 s and 1219 s. The ablation durations were chosen such that ablation zone progression in tissue was adequately captured. Analysis of the images showing the ground truth ablation zone enabled us to assign a measure of ablation completion ($\beta_{av}(t_i)$, ranging between 0 and 1) for each experiment (Figs. 6 and 8). Using linear regression, we identified coefficients, c_m and time delays τ_m , to provide a prediction of the extent of the ablation zone, $\tilde{\beta}_{av}(t_i)$, based on average applicator feedback $\alpha'_{av}(t_i, j)$ (Figure 3. 9).

The predicted extent of ablation, $\tilde{\beta}_{av}(t_i)$, and the ground truth cross-sectional ablation zone, $\beta_{av}(t_i)$, showed similar trends (Figure 3. 9(b), (e), and (h), blue lines represent the predicted extent of ablation. In contrast, black lines represent the ground truth cross-sectional ablation zone). The presented results and low prediction errors ($< 5\%$ between $\beta_{av}(t_i)$, and $\tilde{\beta}_{av}(t_i)$) suggest a relationship between electromagnetic coefficient inferred features (average applicator feedback and related confidence intervals) and ground truth ablation progression in the tissue region between the antennas. Consequently, the developed technique provides a means for intra-procedural feedback on procedure completion in near real-time. The frequency of tissue monitoring is limited by the duration of the heating interval; a fixed interval of 40 s was considered in this study, though shorter intervals may be possible.

Some investigators have explored the potential use of a microwave imaging approach for monitoring the transient spatial spread of ablation zones during microwave tumor ablation [63], [65], [115]. These involve measurement of the scattered field during microwave ablation

procedures with externally positioned antennas. Since a plurality of antennas can be positioned external to the body, given knowledge of the initial scattered field, there exists the opportunity to apply suitable inversion algorithms to determine changes in the dielectric property maps based on transient measurements. Similar to the technique described in the present paper, the basis for microwave imaging monitoring approaches is changes in dielectric properties during the course of the ablation. However, in contrast to imaging approaches, the present approach employs transmission coefficients between antennas that are also used for performing the ablation, rather than requiring use of additional externally positioned antennas. Notably, the presented technique does not provide an image, but rather an estimate of ablation completion. Further, the microwave imaging techniques that have been used for monitoring ablation have involved reflection-based measurements only. Some microwave tomographic imaging techniques have used transmission approaches with application to imaging of the breast, brain, and bone to detect anomalies [116], [117], [118]. Some investigators have also explored thermoacoustic imaging techniques for monitoring microwave ablation procedures [119].

Although the presented technique seems promising for intraprocedural ablation monitoring, it provides a rather modest amount of information in comparison to MRI thermometry monitoring which affords 3D temperature maps. Similarly, microwave imaging can provide 2D or 3D maps of dielectric changes in the targeted region. In comparison with imaging modalities used for intra-procedure monitoring, the presented approach offers limited added cost and complexity to the procedure. The presented method can be augmented with additional post-procedural imaging, such as with contrast-enhanced CT, for post-treatment measurement of the spatial profile of the ablation.

While the results of this study illustrate the potential for multiple directional antennas to serve as a feedback method for monitoring ablation zones, these findings are currently based on experiments in non-perfused *ex vivo* tissue. Blood flow in tumors can be expected to impact the rate of heating and dynamics on the growth of the ablation zone. Additionally, it should be noted that there are few studies reporting on the temperature-dependent dielectric properties of tissue *in vivo*; if the temperature-dependent changes in dielectric properties of tissue *in vivo* are different than reported data for *ex vivo* tissue [120], they may also impact the findings. Further, during clinical liver ablation procedures, there may be additional dielectric contrast between the targeted tumor and background normal tissue [121]. The present study was conducted in relatively homogeneous *ex vivo* bovine liver tissue and did not include a tumor mimic. In the clinical scenario, the background normal tissue may be fatty or cirrhotic, which may have temperature-dependent dielectric properties that vary in a manner different than the tissue used for this study [120], [121], [122], further investigation is needed to assess the feasibility of this monitoring method for *in vivo* scenario. Since blood perfusion reduces considerably above approximately 60 °C, it is possible that an even greater change in dielectric properties and therefore transmission coefficient may be observed in the *in vivo* setting.

In the present study, we have demonstrated the relationship between changes in the transmission coefficient spectra during ablation and extent of ablation between a pair of directional microwave ablation antennas; further studies building on this effort are warranted to develop methods for determining the treatment endpoint in real time.

From a procedural perspective, our study involved applicators carefully positioned in a precisely machined template; in clinical practice, such alignment may vary considerably across procedures and thus serve as another source of uncertainty. Even within the benchtop experimental scenario,

additional studies are warranted to further assess the impact of different applicator designs and operating frequencies, inter-applicator distance, tissue type (i.e., lung and kidney), a wider range of applied power levels, and 3D assessment of ablation pattern. A similar analysis can be conducted on the phase of the transmission coefficient, as well. Finally, although this study was designed with directional ablation applicators in mind, the presented method may also have merit for ablation performed with multiple non-directional antennas.

3.5 Conclusion

We measured broadband transmission scattering coefficients at multiple time points during the course of microwave ablation of *ex vivo* liver tissue with a pair of directional MWA applicators and compared against ground truth assessment of ablation progression. Prediction of the extent of ablation completion following analysis of the transmission coefficients ranged between 1.6–2.3% of the ground truth assessment for the three power levels considered in this study. These data illustrate the potential of microwave transmission coefficient-based prediction of ablation completion when using multiple directional microwave ablation applicators.

Chapter 4 - Microwave Transmission-Based Monitoring of Dual Applicator - Microwave Ablation: Experimental Assessment in an *In vivo* Porcine Liver Model

4.1 Introduction

Microwave Ablation (MWA) is a minimally invasive procedure for treatment of unresectable primary liver cancer and localized colorectal liver metastases [123]. Ablation procedures are considered a technical success if the ablation zone encompasses the targeted tumor and a 5-10 mm margin of surrounding normal tissue [124]. Several studies have demonstrated the significance of achieving adequate treatment margins for local control [110], [125], [126], [127]. In addition to clinician experience, delivering technically successful ablations benefits from: (1) treatment planning to identify applicator trajectory and placement and energy-delivery settings most likely to achieve adequate treatment margins; (2) accurate placement of the ablation applicators under image-guidance based on the anatomical constraints; (3) intra-procedural treatment monitoring to assess spatial spread of the ablation zone relative to the targeted tumor for identifying treatment endpoint; (4) and post-treatment ablation confirmation with contrast-enhanced imaging to determine the extent of achieved margins.

Existing guidelines recommend evaluating ablation margins with contrast-enhanced imaging at initial follow-up 3-4 weeks post-treatment, allowing acute effects like hyperemia and inflammation to subside. Immediate post-ablation contrast-enhanced CT for assessing ablation zone extents is employed at some centers, although the benefits of this approach relative to delayed imaging are the subject of current investigation. A ~3-4-week delay may introduce uncertainties in registration, analysis, and interpretation of post-procedural imaging relative to pre-procedural

imaging, due to the significant time gap between data acquisition [28]. A validated intra-procedural monitoring tool could bridge this gap by enabling real-time assessment of ablation progression, allowing for intra-procedural adjustments prior to proceeding with contrast-enhanced imaging. Achieving reliable intra-procedural treatment monitoring to ensure consistent clinical outcomes remains an unmet need.

An ideal intra-procedural treatment monitoring method would afford real-time, 3D identification of the isothermal contours of the ablation zone, thus providing clinicians with key information to determine treatment endpoint. Given the well-established relationship between transient temperature profiles and thermal injury, methods for temperature monitoring/imaging are of particular interest [128]. MRI thermometry is in clinical use for guiding and monitoring therapeutic ultrasound [129] and laser interventions [130]. While the technical feasibility of monitoring microwave liver ablation procedures with MRI thermometry has been demonstrated, this technique has found limited practical clinical use due to the need for developing MRI conditional ablation systems, considerable susceptibility artifact adjacent to the ablation applicators, and challenges with MRI thermometry in the presence of cardio-respiratory motion [131], [132]. Ultrasound thermometry [133], [134] and elastography [135], [136], and CT-based thermometry [137] techniques have also been investigated.

In a prior study, we introduced an approach for treatment monitoring based on transient changes in the electromagnetic transmission coefficient during dual-applicator MWA [30]. This approach leverages temperature-dependent changes in electrical conductivity and relative permittivity of liver tissue that are well-established in the literature [40]. The transmission coefficient between the microwave antennas represents the fraction of power emitted by one antenna and received by the other, which we showed dynamic shifts in response to changes in

tissue properties throughout the ablation process. We demonstrated this signal can be used as an intraprocedural monitoring tool to assess the extent of the ablation zone between a pair of directional antennas in *ex vivo* liver tissue [30]. Microwave imaging systems under development for monitoring thermal ablation procedures similarly exploit temperature dependent changes in tissue dielectric properties, though these approaches require additional externally positioned microwave antennas [115]. Similar temperature-dependent changes in tissue electrical properties have been employed for monitoring the extent of ablation zones during radiofrequency ablation [85].

While our prior study demonstrated the technical feasibility of transmission-based monitoring of dual-applicator MWA, our experiments were conducted on *ex vivo* tissue, an idealized scenario allowing precise positioning of ablation applicators. This setup lacks the complexities of blood perfusion heat sinks and is unaffected by cardio-respiratory motion. As a translational step, the aim of the present study was to evaluate the technical feasibility of distinguishing between contiguous and discontinuous ablation zones between a directional and an omni-directional MWA antenna based on time-dependent changes in the microwave transmission signal in an *in vivo* porcine liver model. The directional antenna, recently developed, creates an ablation zone in a single direction, enhancing safety on one side [138]. In contrast, omnidirectional antennas, which are commonly used in current clinical procedures, provide a near-spherical ablation zone. The present study advances our prior technical development and *ex vivo* tissue evaluation by incorporating factors such as the blood perfusion, cardio-respiratory motion, and non-ideal applicator positioning such as that practicable with percutaneous image-guided placement, as well as assessment of system performance validated against contrast-enhanced CT (CECT) and histopathologic assessment of ablation zones.

4.2 Methods

4.2.1 Study Design

This study assessed the feasibility of distinguishing between contiguous and discontinuous ablation zones by measuring the transmission signal between two applicators during ablation. We designed the study using two water-cooled 2.45 GHz MWA applicators—one directional ("side-firing") and one omnidirectional—in an *in vivo* porcine liver model. Fifteen ablations were conducted in four swine, with 3 to 5 ablations per liver. Applicators were positioned in anesthetized swine using ultrasound guidance and confirmed by CT imaging (Figure 4.1). Microwave power was applied for 200 s ($n = 8$) or 600 s ($n = 7$); these two time points were selected with the intent of achieving discontinuous (200 s) or contiguous (600 s) ablation considering a 3 cm inter-applicator spacing. A custom hardware setup switched between ablation and monitoring modes during ablations as previously described in [30]. Post ablation CECT images were acquired then pigs were euthanized, livers harvested, and ablation zones measured to assess ablation contiguity. These data were compared against the transmission coefficient-based estimation of ablation zone contiguity.

