I, Swetha Subramanian, hereby submit this original work as part of the requirements for the degree of Doctor of Philosophy in Biomedical Engineering.

It is entitled:
Thermal Ablation Monitoring Using Ultrasound Echo Decorrelation Imaging

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Thermal Ablation Monitoring Using Ultrasound Echo Decorrelation Imaging

A dissertation submitted to the Graduate School of the University of Cincinnati in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Biomedical Engineering Program of the College of Engineering and Applied Sciences by

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Hepatocellular carcinoma (HCC) and colorectal metastases (CRC) are common tumors worldwide with an increasing incidence in the United States. Thermal ablation techniques such as radiofrequency ablation (RFA), high intensity focused ultrasound (HIFU), microwave and laser ablation techniques have shown potential to treat unresectable tumors. Still lacking is a treatment monitoring technique that can accurately predict ablation. Echo decorrelation imaging is a novel pulse-echo ultrasound imaging method that quantifies and maps changes in echo signals occurring over millisecond time scales during thermal ablation.

In this dissertation, the utility of echo decorrelation imaging as a treatment monitoring tool was assessed during *in vivo* and *in vitro* thermal ablation. To test the utility of echo decorrelation imaging for the prediction of ablation, RFA was performed on *ex vivo* bovine liver (*N* = 9). Echo decorrelation was computed from the Hilbert transformed pulse-echo data acquired during RFA treatments. For comparison, integrated backscatter was also computed from the same data. Pixel-by-pixel comparison between the echo decorrelation and integrated backscatter maps and the ablated region from gross tissue histology was performed using receiver operating characteristic (ROC) curves. Echo decorrelation and integrated backscatter were then quantitatively evaluated as predictors of ablation. The area under the ROC curves (AUROC) was determined for both echo decorrelation and integrated backscatter imaging methods. Ablation was predicted more accurately with echo decorrelation (AUROC = 0.820) than with integrated backscatter (AUROC = 0.668).

To test the utility of echo decorrelation imaging for the prediction of ablation during *in vivo* thermal ablation, RFA was performed on normal swine liver (*N* = 5) and ultrasound ablation using image-ablate arrays was performed on rabbit liver implanted with VX2 tumors (*N* = 2). Consistent with the *in vitro* studies, ablation was predicted more accurately with echo decorrelation (AUROC = 0.833 and 0.776 for RFA and ultrasound ablation,
respectively) than with integrated backscatter (AUROC = 0.733 and 0.494).

Mean cumulative echo decorrelation was greater in the ablated tissue regions compared to the unablated regions for both *in vitro* \((t = 6.808, p = 6 \cdot 10^{-6}, N = 9)\) and *in vivo* \((t = 3.498, p = 0.036, N = 5)\) RFA treatments, indicating the ability of echo decorrelation to delineate between the ablated and unablated regions. For *in vivo* RFA, motion gating reduced the mean echo decorrelation in both ablated \((t = 3.526, p = 0.036, N = 5)\) and unablated \((t = 5.173, p = 0.013, N = 5)\) regions. However, with or without motion gating, the mean cumulative echo decorrelation was significantly greater in the ablated region than in the unablated region \((t = 3.883, p = 0.008, N = 5)\).

The effect of tissue temperature on echo decorrelation was assessed during *in vitro* RFA. RFA experiments \((N = 15)\) were performed on *ex vivo* bovine liver tissue. Temperature maps were simulated by a finite element method, with tissue parameters determined using an unscented Kalman filter to best match measured ablation results. Significantly higher AUROC values \((p = 0.019, p \leq 10^{-14}, p \leq 10^{-14})\) were obtained for the prediction of tissue temperatures greater than 40, 60, and 80°C with echo decorrelation (AUROC = 0.871, 0.948 and 0.966) when compared to integrated backscatter (AUROC = 0.865, 0.877 and 0.832). Overall, the results presented in this dissertation show potential for the utility of echo decorrelation imaging as a treatment monitoring tool.
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“As Shakespeare says, if you’re going to do a thing you might as well pop right at it and get it over.” - P.G. Wodehouse.

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Chapter I

Introduction

1.1 Background

1.1.1 Liver Cancer - Current status

Liver cancer is the fifth most common cancer in men with 522,000 estimated cases per year worldwide and the seventh most common cancer in women with 226,000 estimated cases (Ferlay et al., 2010). Liver cancer is also the second most common cause of cancer related death worldwide (Jemal et al., 2011). Primary liver cancers include hepatocellular carcinoma (HCC) and cholangiocarcinoma. Among primary liver cancers occurring worldwide, HCC accounts for 85% to 90% of cases (Perz et al., 2006; El-Serag and Rudolph, 2007). Main risk factors for HCC include Hepatitis B and C virus infections, alcoholic liver disease, obesity, and diabetes (El-Serag and Rudolph, 2007; Nordenstedt et al., 2010). HCC typically associated with chronic hepatitis B and C virus infections is usually observed in Asia, where these infections are or have been endemic (El-Serag et al., 2009; Starley et al., 2010; Nordenstedt et al., 2010). However, cases of HCC are increasing in the United States (El-Serag, 2012).

Secondary liver tumors or liver metastases, are caused due to primary cancers originating in colon, stomach, pancreas, breast, esophagus and lungs that can metastasize to the liver. Colorectal cancer (CRC) is one of the most common malignancies in North America and is the most frequent metastatic disease of the liver (Quan et al., 2012). In approximately
30% of patients with CRC, disease spreads to the liver within 5 years of diagnosis with an incidence of 48,000 cases per year in the United States (Rees et al., 2012).

Surgical resection is the treatment of choice for patients with resectable tumors in normal liver (Maluccio and Covey, 2012). However, only 5-10% of patients with secondary liver cancer qualify for surgical resection (Rossi et al., 1996; Dick et al., 2002; Ruers and Bleichrodt, 2002). For patients with HCC, surgical resection is restricted to those with a single small tumor and well preserved liver function (Bruix and Llovet, 2002; Bruix and Sherman, 2005). Most patients with HCC have underlying cirrhosis, hence they do not qualify for surgical resection even when the cancer is found at an early stage (Bruix and Llovet, 2002). Although liver transplantation is an effective treatment option for patients with unresectable tumors, it is limited by availability of donor livers and long waiting times (Mazzaferro et al., 1996). Chemotherapy has been shown to be ineffective against liver cancer, with no impact on survival (Bruix and Sherman, 2005). Thus, non-surgical methods play an important role in the treatment of liver cancer.

For unresectable liver tumors, non-surgical methods such as percutaneous ethanol injection (PEI), cryotherapy, and thermal ablation can be used (Bruix and Llovet, 2002). PEI involves injecting ethanol in the tumor tissue, causing immediate denaturation of cellular proteins (Shiina et al., 1991). Although PEI can destroy a relatively large area with a single treatment, it is difficult to predict the extent of the ablated region because the distribution of injected ethanol is affected by the capsule and septa of the lesion (Shiina et al., 2002). Although PEI can cause complete necrosis of small tumors, there still exists the issue of long treatment times due to the need for multiple treatment sessions as well as high tumor recurrence rates (Lencioni et al., 2003). Furthermore, PEI has been shown to be ineffective for the treatment of colorectal metastases (Padma et al., 2009).

In cryotherapy procedures, a needle is inserted into the tumor and cooled using liquid nitrogen in freeze-thaw cycles, where temperatures typically reach $-190^\circ$ C (Tait et al.,
2002). However, cryotherapy has high complication rates (10–20%) due to hemorrhage and cryoshock resulting in patient deaths (Seifert and Morris, 1999; Hinshaw and Lee Jr, 2007). The high complication rates caused during cryotherapy and the lack of proven efficacy makes thermal therapies a more viable alternative (Sheen and Siriwardena, 2005; McWilliams et al., 2010).