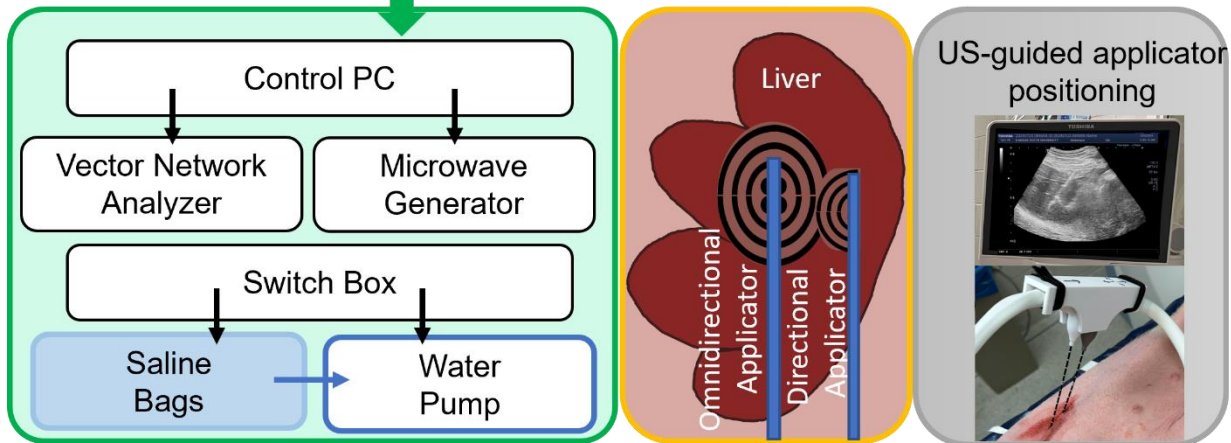


Figure 4.1. System setup for *in vivo* large animal hepatic microwave ablation study. Microwave applicators were placed under ultrasound guidance, and positioning was confirmed with CT imaging. A custom computer-controlled system enabled 46 s periodic switching of the applicators between ablation mode and monitoring mode.

4.2.1.1 *In vivo* Ablation Procedures

Experimental procedures were conducted under a protocol approved by the KSU Institutional Animal Care and Use Committee in anesthetized female domestic pigs. Animals (45–

60 kg) were premedicated with intramuscular atropine (0.05 mg/kg) and anesthesia was induced with intramuscular Telazol (4.4 mg/kg) and Xylazine (2.2 mg/kg). Orotracheal intubation was performed, and anesthesia was maintained with isoflurane in oxygen. The pigs were positioned dorsally during procedures.

At the beginning of each experimental session a baseline whole abdomen breath-hold contrast-enhanced CT scan (GE Brightspeed, Waukesha, WI) was performed. Under ultrasound imaging guidance (Toshiba), a board-certified veterinary radiologist positioned both an omnidirectional and a directional applicator in liver parenchyma, with the omnidirectional applicator placed deeper due to the anticipated larger ablation along the antenna axis. Applicator placement was confirmed via CT and adjusted, if necessary. The directional applicator was oriented to align the axis of greatest radial penetration of ablation towards the omnidirectional applicator (see Figure 4.1). A custom fixture maintained the directional applicator's orientation, an inter-applicator spacing of ~3 cm, and near-parallel alignment. Ablative power was then applied for either 200 s or 600 s. Following each ablation, a CT scan was taken, the applicators were withdrawn, and then repositioned in another site within the liver. Following completion of all ablations in each animal, a post-treatment CECT scan was taken, after which the animal was euthanized.

Post-euthanasia, livers were excised, and gross sections of the ablation zones were stained with Triphenyl Tetrazolium Chloride (TTC) to assess gross extents of the thermal ablation zones. The tissues were then fixed in 10% neutral buffered formalin for 24 hours, processed for histopathological examination, and embedded in paraffin. Slide-mounted tissue sections were stained with Hematoxylin and Eosin (H&E) and evaluated by a veterinary anatomic pathologist.

4.2.1.2 Microwave Energy Delivery

We used a custom software-controlled generator (Leanfa Srl, Bari, Italy) that switched between two modes: heating mode, for applying ablative microwave power to the applicators, and measurement mode, for intermittent recording of transmission signals. During heating mode, microwave power was split between two applicators via a 1:2 power splitter (Pasternack, Irvine, CA, USA), with 200 W at the generator, resulting in approximately 60 W delivered to each applicator after accounting for attenuation in the signal transmission chain. In measurement mode, the antennas were connected to a broadband vector network analyzer (Keysight FieldFox VNA N9923A, Schaumburg, IL, USA). The 14 G applicators (experimental devices; Precision Microwave, Inc., Manhattan, KS, USA) operated at 2.45 GHz and were cooled with room temperature water.

4.2.1.3 Treatment Groups and Validation Assessment of Ablation Zones

Based on pilot experiments in *ex vivo* tissue, we hypothesized that 200-second ablations would yield incomplete ablation zones (discontiguous), while 600-second ablations would result in complete zones (contiguous). We collected multivariable validation data, including post-procedure contrast-enhanced CT scans, gross pathologic assessment, and histopathologic assessment of thermal injury (Figure 4.2(A)). Transient changes in the broadband transmission spectra were analyzed and compared to pre-ablation baseline spectra to measure ablation progress quantitatively. These results were compared against validation data to assess the technique's effectiveness (Figure 4.2(B)).

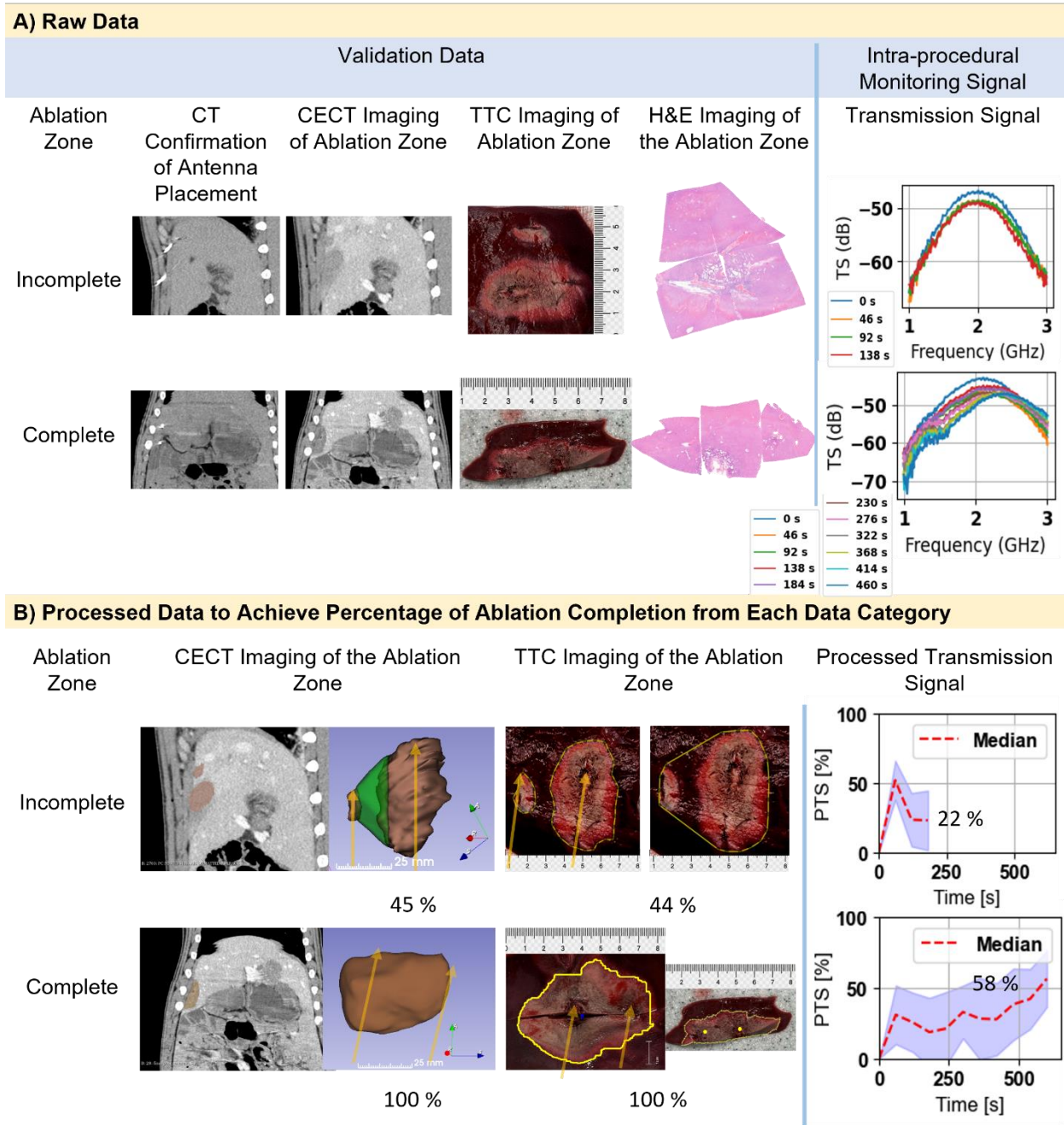


Figure 4.2. (A) Raw data acquired during *in vivo* procedures included: CT images of pre-ablation applicator placement; post-ablation contrast-enhanced CT images to assess ablation zone boundary; TTC-stained gross sections; H&E-stained fine sections; broadband transmission signal. (B) The raw data were processed to identify the fraction of ablation zone completeness on both CECT and TTC-stained sections. For incomplete samples, the green segmented part of CECT images hypothetically represents the ablation zone volume if two zones merged, and the ratio of brown segmented volume over brown + green gives the ablation evolution percentage. For TTC images, the ablation evolution percentage is determined by the ratio of the segmented ablation zone to the actual ablation zone plus the area that is supposed to be ablated; complete samples were assigned 100%. The raw transmission signals were processed to evaluate the transient

changes in the average transmission data. The Processed Transmission Signal (PTS) represents the percentage change relative to the baseline signal at zero seconds when the tissue had not yet undergone ablation. PTS [%] values range from 0 to 100, where 0 indicates non-ablated tissue and 100 signifies a contiguous ablation zone between two applicators. In the results section, a threshold value will be introduced as an indicator of contiguity. data.

4.2.2 Data Analysis

The primary objective of this study was to determine if the transient broadband transmission signal could indicate a difference between discontinuous (“incomplete”) and contiguous (“complete”) ablation zones.

4.2.2.1 Validation Ablation Zones

CT images were the primary source for establishing validation data and conducting causal analysis. First, the tip-to-tip distance between the two applicators was measured. Ablation zones were segmented and validated by an interventional radiologist (F.C.) and a veterinary radiologist (C.H.). The ablation boundary on CECT was identified by the non-enhancing zone, indicating ablated tissue. Ablation zones were manually segmented on CECT images using 3D-Slicer to compute the volume and classify them as complete or incomplete. For incomplete ablation zones, we estimated the ablation evolution percentage (ratio of ablated tissue to approximated complete ablation zone) by defining an idealized zone of complete ablation. In CECT images, the green segmented part hypothetically represents the ablation zone volume if two zones merged. The ratio of brown segmented volume to brown + green gives the ablation evolution percentage (see Figure 4.2(B)). This method was also used to assess contiguity and compute ablation evolution percentages from TTC-stained gross sections. The ratio of the segmented area in the actual ablation zone to the actual ablation zone + the area that is supposed to be ablated provides the ablation evolution percentage. Complete samples were assigned 100% (Figure 4.2(B)). Finally, H&E-

stained sections were analyzed to verify the boundaries of segmented ablation zones and described local tissue changes at the cellular level. Four main zones were described: normal liver tissue in zone 3 shows no lesions, maintaining its architecture and cellular integrity. In contrast, areas affected by ablation exhibit varying degrees of damage: zone 2 shows early reversible cell damage and hyperemia, zone 1.b displays severe irreversible coagulative necrosis with significant cellular changes, and zone 1.a shows extensive tissue damage with loss of structure and neutrophil recruitment (Figure 4.3).

4.2.2.2 Transmission Signal

Here, an adapted version of the tissue state monitoring algorithm from [30] was presented, with a reduced computational load. Similar to the previous approach, the transmission signal was collected at 46-second intervals during each experiment within the frequency range of 1-3 GHz, and then further processed (see Appendix B – Transmission Signal Analysis). The computed values for two samples are plotted in Figure 4.2(B) under “Processed Transmission Signal.” Due to the unknown probabilistic distribution and the small sample size of the acquired dataset, the scaled median was chosen as the summary statistic of the signal's central tendency. This metric, representing tissue state estimation, is referred to as the “processed transmission signal”. The computed values of the percentage change of the processed transmission signal relative to the time zero are shown in Figure 4.2(B) for two samples, one per each MWA setting.

4.2.2.3 Statistical and Exploratory Data Analysis

All the data were collected to determine if there was a statistically significant difference ($p < 0.05$) between the validation data and transmission signals for the complete and incomplete ablation groups. The Mann-Whitney U test was used for analysis due to the unknown data

distribution. Both validation and transmission signals were unified onto a percentage scale for direct comparison. Given the small sample size, non-normal distribution, and presence of outliers, Spearman's rank coefficient was calculated to identify potential correlations between the transmission signal and the validation data.

4.3 Results

Data gathered from 15 *in vivo* MWAs in porcine liver are reported in Table 1.

Table 4.1 Summary of processed transmission data-based estimation of ablation zone completeness relative to validation data from TTC-stained sections and contrast enhanced CT imaging. Cells shaded in green were labelled as incomplete and cells brown shading were labelled as complete.

Experiment Number	Duration of Ablation (s)	Distance between applicators tip-to-tip (mm)	TTC (%)	H&E with zone 2 & 3	CECT (%)	Processed Transmission Signal (%): Median [std]
1	600	28.08	100	0	100	73.01 [24]
2	600	34.35	100	0	100	73.20 [32]
3	600	32.37	100	0	100	73.11 [28]
4	200	18.80	51.7	1	53.2	41.22 [7]
5	600	32.61	100	0	100	98.34 [15]
6	600	29.06	100	0	100	89.83 [32]
7	600	23.63	100	0	100	85.10 [10]
8	200	24.85	100	0	100	52.66 [14]
9	200	34.58	100	0	100	100 [23.5]
10	200	29.47	75	1	74	33.25 [10]
11	600	32.27	100	0	100	23.06 [11]
12	200	32.62	43	1	45.3	45.27 [17.2]
13	200	30.78	41.85	1	42.4	18.34 [6]
14	200	35.02	44	1	44.8	24.97 [8]

15	200	33.73	48	1	52.5	45.73 [16]
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4.3.1 Validation Ablation Zones

Analysis of CECT images using 3D Slicer identified a total of 9 complete ablation zones (2 from 200 s ablations and 7 from 600 s ablations) with 100% completion. Conversely, 6 ablation zones from the 200 s ablations were incomplete (mean completion: 52.0%, std: 11.6%). A statistically significant difference was found between the complete and incomplete groups (U-test, $p = 0.0002$). For TTC images, a similar method was used, assessing area ratios instead of volume. Complete ablation zones (9 total) showed 100% completion, while incomplete zones (6 total) had a mean completion of 50.5% (std: 12.5%). A statistically significant difference in completion was also found between these groups (U-test, $p = 0.001$).

Pre-ablation CT images showed a mean distance between the two applicators of 2.5 cm for complete 200 s ablations and 3 cm for incomplete ones, suggesting that shorter distances (below 3 cm) might yield contiguous zones even for short duration ablations. Further analysis was based on actual ablation zone contiguity rather than duration alone. Post-ablation CECT images showed a difference in ablation zone volume as a function of ablation site within the liver. The factors contributing to this can be the boundary effect [139] and differences of blood perfusion in different lobes, especially near portal and hepatic veins or arteries. Notably, ablations at the periphery of the liver were larger (16.41 cm³) than those at deeper sites (6.51 cm³), potentially due to differences in blood perfusion rate in the periphery and center of the liver [140], [141].

To evaluate the efficacy of ablation therapies and distinguish between complete and incomplete ablation cases, histological examination was conducted on H&E-stained fine sections. For this study, tissue samples from four distinct zones of the ablation area were analyzed (Figure 4.3): Zone 1.a, adjacent to the antenna shaft, exhibits extensive tissue damage

with loss of structure and neutrophil recruitment; Zone 1.b, the zone of coagulation necrosis, shows severe irreversible necrosis with significant cellular changes; Zone 2, the zone of hyperemia, displays early reversible cell damage and hyperemia; and Zone 3, the normal tissue, shows no lesions, maintaining its architecture and cellular integrity. A detailed description of the features characteristic of each zone is provided in the Appendix C – Histological Assessment of Validation Ablation Zones. For all sections that appeared as 100% complete on TTC samples, zones 2 and 3 were not present between the two antennas on H&E sections. Conversely, for all TTC samples that appeared as less than 100% complete, zone 2 and/or 3 were observed on H&E sections.

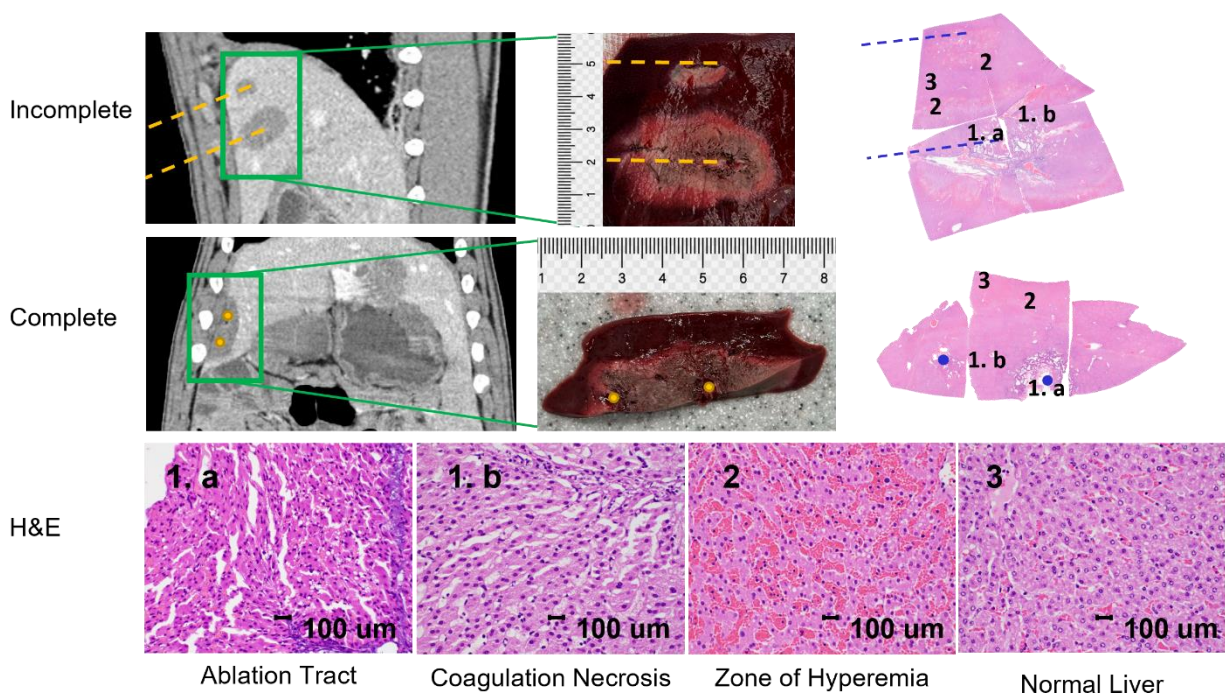


Figure 4.3. Illustration of complete and incomplete ablation zones on CECT imaging, and TTC-stained sections. Four zones were identified on H&E sections as illustrated here. Normal liver tissue in zone 3 shows no lesions, maintaining its architecture and cellular integrity. In contrast, areas affected by ablation exhibit varying degrees of damage: zone 2 shows early reversible cell damage and hyperemia; zone 1.b displays severe irreversible coagulative necrosis with significant cellular changes; and zone 1.a shows extensive tissue damage with loss of structure and neutrophil recruitment.

4.3.2 Transmission Signal

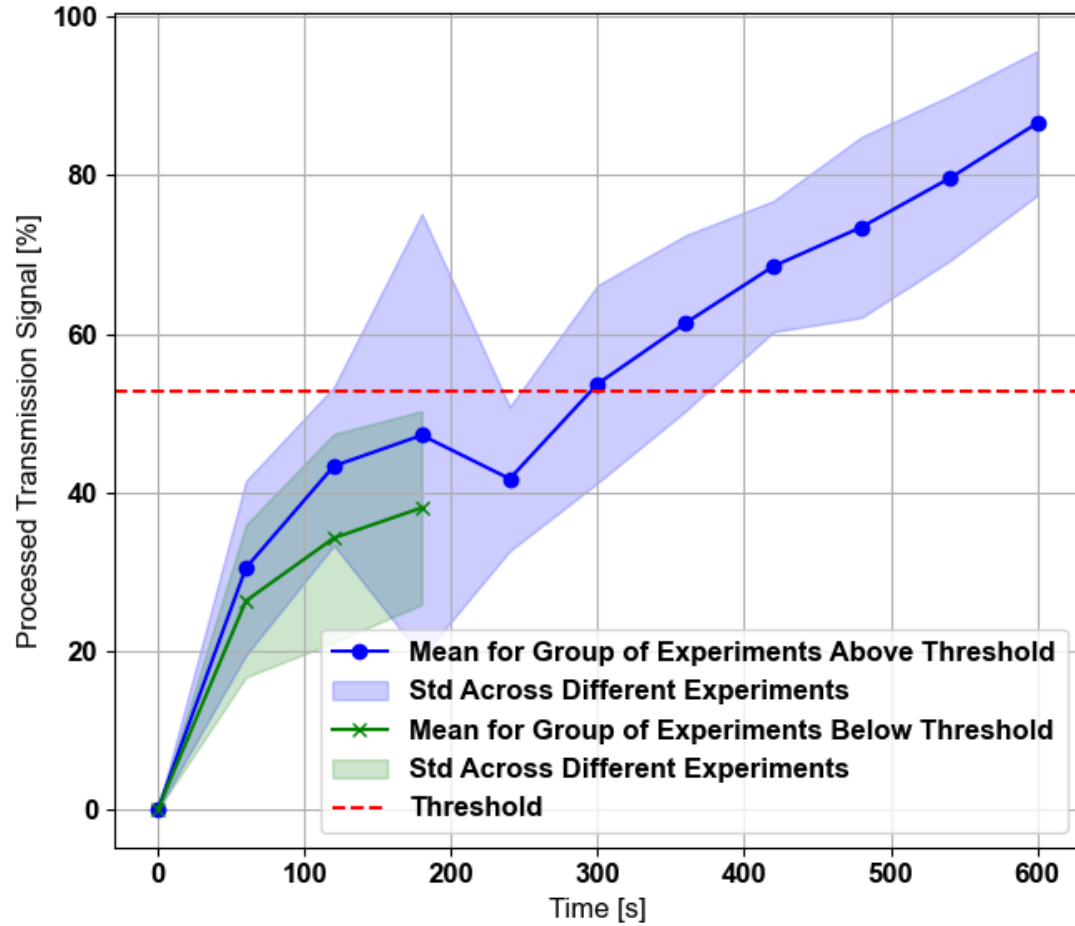


Figure 4.4. The Processed Transmission Signal (PTS [%]) represents the percentage change relative to the baseline signal at zero seconds when the tissue had not yet undergone ablation. PTS values range from 0 to 100, where 0 indicates non-ablated tissue and 100 signifies a contiguous ablation zone between two applicators. The mean and standard deviation of the processed transmission signal across different experiments ($n = 15$) were calculated. Experiments with above 53% of processed transmission signal were labeled as complete ablations.