1.1.2 Thermal ablation

Thermal ablation is the treatment of choice for unresectable tumors within the liver, kidneys, and other organs (Dupuy et al., 2000; Gervais et al., 2005). Thermal ablation involves application of energy from the electromagnetic spectrum at the tumor site causing heating in the tissue, thereby resulting in coagulative necrosis of the tumor. Common thermal ablation methods include radiofrequency ablation (RFA), ultrasound ablation, laser ablation, and microwave ablation (Murakami et al., 1995; Rhim and Dodd, 1999; Kennedy et al., 2004; Caspani et al., 2010).

RFA involves application of high frequency alternating current (350–500 kHz) through a radiofrequency (RF) electrode at the tumor site. The current propagates through the tissue causing ionic agitation and frictional heating, resulting in coagulative necrosis of greater than 10 cm diameter (Livraghi et al., 2000; Shiina et al., 2002; Gao et al., 2013). RFA has been shown to be effective for the treatment of unresectable liver and other soft tissue tumors clinically (Curley et al., 1999; Solbiati et al., 2001; Tateishi et al., 2005; Shiina et al., 2012), offering several advantages over surgical resection, such as reduced morbidity and better survival rates, reduced tumor recurrences, costs, and hospital stays (Curley et al., 1999; Livraghi et al., 2008; Lencioni et al., 2003; Germani et al., 2010). RFA with lower recurrence rates and fewer complications is shown to be superior to PEI and cryotherapy (Lencioni et al., 2003; Hinshaw and Lee Jr, 2007; Dunne et al., 2014).

Ultrasound ablation methods, including high intensity focused ultrasound (HIFU) have
also shown potential for clinical applications (Yang et al., 1991; Illing et al., 2005; Mast et al., 2005, 2011). HIFU offers the advantage of being non-invasive over other treatment modalities, thus avoiding the issue of tumor seeding along needle tracks that has been reported for both RFA and PEI (Shimada et al., 1995; Jaskolka et al., 2005; Kennedy, 2005). HIFU involves focusing ultrasound energy at a point inside the tissue to induce local temperature elevations over short time durations (1–20 s). HIFU has been used clinically for the treatment of liver cancer (Wu et al., 2004a,b). Large tumors can be treated by targeting multiple overlapping locations (Jolesz et al., 2004). The advantage of HIFU is that the lesion formed is very precise and each sonication is delivered within a few seconds (Dick et al., 2002; Jolesz, 2009). Although ultrasound ablation can offer high precision and greater selectivity when compared to RFA, the inability of ultrasound to pass through air filled structures such as lungs or bowel and strongly reflecting structures such as bone is a major limitation (Illing et al., 2005). Also, HIFU can take longer than RFA for treating large tumors (Al-Bataineh et al., 2012).

Ultrasound ablation has also been performed trans-rectally for the treatment of benign and malignant prostate diseases. Sonablate (Focus Surgery, Indianapolis, IN) and Ablatherm (EDAP-Technomed, Lyon, France) are two commercially available devices with capability for imaging and therapy that are currently available for trans-rectal treatment of prostate cancer (Crouzet et al., 2010). This method has demonstrated feasibility for clinical application for the treatment of prostate cancer (Gelet et al., 2000; Blana et al., 2008).

Alternatively, ultrasound energy can be applied interstitially or laparoscopically to cause bulk ablation comparable to RFA (Makin et al., 2005; Mast et al., 2005; Prat et al., 2002). This method could potentially allow for faster treatment times at the expense of being minimally invasive. Preliminary in vivo studies conducted on rabbit livers implanted with VX2 tumors show the feasibility for treatment of liver tumors (Mast et al., 2011).

Microwave ablation also has shown capability in treating liver cancers (Shibata et al.,
Microwave ablation involves the application of microwaves (1–3 GHz) into the tissue via an inserted electrode to produce dielectric heat by stimulation of water molecules within tissues and cells (Izzo, 2003). Because the heat is conducted homogeneously in all directions, small lesions (1.5 cm in diameter) can be induced in a reproducible manner (Shiina et al., 2002). Rates of complete therapeutic effect and complication rates of microwave ablation have been similar to RFA treatments (Shibata et al., 2002; Liang et al., 2009). Because the lesion area created using microwave ablation is very small, multiple treatments would be required to treat a large area, increasing the treatment time (Shiina et al., 2002).