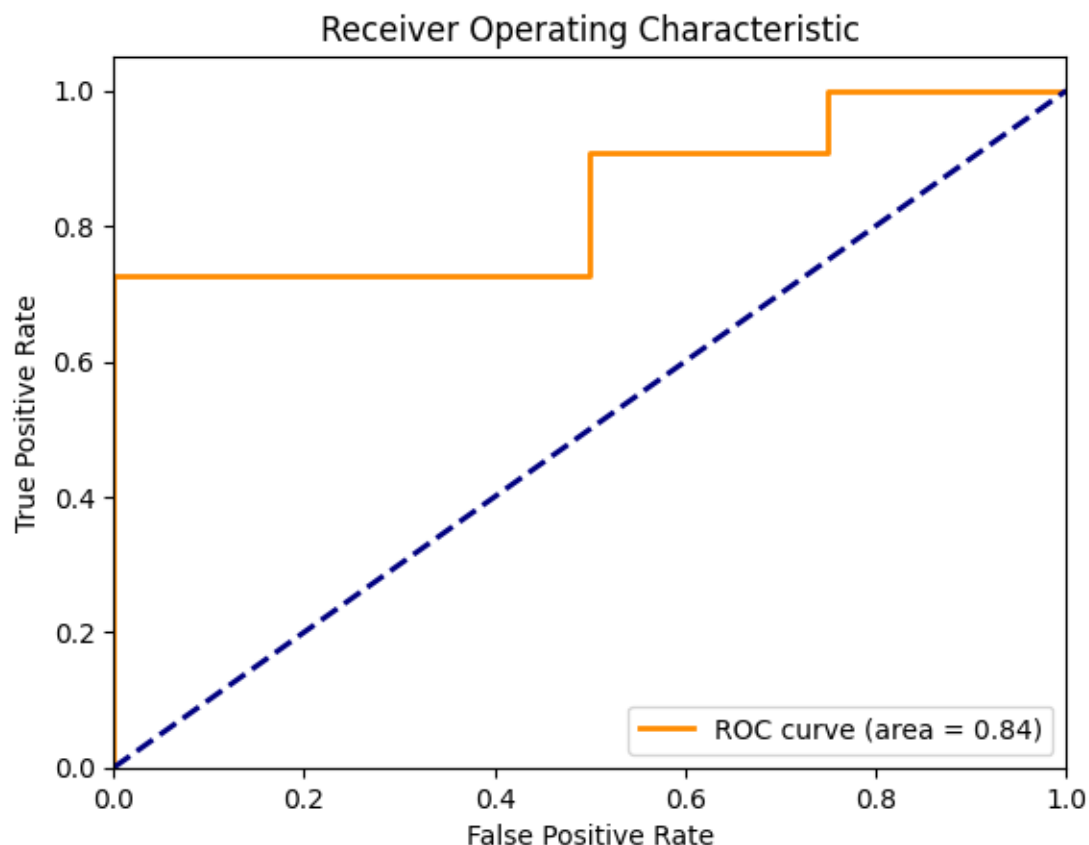


Figure 4.5. The ROC curve plots the True Positive Rate (sensitivity) against the False Positive Rate (1-specificity) at various threshold settings. The dashed line represents the performance of a random classifier and serves as a baseline for evaluating a classifier's performance.

The validation data (i.e., CECT images, TTC-stained gross sections, and H&E fine sections) showed that groups classified based on ablation zone contiguity—complete and incomplete—exhibit statistically significant variation. Subsequently, the investigation focused on transmission signals to ascertain whether these could distinctly differentiate the two groups. The analysis involved representing processed transmission signal values on a percentage scale.

Processed transmission signal at time-endpoint each experiment was computed, these values were reported in the Table 1, underlying labels are either 0 (if ablation from an experiment was identified as discontinuous) or 1 (if ablation from an experiment was identified as contiguous). ROC analysis revealed, that processed transmission signal appears to distinguish

well between contiguous and discontinuous ablation zones with high area under curve (AUC) of 0.84 ($p = 0.02$ for permutation test, 100,000 permutations) with a threshold value of 53% that yields highest ratio of true positive vs false positive detections (Figure 4.4 and 4.5).

A U test performed on these categorized data demonstrated a statistically significant ($p = 0.0007$) difference in the processed transmission signal for the complete and incomplete groups, confirming that the processed transmission signal effectively differentiates between complete and incomplete ablation.

4.3.3 Correlation of Validation Ablation Zones and Transmission Signal

Spearman's rank correlation revealed a strong association ($\rho = 0.87$, $p < 0.0001$), between the ablation completeness validation and the completeness derived from the processed transmission signal, suggesting high concordance between these measures.

4.4 Discussion

Without a monitoring method for microwave ablation procedures, there remains a risk of incomplete ablation, which increases the risk of tumor local progression, that may not be detected until contrast-enhanced imaging is performed; this risk should be balanced against that of over-ablation, which has potential to cause thermal damage to surrounding normal tissues. Evaluating ablation margins 3-4 weeks post-treatment may introduce inaccuracies due to tissue changes over time, such as inflammation or healing processes. This delay may influence conclusions about the treatment's effectiveness and thus treatment course, increasing patient burden and overall costs. Having a reliable monitoring method during the procedure can increase the likelihood of achieving technically successful ablations and optimize treatment outcomes.

This study was initiated to evaluate in an *in vivo* large animal model the technical feasibility of distinguishing between contiguous and discontinuous ablation zones using a microwave transmission-based approach during dual-applicator hepatic MWA. In a prior study, we demonstrated the feasibility of determining treatment endpoint using a microwave transmission-based approach in an *ex vivo* liver tissue model. The presented method demonstrates the potential of a broadband transmission coefficient-based monitoring method to distinguish between contiguous and discontinuous ablation zones with a threshold processed transmission signal value of 53 %.

We noted variations in the volume of the ablation zones depending on their location within the liver. This can be attributed to the boundary effect [139] and variations in blood perfusion across different lobes, particularly near the portal and hepatic veins or arteries. No differences in the transmission system estimation of ablation zone contiguity were observed as a function of ablation site, indicating the robustness of the approach to potential variations in perfusion rate.

Successful image-guided thermal tumor ablation relies on pre-procedural planning, peri-procedural applicator targeting, intra-procedural monitoring, and post-procedural confirmation. In contrast to ablation with a single applicator, using two or more applicators, although it increases invasiveness, may facilitate defining the treatment margin through appropriate placement of the applicators and offer more degrees of freedom for tailoring ablation zone profiles. The treatment monitoring problem then shifts to confirming the achievement of a contiguous ablation zone between the applicators. This study demonstrates the feasibility of distinguishing between contiguous and discontinuous ablation zones in porcine liver *in vivo*, confirmed by CECT, gross pathology, and histopathology. Future work should further define and evaluate thresholds for prospectively terminating treatment based on the transmission signal. This method can inform

clinicians when adequate ablation is achieved, delaying CECT imaging until there is high confidence in a successful outcome. While CECT confirmation remains necessary, the transmission signal offers a binary measure of contiguity, and potentially offers time saving by delaying the treatment endpoint until there is a high likelihood of a contiguous ablation zone. Notably, this technique does not require modifications to existing ablation applicators, while the monitoring electronics and software can be readily integrated into ablation generators. Moreover, the system does not preclude the use of contrast-enhanced imaging assessment.

In the present study, ablations were performed in normal porcine liver *in vivo*, and thus lacked a tumor target. Definitive evaluation of the presented method would consider histopathologic assessment of the targeted tumor as a function of ablation completeness predicted by the transmission technique. Furthermore, the temperature-dependent changes in tissue dielectric properties may vary for tumors and other pathologic tissue (i.e., cirrhotic or steatotic liver that are often observed in patients with liver tumors) and may potentially impact performance of the presented technique. We expect to find the dielectric change of fatty liver less sensitive to temperature variations, due to lower water content [142]. In clinical practice, the system and method proposed in this study offer additional quantitative information to assess the success of ablation procedures, which could be coupled with current imaging modalities. However, it may not always be feasible to place ablation applicators in a parallel manner, which may also impact performance.

4.5 Conclusion

The present study investigated the feasibility of a transmission coefficient-based microwave ablation monitoring method and assessed its ability to distinguish between contiguous and discontinuous ablation zones in an *in vivo* porcine liver model. The study

demonstrated the efficacy of using broadband transmission signals to distinguish between contiguous and discontinuous ablation zones with the threshold level of 53% in a large animal model. This approach has the potential to provide additional insights for real-time monitoring of ablation zones.

Chapter 5 – Conclusion and Future Work

5.1 Main Findings

In this chapter, concluding remarks of this dissertation are provided as well as a summary of the results and suggestions for possible future research directions. In response to the unmet need for defining the endpoint of microwave ablation procedures, this dissertation explored the feasibility of a microwave transmission-based method for monitoring dual-applicator ablation, and presented the design and detailed experimental evaluation. Utilizing a dual-applicator setup during microwave ablation procedures, this system measures the broadband, complex-valued transmission signal (s_{21}) transmitted between the antennas by coupling the ablation antennas to a vector network analyzer during the monitoring mode phase. It is hypothesized that variations in the s_{21} signal correspond to changes in the tissue state during the ablation process. By quantifying these transient changes, a real-time indication of the tissue state, ranging from non-ablated to fully ablated, can be provided by the system, thereby offering insights during the procedure.

To test this hypothesis, a platform capable of sequentially measuring the broadband, complex-valued transmission coefficient between a pair of water-cooled MWA antennas during ablation procedures was designed and developed. The feasibility of this system was assessed under various experimental scenarios: *ex vivo* with a pair of directional antennas, as presented in Chapter 3, and *in vivo* with a pair of omnidirectional and directional antennas, as presented in Chapter 4.

From the *ex vivo* studies, it was observed that the normalized average transmission coefficient initially decreased rapidly and then increased before asymptotically approaching a steady state. The transition time ranged between 53 s (45 W) and 109 s (30 W). Analysis of

ground truth ablation zone images indicated a time to complete ablation of 230–350 s. The relative prediction error for the time to complete ablation derived from the s_{21} data was in the range of 1.6%–2.3% compared to the ground truth.

In the *in vivo* study, statistical analyses revealed statistically significant differences between contiguous and discontinuous ablation zones in both ground truth and transmission signal datasets. This validates the capability of both datasets to effectively discriminate between the two types of ablation zones. Additionally, a high correlation coefficient of 0.87 indicates a strong relationship between ground truth and transmission signals. K-means clustering was utilized to further illustrate the transmission signal's ability to detect patterns within the ground truth data. This analysis achieved a high silhouette score of 0.7, suggesting that clusters are well-separated and that data points within the same cluster are similar.

Upon successful implementation, this system setup is not anticipated to add complexity to the existing microwave ablation procedure, as the ablation monitoring instrumentation can be incorporated into the microwave generator and does not require any additional hardware interfacing with the patient. Rather, it provides complementary information alongside imaging modalities.

5.2 Gaps in Research and Proposed Future Studies

Below, the gaps identified during the research were detailed, and potential directions for future work were proposed.

Does the microwave transmission method for monitoring microwave ablation progress predict endpoint in the presence of tissue heterogeneity?

To date, the ablation monitoring system has been evaluated in normal liver tissue. A next phase of evaluation should involve testing the system in the presence of tumors [143], [144],

including both normal background liver tissue and background liver with induced cirrhosis or steatosis [145]. Furthermore, these studies should advance on the *in vivo* study presented in chapter 4 to determine the ablation treatment endpoint based on real-time signals; the *in vivo* study reported in chapter 4 limited to offline analysis to distinguish between contiguous and discontinuous ablation zones. Subsequently, the treatment's efficacy and biomarkers can be assessed, alongside comprehensive pathology assessments.