Laser ablation involves the placement of laser fibers into the affected site. Heating is caused when the photons from low-intensity laser energy interact with molecular chromophores that are inherent to all mammalian cells (Izzo, 2003). Laser ablation has been shown to be effective clinically (Vogl et al., 2002). However, as the light is easily scattered and absorbed, this modality can only be used to treat very small areas of about 1–2 cm² (Chu and Dupuy, 2014).

While thermal ablation has proven to be superior to PEI and cryoablation, as a suitable alternative to surgical resection, presence of blood vessels near the tumor site can affect the shape and size of the thermal lesion. This often causes incomplete tumor ablation resulting in high tumor recurrence rates. In addition, the treatments can cause damage to adjacent organs such as the diaphragm and bowel. Treatment monitoring could ensure irreversible damage to the tumor and also prevent heating of adjacent tissues and organs.

The tissue damage induced during thermal ablation is directly related to the degree of temperature rise in the tissue, heat energy applied and treatment duration (Rhim and Dodd, 1999; Goldberg, 2001). The relationship between treatment time, tissue temperature and thermal damage is described by the thermal dose equation, cumulatively calculated in units
Figure 1.1: Thermal damage in the tissue as a function of tissue temperature and treatment duration. The white region represents the healthy liver. The red and blue regions indicate the regions of ablation (based on an $EM_{43} = 200$ min threshold) and severe ablation (based on an $EM_{43} = 10^7$ min threshold).

of equivalent minutes at 43 °C as (Sapareto and Dewey, 1984)

$$EM_{43}(t) = \sum R^{T(t) - 43} \Delta t / 60.$$  \hspace{1cm} (1.1)

Here, $\Delta t$ is the time step in seconds, $R = 2$ for $T \geq 43$ °C, and $R = 4$ for $T < 43$ °C. Figure 1.1 illustrates the relationship between treatment duration, temperature elevation, and tissue damage induced during thermal ablation as described by the thermal dose equation, assuming a constant temperature during treatment. Here, the red region indicates the region of ablation (based on an $EM_{43} = 200$ min threshold) (Mast et al., 2005). The blue region indicates the region of severe ablation (based on an $EM_{43} = 10^7$ min threshold) (Mast et al., 2005). When the tissue temperature is increased to 42–45 °C, prolonged heating over several hours would be needed to cause cell death (Dewhirst et al., 2003). However, even prolonged heating at these temperatures will not effectively destroy all the cells in a given volume.
(Thomsen, 1991). Increasing tissue temperature to 50–52 °C markedly reduces the time (4–6 min) required to induce cytotoxicity (Goldberg et al., 2000), whereas irreversible tissue damage occurs almost instantaneously when temperatures exceed 60 °C from protein denaturation (Zervas and Kuwayama, 1972; Izzo, 2003). When the tissue temperature is raised above 100 °C, boiling and vaporization occur and gas is formed, preventing conduction of heat. The key aim for thermal ablation is to achieve and maintain a 50–100 °C temperature range throughout the entire treatment volume, to induce irreversible damage and also to prevent heating of the adjacent tissues and organs (Goldberg et al., 2000). Monitoring temperature rise in the tissue could aid treatment monitoring and control. Invasive temperature measurement techniques such as the use of thermal sensors are undesirable, because they can only measure temperature at the sensor location. Hence, they cannot provide enough information if the treatment area is large. Use of image-guided methods to monitor thermal ablation would greatly improve the quality of treatment.

1.1.3 Treatment monitoring methods

Treatment guidance and probe placement for RFA can be performed using magnetic resonance imaging (MRI) (Hynynen and McDannold, 2004), ultrasound imaging (Chiou et al., 2007), or x-ray computed tomography (CT) (Dupuy et al., 2000). CT offers better visualization of the lesion liver interface when compared to ultrasound imaging, but is ionizing, requires the use of contrast agents, and is not real-time (Cha et al., 2000).

MRI has shown great potential for monitoring thermal ablation, being capable of accurate temperature monitoring and control (Smith et al., 2001; Melodelima et al., 2004; Hynynen and McDannold, 2004; Arora et al., 2005; McDannold, 2005). Various MRI based thermometry techniques have been reported in the literature based on exploiting the changes in temperature sensitive MR parameters such as proton resonance frequency (PRF), the diffusion coefficient, T1 and T2 relaxation times, magnetization transfer, the proton density,
and temperature sensitive contrast agents (Rieke et al., 2004; Chen et al., 2006; Rieke and Butts Pauly, 2008). Accuracy as high as 1–2 °C can be achieved using MR thermometry (Rieke and Butts Pauly, 2008). MR thermometry has shown feasibility for treatment guidance, monitoring of thermal ablation, and controlling energy deposition clinically (Puls et al., 2009; Terraz et al., 2010).

MR guided focused ultrasound (MRgFUS) procedures have the advantage of being completely non-invasive. In MRgFUS procedures, targeting is performed using MRI. When ultrasound energy is applied at the target tissue, temperature sensitive phase difference sequences are used to form instantaneous thermal maps of the target area. MRgFUS procedures with ExAblate (Insightec, Haifa, Israel), a commercially available focused ultrasound system, have the U.S. Food and Drug Administration (FDA) approval for the treatment of uterine fibroids and bone metastases (Hesley et al., 2013; Napoli et al., 2013; Schlesinger et al., 2013). MRgFUS has demonstrated feasibility for the treatment of breast fibroadenoma, breast cancer and liver cancer clinically (Hynynen et al., 2001; Gianfelice et al., 2003; Stewart et al., 2003; Okada et al., 2006). Although MRgFUS for the liver is capable of accurate targeting and real-time temperature monitoring, the treatment is hindered by the ribcage, limiting the acoustic windows to the liver, and by respiratory motion (Jolesz and McDannold, 2014). The feasibility of using MR guidance for laser, microwave and RFA procedures has also been demonstrated (Vogl et al., 2002; Morikawa et al., 2002; Clasen et al., 2007). However, use of MRI in a standard operating room is impossible. For RFA and microwave ablation procedures, MR systems are highly prone to RF interference and additionally require the use of MR compatible ablation tools (Boaz et al., 1998; Morikawa et al., 2002; Vigen et al., 2006; Rieke and Butts Pauly, 2008).

Ultrasound imaging offers a real-time, portable and inexpensive alternative. B-mode ultrasound imaging is currently used clinically in RFA for probe placement and treatment guidance (Chiou et al., 2007). Ultrasound guided focused ultrasound (USgFUS) devices
such as Haifu (Chongqing Haifu Technology, Chongqing, China) have been developed for commercial use, with clinical applications in the non-invasive treatment of uterine fibroids (Zhao et al., 2013), breast tumors (Wu et al., 2003), bone metastases (Chen et al., 2010), kidney tumors (Illing et al., 2005) and liver tumors (Jung et al., 2011). However, the lack of reliable temperature feedback and imprecise real-time evaluation of the extent of thermal necrosis are major limitations. Often necrosis is not visualized due to low contrast between the ablated and unablated regions or artifacts caused by microbubble formation at the ablation site, resulting in over- or under-prediction of treated regions (Solbiati et al., 1999; Cha et al., 2000; Leyendecker et al., 2002). However, changes in raw ultrasound pulse-echo signals could provide real time information about thermal ablation.

1.1.4 Ultrasound monitoring of thermal ablation

Ultrasound temperature monitoring techniques reported in the literature include quantifying shifts in radiofrequency (RF) pulse-echo signals due to thermal expansion and local changes in speed of sound (Seip and Ebbini, 1995; Maass-Moreno et al., 1996; Simon et al.,
1998; Sun and Ying, 1999; Varghese et al., 2002a; Souchon et al., 2005). Figure 1.2 shows the relationship between tissue temperature and speed of sound in liver tissue (Bamber and Hill, 1979; Hallaj et al., 2001). The relationship between speed of sound in liver tissue and tissue temperature is non-linear, with smaller variations for temperatures between 40–50 °C (Bamber and Hill, 1979; Hallaj et al., 2001). As many of these methods assume a linear relationship between acoustic properties of the tissue and temperature, these techniques fail to measure large changes in tissue temperatures. Methods involving mapping of attenuation changes have also been studied for monitoring tissue temperature (Ueno et al., 1990; Bevan and Sherar, 2001; Tyréus and Diederich, 2004; Zhong et al., 2007), as attenuation has been shown to be highly dependent on tissue temperature at temperatures greater than 50 °C (Bamber and Hill, 1979; Damianou et al., 1997; Techavipoo et al., 2002). Another approach is to exploit changes in backscattered energy (Arthur et al., 2003; Zhong et al., 2007).