Similar to the *in vivo* study, multimodal ground truth data will be gathered for comparative assessment of the transmission coefficient signal. In addition to having a tumor, the procedure will be stopped when the signal indicates completion (contiguous ablation zones). Image-guided microwave ablation with two antennas will be used to target the tumor, delivering energy while periodically switching to monitoring mode to capture and analyze the transmission coefficient data in real-time, determining the completion of the ablation procedure. After data collection, biomarker analysis can be conducted. The expected outcome is to achieve complete coverage of the tumor with informative real-time transmission signals. Potential challenges include antenna positioning issues similar to those encountered in the *in vivo* study, which may be addressed with robotic assistance in future investigations. A comprehensive study comparing normal liver to cirrhotic liver antennas should be conducted to establish a baseline before the *in vivo* study.

Can computational modeling be used to measure transmission coefficient signal between two applicators?

Computational models provide a powerful tool for assessing medical devices under a variety of conditions [41], [146], [147]. In the context of ablation monitoring, a computational model of microwave ablation and broadband electromagnetic transmission coefficient would

offer the opportunity for systematic investigation of a number of parameters, including: effect of different tissue types; effect of different applied power levels; effect of different applicator types; effect of varying inter-applicator distance; effect of parallel vs. non-parallel applicator positioning; and others. After validating these computational models and the successful completion of this step, and integration with practical ablation systems, the simulations could also offer the opportunity to augment measurements. This integration would not only display the thermal profile but also inform the physician about the completion of ablation based on the s_{21} signal.

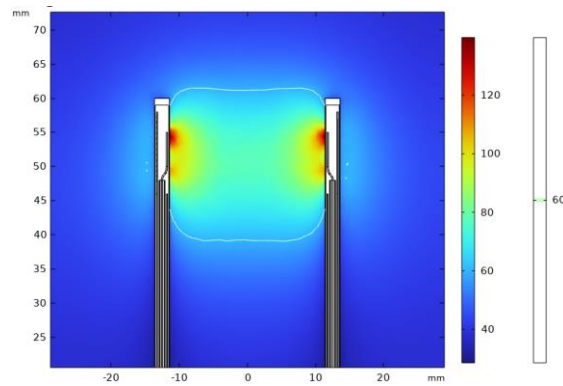


Figure 5.1. Temperature profile of two directional applicators, COMSOL Multiphysics.

The methodology involves implementing a 3D model featuring two antennas (directional, omnidirectional, or both) set at a specific distance, power and duration of ablation. Since there is no direct method to compute s_{21} during ablation, one ablation lasting 600 seconds, either *ex vivo* or *in vivo*, will be conducted using electromagnetic-bioheat modules. From this simulation, relative permittivity and conductivity maps will be extracted, with antenna positions masked at predetermined intervals. These maps will serve as inputs for a second simulation that swaps frequency (1 to 3 GHz in 0.5 GHz intervals), where s_{21} can be extracted by deactivating one

antenna. Frequency-based simulations will be generated from the initial simulation, and s_{21} data from all simulations will be collected and analyzed across time and frequency, following this protocol for each scenario. Expected outcomes include aligned results with experimental data, contributing to the microwave ablation field by enabling s_{21} computation for various tissue types, distances, and power levels. Potential challenges include the computational cost of simulations, making a mesh study useful before starting, and validating the thermal profile of ablations with cross-sectional ablation zone images from experimental studies. The next step could involve implementing the model on GPU instead of CPU-based modeling, exploring faster inferences.

Can the transmission monitoring tool be used as tissue sensing?

This monitoring system can also function as a tissue sensing system. From our *in vivo* study, it was observed that the transmission signal differs among tissue types and its change over the course of ablation varies based on the tissue type. A study can be designed to collect s_{11} and s_{21} data by positioning antennas close and far apart, and gather s-parameter data for different tissue types [33], [50]. This data of non-ablated tissue would provide a second confirmation for physicians, ensuring correct placement and tissue targeting. Furthermore, changes in the signal during ablation can be collected to build a framework similar to research conducted on measuring tissue dielectric properties across different tissue types, over a range of frequencies and temperatures. Temperature can also be systematically collected to provide a temperature map at different points in the thermal ablation zone and surrounding areas with Fiber Bragg Grating (FBG) optical fiber or MR thermometry. The ultimate goal of this study would be to develop generalized equations for each type of tissue, predicting how the s_{11} and s_{21} signals will behave during ablation based on frequency, time, and temperature.

An experimental study will be designed to measure s-parameters and temperature in specific tissues, repeated for different tissue types. Data on temperature at different points, frequency, and s-parameters will be collected in non-ablated tissue and during ablation. This data will help build a framework for later analysis and develop unique equations for s-parameters (f , t , T) for each tissue type. Expected outcomes include collecting s_{11} and s_{21} measurements over time and across frequencies, with separate temperature recordings, which can then be integrated to provide a correlation temperature map based on s-parameters. Potential challenges include placing temperature sensors consistently across experiments, necessitating a custom-built template to hold tissue, antennas, and sensors. A plan for data collection and storage will facilitate later analysis.

Continued research in this area will lead to technical advancements for clinical use, providing physicians with deeper insights and reducing the reliance on experience. This will decrease uncertainties during microwave ablation procedures, ultimately improving patient outcomes.

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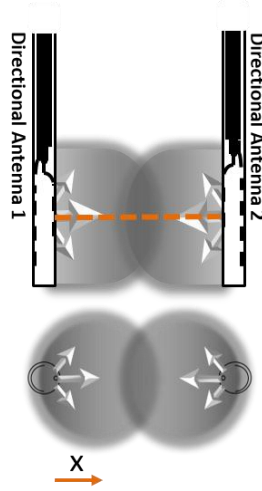
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Appendix A Theoretical Analysis

To gain a deeper understanding of the theory behind the method, simulated temperature data of tissue along a line perpendicular to and between the two antennas at different time points ($T(t, x)$) was utilized, using a model adapted from our prior computational modeling studies.



Appendix Figure A.1. Two directional antennas are shown, and the dashed line indicates the position where the temperature $T(x)$ is being measured during the ablation process.

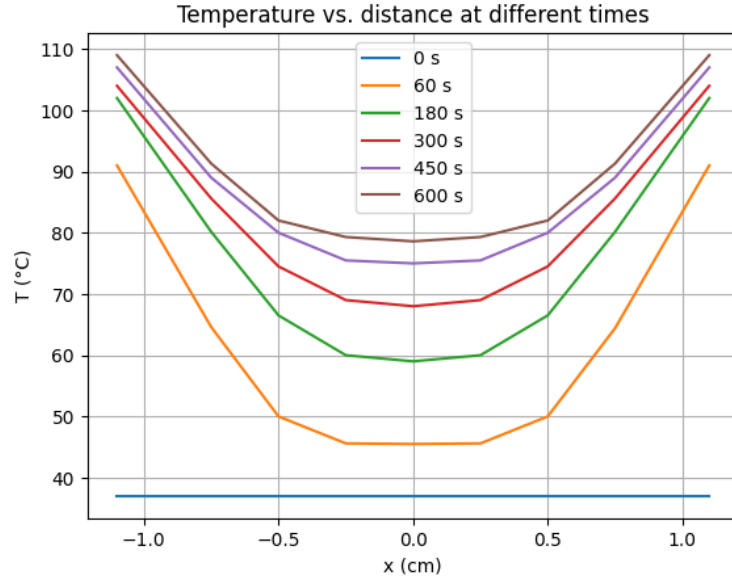
By applying the methodology outlined in [37], the broadband relative permittivity and electrical conductivity values at each point along the line between the antennas, based on the local temperature at each point were computed. These values, obtained at various locations, times, and frequencies, enabled us to determine the attenuation (α) in the liver tissue over the course of ablation. The complex valued attenuation coefficient was computed based on equation below at frequencies $f = 1, 1.5, 2, 2.45, \text{ and } 3$ GHz [148]:

$$\alpha = \omega \left\{ \frac{\mu \epsilon'}{2} \left[\sqrt{1 + \left(\frac{\epsilon''}{\epsilon'} \right)^2} - 1 \right] \right\}^{1/2} \text{ (Np/m)}$$

$$\omega = 2\pi f,$$

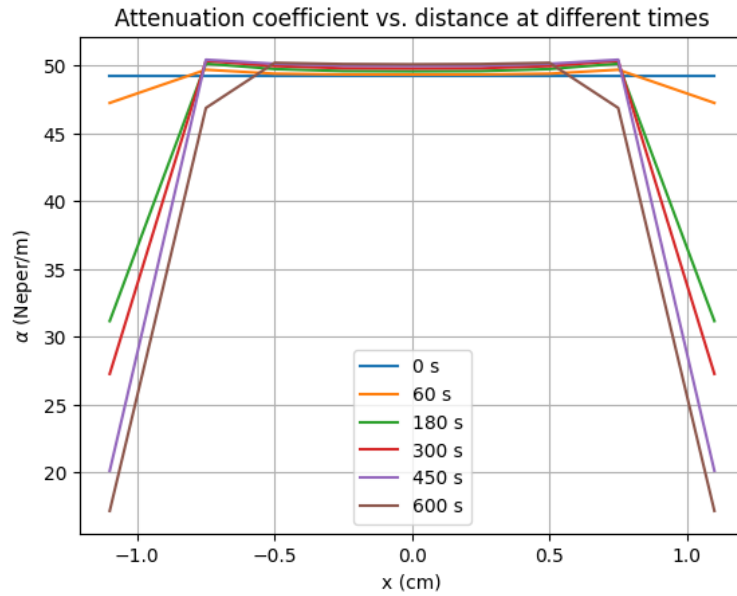
where $\epsilon_0 = 10^{-9} / 36\pi$ F/m, $\mu = \mu_0 = 4\pi \times 10^{-7}$ H/m, and

$$\varepsilon = \varepsilon_0(\epsilon' - j\epsilon'')$$



Appendix Figure A.2. Temperature (°C) variation over x (cm) between two directional antennas at different times.

Using the above equations, the corresponding attenuation coefficient vs. distance plots are shown in Fig. S3.

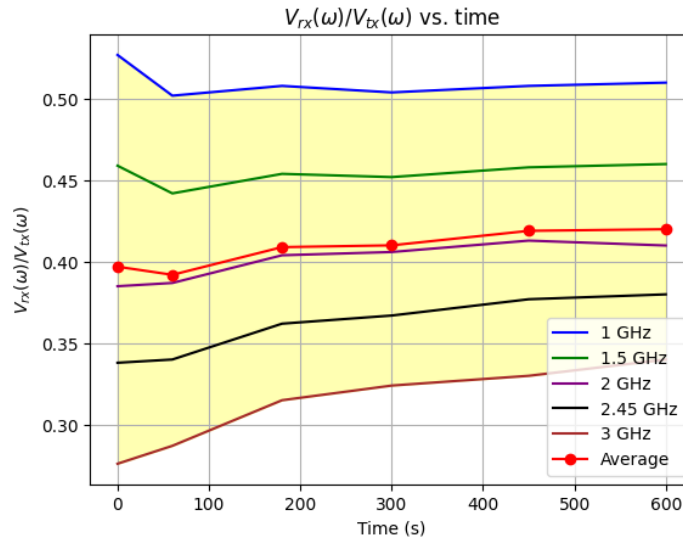


Appendix Figure A.3. Attenuation coefficient (Neper/m) variation over x (cm) between two directional antennas at different times.

Assuming a plane wave propagation, for each frequency, the exponential decay of the electromagnetic wave as it propagated from the transmitting antenna towards the receiving antenna was considered. Thus, the following quantity was calculated:

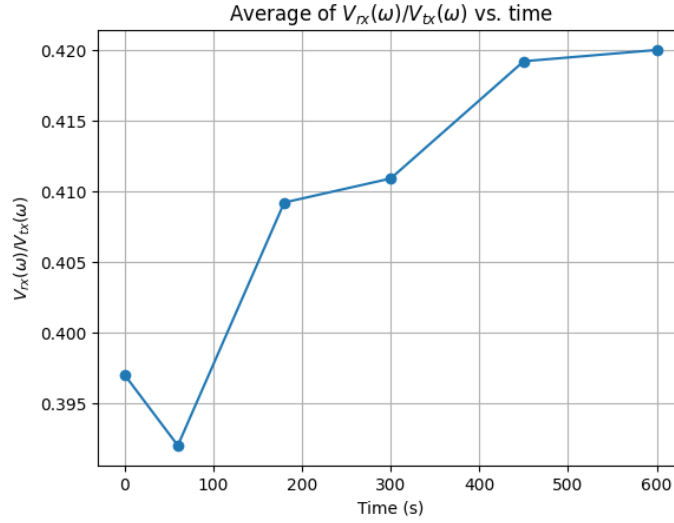
$$V_{rx}(\omega) = V_{tx}(\omega)e^{-\int \alpha(x,\omega,T) dx}$$

The results presented below depict the attenuation profiles at each time point during the ablation procedure, as well as the average across the five frequencies considered in this preliminary analysis.



Appendix Figure A.4. Attenuation profiles at each time point during the ablation procedure, across frequencies 1, 1.5, 2, 2.45, and 3 GHz.

Zoom in on the aforementioned figure and focus on displaying only the average power value, set at 45 watts, for each antenna input:



Appendix Figure A.5. Average of attenuation profiles at each time point during the ablation procedure, across frequencies 1, 1.5, 2, 2.45, and 3 GHz.

This preliminary theoretical analysis illustrates the influence of temperature dependent changes in the broadband dielectric properties of tissue on transient changes in attenuation coefficient between a transmitting and receiving antenna. Further detailed analysis of this is warranted to gain a deeper theoretical understanding of the presented technique for ablation monitoring.

Appendix B Transmission Signal Analysis

Although the s_{21} coefficients were collected in the range of 1-3 GHz, average magnitude of s_{21} coefficients in the 1-2 GHz range demonstrates the most significant differences between the two groups of incomplete and complete ablations. In further text, s_{21} magnitude was represented by $m(f_i, t_r, j)$, where f_i denotes i -th frequency, $i \in \{1, 2, \dots, n\}$, ($n = 101$ linearly spaced frequencies between 1-2 GHz), t_r represents r -th time point of collecting transmission signal, where $r \in \{0, 1, \dots, R - 1\}$ with R total sampled time-points and experiment index $j \in \{1, \dots, J\}$, with J total number of experiments.

First, the absolute value of the relative change of $m(f_i, t_r, j)$ to $m(f_i, t_0, j)$ at timestep 0 (i.e., non-ablated tissue) is computed for each frequency/time/experiment combination (f_i, t_r, j) as:

$$m_d(f_i, t_r, j) = |m(f_i, t_r, j) - m(f_i, t_0, j)|.$$

Subsequently, $m_d(f_i, t_r, j)$ was normalized to restrict all values to interval $<0,1>$:

$$\hat{m}_d(f_i, t_r, j) = \frac{m_d(f_i, t_r, j) - m_{min}}{m_{max} - m_{min}},$$

where m_{min} , m_{max} are global minimum and maximum found from whole dataset respectively.

$$m_{max} = \max_{f_i, t_r, j} m_d(f_i, t_r, j).$$

Next, the mean $\mu(t_r, j)$, median $\tilde{\mu}(t_r, j)$, and standard deviation $\sigma(t_r, j)$ of the normalized data were computed over the range of N frequencies. These values, which range between 0-1, were also multiplied by 100 to be further explainable in terms of percentages:

$$\mu(t_r, j) = 100 \cdot \frac{1}{n} \sum_{i=1}^n \hat{m}_d(f_i, t_r, j) \text{ [%]}$$

$$\tilde{\mu}(t_r, j) = 100 \cdot \text{median} (\{\hat{m}_d(f_i, t_r, j)\}_{i=1}^N) [\%]$$

$$\sigma(t_r, j) = 100 \cdot \sqrt{\frac{1}{n} \sum_{i=1}^n (\hat{m}_d(f_i, t_r, j) - \frac{\mu(t_r, j)}{100})^2} [\%]$$

The computed values for two samples are plotted in Figure 4.2(B), under “Processed Transmission Signal”. Due to the unknown probabilistic distribution and rather smaller sample size of acquired dataset, scaled median $\tilde{\mu}(t_r, j)$ was chosen as the best representative of signal central tendency, is chosen as a metric representing tissue state estimation and is further referred to as the “processed transmission signal”.

Appendix C Histological Assessment of Validation Ablation Zones

Grammar check: Four zones in Figure 4.3 are described in detail below:

Histologic changes in zone 3 (normal liver): Histologic cellular lesions are not observed in areas of normal liver. Normal hepatic architecture is observed (portal triads, central veins), and hepatic cords are well formed and that lie adjacent sinusoids containing few intact erythrocytes. Hepatocytes lack evidence of injury; cells have normal nuclei with open chromatin pattern and small basophilic nucleoli. Supporting collagen fibrils in portal zones are histologically normal.

Changes in zone 2 (transition, zone of hyperemia): Histologic lesions are minimal in areas of transition. Subgrossly, there is a distinct zone of transition from normal liver (right) through a band of hyperemia (zone 2) and then into a zone of coagulative necrosis (left). In the area of hyperemia (zone 2), hepatocytes retain their subgross architecture, and are arranged in hepatic cords, lining sinusoids markedly dilated and filled with abundant intact erythrocytes. Hepatocytes often have slightly hypereosinophilic cytoplasm, and individual cells are mildly to moderately swollen due to a single or multiple cytoplasmic vacuoles. Nuclei are basophilic and have condensed chromatin pattern. These changes are interpreted to be early reversible cell damage (vacuolar degeneration, nuclear condensation).

Changes in zone 1.b (coagulation necrosis, zone adjacent to the ablation tract): Histologic lesions in zone 1 (adjacent to the ablation probe tract) include hepatocytes retain architecture, but also show significant cellular changes including diffuse swelling of hepatocytes due to finely vacuolated eosinophilic cytoplasm, indistinct cell borders, hepatocytes are disorganized and no longer line distinct intact erythrocyte-filled sinusoidal spaces. Nuclei are condensed, basophilic,

and have condense chromatin pattern. Collagen fibrils forming the supporting stroma of the portal zones, and lining sinusoidal spaces is often fragmented and densely basophilic. Eosinophils within sinusoidal spaces are either not visible, or they are markedly fragmented and coagulated. These changes are interpreted to be consistent with peracute to acute irreversible cell injury, or coagulative necrosis of erythrocytes and hepatocytes.

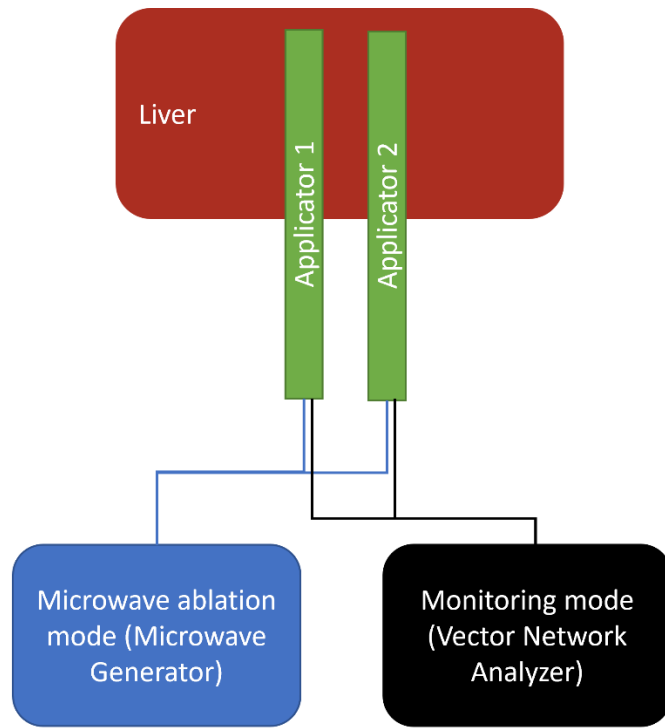
Change in zone 1.a (ablation tract): Histologic lesions at the ablation tract include hepatocytes have lost their architectural arrangement with loss of hepatic cords and sinusoids, and frequent fractures (clear irregular clefts) are present throughout the parenchyma. Erythrocytes are not visible, or are hyposinophilic and coagulated within sinusoids; hepatocytes are swollen due to multiple cytoplasmic vacuoles, have condensed basophilic nuclei with no visible chromatin structure. Supporting collagen is basophilic and fragmented. In some sections, there is karyorrhexis and scattered neutrophils are present. These changes are interpreted to be consistent with peracute to acute coagulative necrosis, with early karyorrhexis and neutrophil recruitment.

These images aided us in assessing and labeling the ablation zones, providing valuable insights into the characteristics and extent of tissue damage resulting from the ablation procedure. When there is an absence of zones 2 and 3 between the two antennas, the ablation is considered complete, as no non-ablated tissue exists between the two antennas.

Appendix D Microwave Ablation Transmission Coefficient-Based Monitoring System Documentation

The purpose of this appendix is to describe the architecture and implementation of the hardware and software components of the microwave ablation transmission coefficient-based monitoring system. A custom computer-controlled switching apparatus was developed to periodically switch the applicators from ablation mode (i.e., coupled to the generator) to monitoring mode (i.e., coupled to the Vector Network Analyzer (VNA)), as illustrated in Figure D.1. To implement this system, several hardware components are required:

- Microwave Generator: 2450 MHz, 250 W, compatible with the system's power requirements.
- Microwave Applicators: Dual 2.45 GHz, water-cooled microwave applicators.
- Cooling System: Peristaltic pump, water reservoir, closed-loop water circulation.
- Custom-Made Switch Box: Cold switches, power splitter, low-loss cables.
- VNA: Frequency range 1-3 GHz, Ethernet connectivity.
- Control and Switching Mechanism: Digital relays, transistors, resistors, Arduino.
- Custom Control Software: MATLAB R2024a, handles switching, measurement requests.
- Data Processing and Visualization: Computer with MATLAB, Ethernet and USB connectivity.
- Measurement and Analysis Setup: 3D printed fixtures, applicator and tissue holders.



Appendix Figure D.1. Schematic of the system with microwave ablation and monitoring modes.

1. System Overview

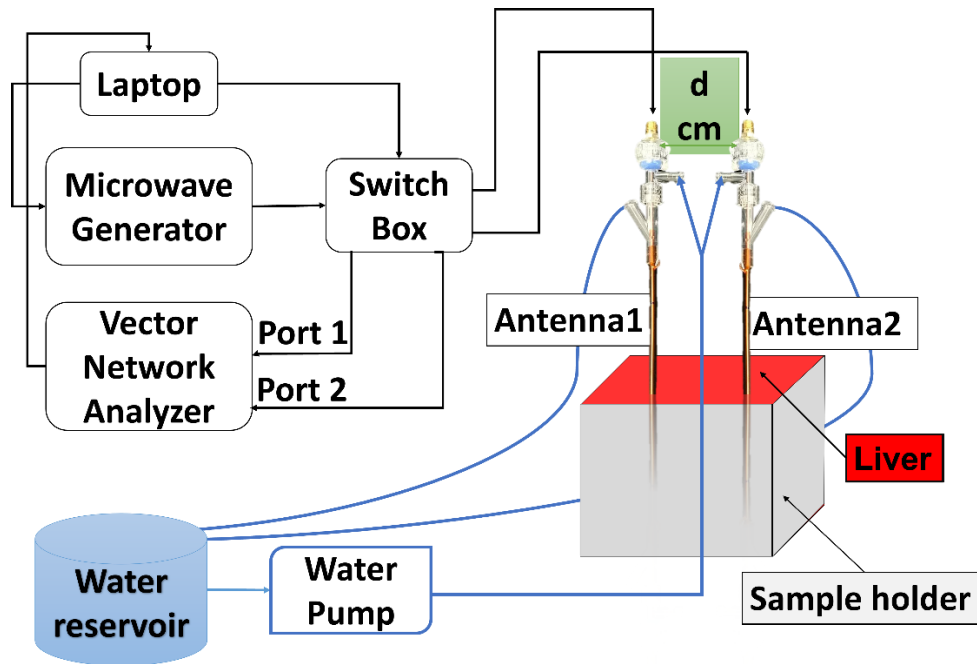
System Description: The microwave ablation/monitoring system is designed to run microwave ablation for dual microwave applicators (microwave ablation mode) and periodically record inter-applicator transmission signal measurements during the ablation process (monitoring mode/transmission signal collection). The system consists of specialized hardware components, including a microwave generator, microwave applicators, cooling system, an electrical switching apparatus to switch between the two modes, vector network analyzer, and custom-developed software for data processing and visualization.

Microwave power is passed from the microwave generator to the custom-made switch box. The main purpose of the switch box is to facilitate electronic switching between ablation/monitoring cycles of the ablation experiment. During the ablation part of the cycle, power from the microwave generator is distributed by a power splitter through dedicated microwave cold

switches to two identical cables, which transfer the microwave power to the SMA connectors of the microwave applicators.

During the measurement part of the cycle, the switches disconnect the power splitter outputs from the microwave ablation (MWA) applicators and connect ports of the VNA through low-loss coaxial cables to the MWA applicators. The VNA then measures the complex-valued transmission coefficient over the frequency range 1-3 GHz.

Since the switches employed require “cold switching,” it is essential to turn off the power from the generator before switching, and correspondingly, when switching back to heating mode, switching must take place before the generator is turned on. Therefore, an interval switch time between the heat time and measurement time intervals was incorporated. A custom control program (implemented with MATLAB R2024a, The Mathworks Inc., Natick, MA) was written to control the generator, switches, and send measurement requests to the VNA during the measurement part of each cycle. The MWA applicators used in our experiments were water-cooled 2.45 GHz directional applicators. A peristaltic water pump (Masterflex Easy-Load, Model 07514-10) was used to circulate room-temperature water from a reservoir through the applicator in a closed-loop manner.

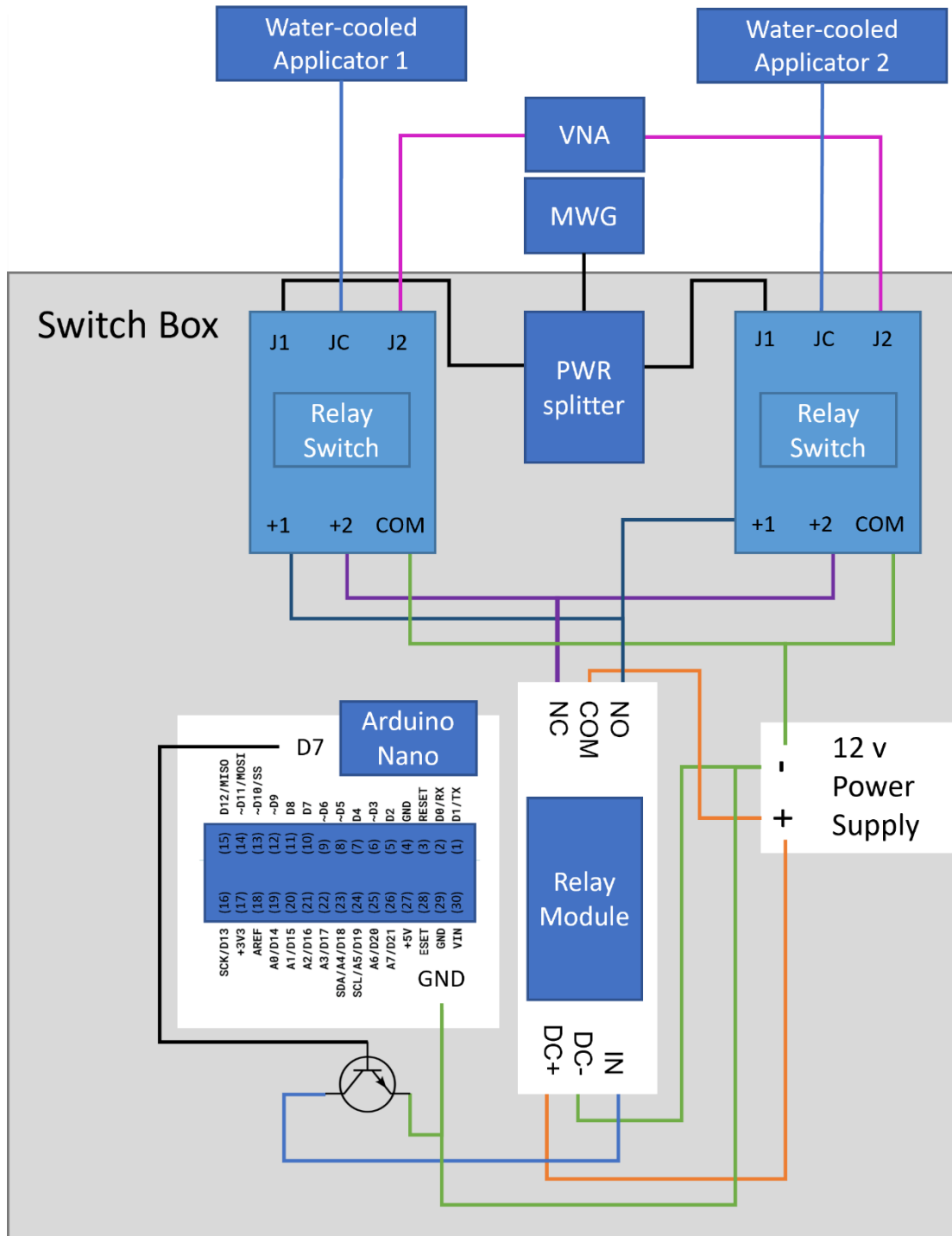


Appendix Figure D.2. Block diagram of microwave ablation-monitoring system components and their interactions.

2. Hardware Documentation

2.1 Hardware Overview

The hardware has three main sub-electrical systems: monitoring (VNA and water-cooled applicators), heating (microwave generator, water-cooled applicators), and the switch box (power splitter, relay switches, Arduino, and other components), as shown in Appendix Figure D.3.



Appendix Figure D.3. Hardware components.

2.2 Components

Detailed list of all hardware components used in the system, including antennas, processors, and other peripherals.

- Vector Network Analyzer (VNA) (Fieldfox N9923 A, Keysight) + Ethernet cable + Flash drive
- Microwave generator (MWG) (LeanFa, MODK-A003A01, 250 W, 2450MHz)
- 2 custom water-cooled 2.45 GHz microwave applicators with directional antennas connected to low-loss transmission cables (1.3 m, HUBER+SUHNER SUCOFORM 122, 50 Ω) with N-type connectors
- 2 relay cold switches (PASTERNAK, PE71S6435)
- Relay digital (DC 12V Relay Module 1 Channel Relay Board with Optocoupler Isolation Support High or Low Level, SRD-12VDC-SL-C)
- Transistor (2N3904)
- Power splitter (HUBER+SUHNER, 5504.17.0009, 2000-6000 MHz, Lot: 1004276917)
- Arduino Nano (A000005)
- Low loss cables (30 cm, Pasternack, RG400)

3. Software Documentation

3.1 Requirements

To implement the microwave ablation transmission coefficient-based monitoring system, the software must meet the following requirements:

1. Control the MWG and VNA to switch between heating and measurement modes:

Switch between modes within 2 s, with at least 10 switches per experiment.

2. Interface with the VNA to collect transmission coefficient data:

Cover the 1-3 GHz frequency range with at least 201 frequency points per measurement.

Measure and save .s2p file in less than 5 s.

Ensure data accuracy within 0.01 dB for s_{21} measurements.

3. Manage and log data to file from the ablation process, including time and s_{21} measurements:

Log data every 1 s.

4. Provide a user interface for inputting parameters and visualizing results:

Update the user interface within 500 ms after input.

Accept input parameters for power level (0-200 W), heating duration (1-1500 s), and measurement points (50-500 points).

5. Ensure reliable communication with hardware components (MWG, VNA, Arduino):

Maintain communication latency below 100 ms.

Ensure a stable connection with no more than 0.1% packet loss.

6. Handle errors and ensure smooth operation without interruptions

3.2 Software Architecture

The software is structured into several key modules:

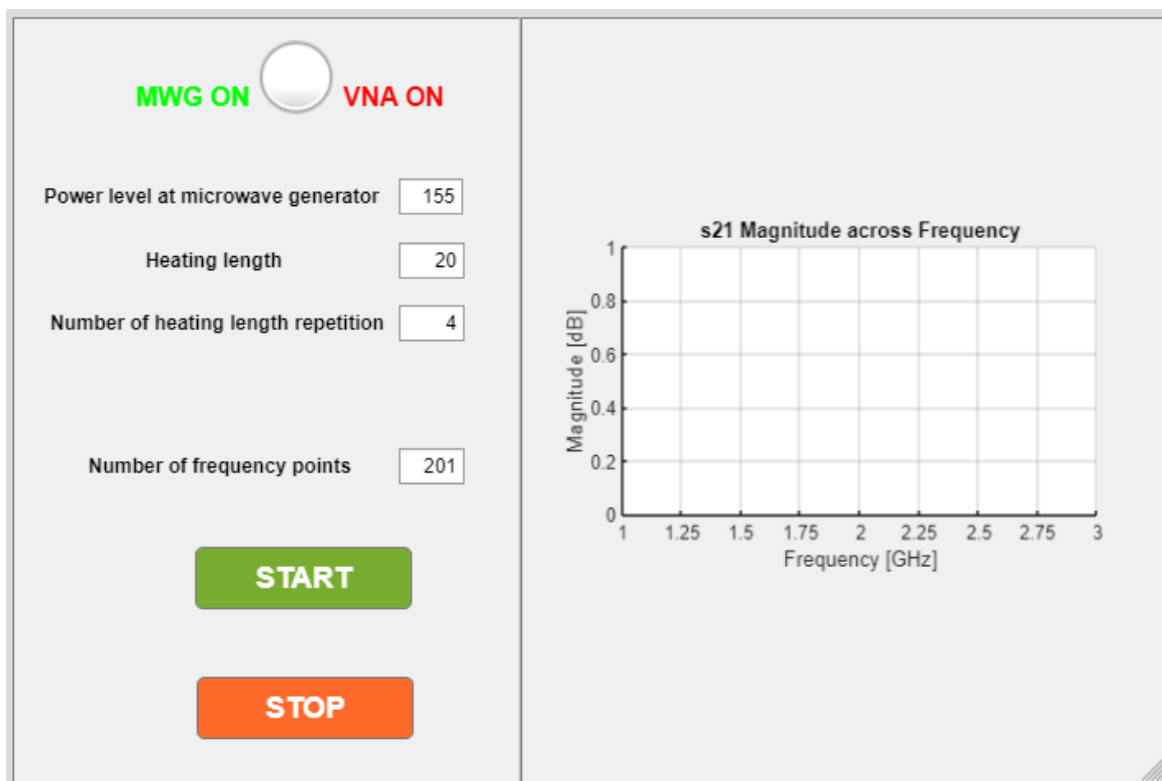
Control Module: Manages the switching between heating and measurement modes, controlling the MWG, VNA, and the relay switches via the Arduino.

Communication Module: Handles the communication with the VNA and the MWG using TCP/IP and serial communication protocols.

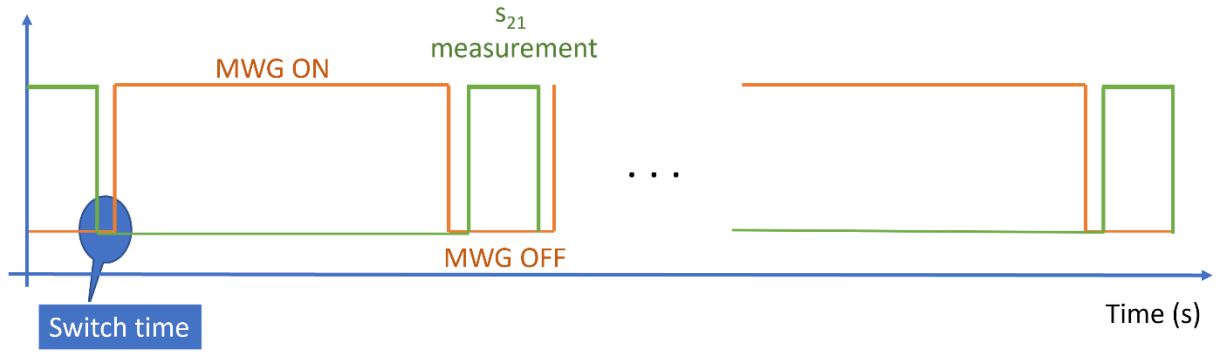
Data Acquisition Module: Collects and processes the transmission coefficient data from the VNA, ensuring accurate and timely measurements.

User Interface Module: Provides a graphical user interface (GUI) for users to input parameters (power level, heating duration, repetition, frequency points) and visualize the results (S_{21} magnitude across frequency). The interface is depicted in Appendix Figure D.4.

Error Handling Module: Detects and manages errors in communication and operation, providing feedback to the user and ensuring the system's reliability.



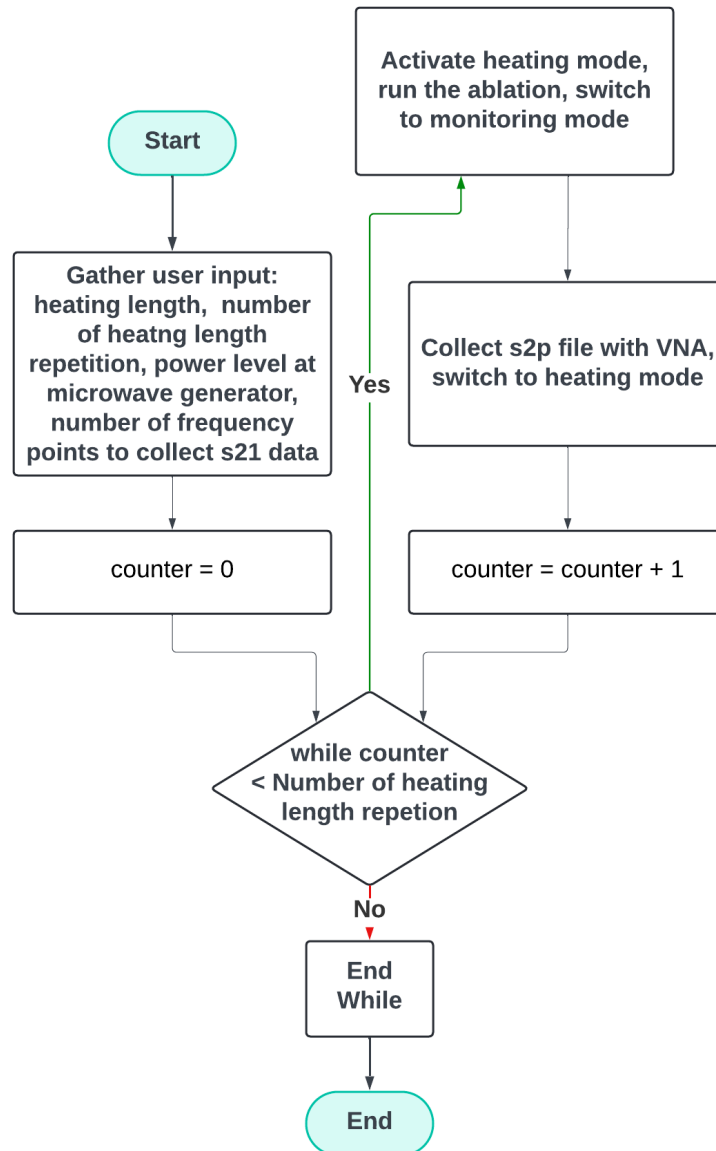
Appendix Figure D.4. Graphical user interface



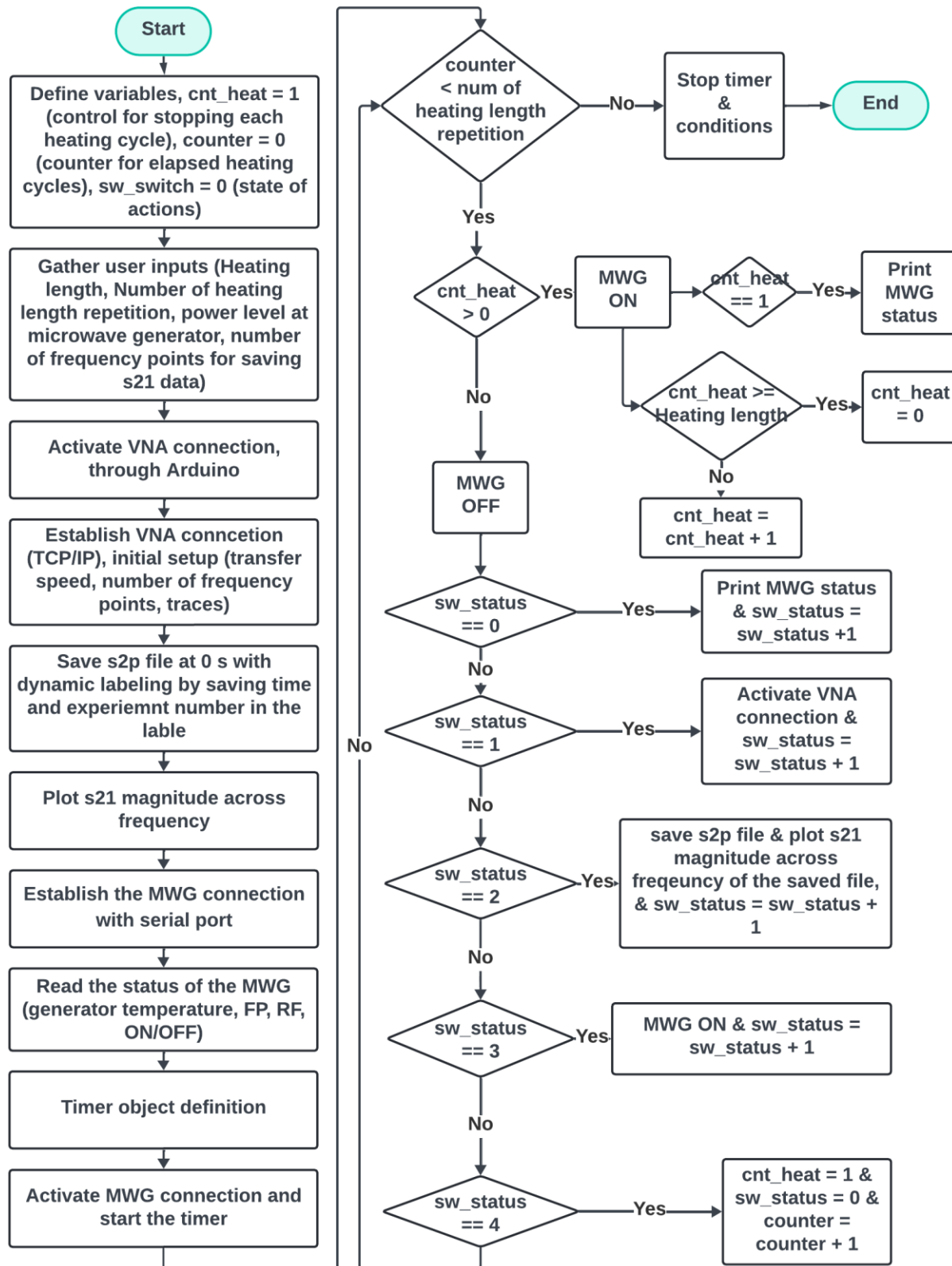
Appendix Figure D.5. Schematic of switching process between two modes of heating and s_{21} measurements.

3.3 Software flowchart

The software begins by initializing the system, then takes user inputs for parameters such as power level, heating duration, repetition of heating part, and number of frequency points. It connects to the VNA and Arduino, performs initial setup, saves initial S2P data, and starts a timer. During each cycle, the software configures the generator to operate in heating mode, switches to measurement mode to measure s_{21} , saves and plots the data, updates the counter, and repeats the cycle until the specified number of repetitions is complete, after which it stops the timer and ends the process. High-level and low-level flowcharts are shown below.



Appendix Figure D.6. High-level software flowchart



Appendix Figure D.7. Software flowchart with details.

To load and run the custom MATLAB control program, these steps are required:

1. Install MATLAB R2020a or later.
2. Install the MATLAB Support Package for Arduino Hardware ([MATLAB Support Package for Arduino Hardware](#)).
3. Connect the microwave generator, VNA, and Arduino to the PC.
4. Configure the Ethernet and USB connections for the VNA and Arduino, respectively.
5. Load and run the custom MATLAB control program.
6. Update the COM port number of the MWG and Arduino in the code, if it's necessary.

4. Operation

User Interface: In the user interface, there are four inputs that the user should enter: power level at generator (power will be split equally between antennas, with around 70% attenuation through the transmission line/cables), heating part (duration of the microwave ablation mode in seconds), repetition of heating part (number of times to repeat the heating part, come up with this number based on the total duration of experiment), and number of points (number of frequency points to measure, set to 1-3 GHz by default with 201 points). On the right side of the figure, the s_{21} -magnitude across frequency will be plotted and updated after each measurement. Measured data is saved on the VNA and can be downloaded later. Additionally, frequency points and s_{21} magnitudes are saved in a .mat file in the current directory with dynamic labeling.

Error Handling: Ensure that the serial port COM port of the Microwave generator matches what is set in the code.

5. System Integration

Integration Steps: The microwave generator should be connected to a PC with MATLAB (and Arduino Package installed) via a USB cable. The VNA should be connected to the PC via an Ethernet cable. The switch box needs power and can be connected to any outlet. The Arduino USB cable should also be connected to the PC, providing 5V for the Arduino and triggering the signals.

Testing: By connecting all parts and immersing the applicators in water, test the system to ensure it correctly measures and saves the .s2p files.



Transmission Coefficient-Based Monitoring of Microwave Ablation: Development and Experimental Evaluation in Ex Vivo Tissue

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