Methods tracking tissue displacement or strain such as elastography (Varghese et al., 2002b), acoustic radiation force imaging (ARFI) (Fahey et al., 2006) and harmonic motion imaging (HMI) (Maleke and Konofagou, 2008) have shown potential for treatment monitoring. Ultrasound elastography relies on the knowledge that the ablated tissue is stiffer than the surrounding tissue (Kallel et al., 1999). In this method, the region of interest (ROI) is compressed by an external force and the ultrasound images are captured to quantify strain. Although this method has demonstrated the capability for visualizing lesion formation (Kallel et al., 1999), in vivo implementation of this method remains unfeasible because of the difficulty in compressing organs deep within the body.

Alternatively, supersonic shear wave imaging (SSI), a shear wave elastography method introduced by Bercoff et al. (2004) relies on shear waves produced by the acoustic radiation force. These shear waves propagate through soft tissues in less than a tenth of a second, with shear wave speeds ranging from 2 to 10 m/s (Arnal et al., 2011a). Hence, ultrafast imaging (Sandrin et al., 2002), an ultrasound imaging method capable of high frame rate (up to
10,000 frames/s) is used (Arnal et al., 2011a). Shear modulus or shear wave velocity is then mapped using the time-of-flight method. This method has shown potential for mapping low temperature elevations and lesion formation (Arnal et al., 2011a,b; Mariani et al., 2014).

In ARFI, an impulse radiation force is used to generate brief mechanical excitations in the tissue and the resulting displacement is tracked during tissue relaxation. However, the inability to simultaneously generate and track lesion formation is a limitation of ARFI. HMI is another radiation force based imaging technique that overcomes this limitation by using a focused ultrasound transducer to induce oscillation at its focus. The resulting displacements are simultaneously imaged using a pulse-echo imaging array.

Most of these methods rely on tracking changes in displacements or strain using time-delay estimation techniques (Cespedes et al., 1999). However, these methods are sensitive to errors caused by formation of microbubble clouds at the ablation site (Solbiati et al., 1999; Leyendecker et al., 2002). Also, large non-uniform scatterer displacements occurring both in-plane and out-of-plane due to bubble activity and tissue motion can cause echo decorrelation degrading the image quality (Kallel et al., 1997; Miller et al., 2002; Varghese et al., 2004; Chandrasekhar et al., 2006).

1.1.5 Echo decorrelation imaging

Echo decorrelation imaging is a novel, real-time pulse-echo imaging method developed at the University of Cincinnati, that uses the degradations in signals described above to map thermal ablation (Mast et al., 2008). Heat-induced tissue changes during thermal ablation are monitored by tracking random millisecond scale fluctuations in echo signals, quantified by the local signal decorrelation. Tracking echo signal changes over smaller time scales would result in greater insensitivity to tissue motion artifacts (Chandrasekhar et al., 2006; Arnal et al., 2011a). In the studies reported in this dissertation, echo decorrelation imaging algorithm is implemented to track echo signal changes over 10–50 ms time scales, which is
related to the default frame rate of the imaging transducers used. These millisecond scale changes in the echo signals are tracked over the duration of a thermal ablation treatment to produce a cumulative echo decorrelation map.

The echo decorrelation imaging algorithm previously introduced in Mast (2008) is described below with some changes. Let the function $p(\mathbf{r}, t)$ represent a pulse-echo frame consisting of a collection of beamformed echo signals in complex radiofrequency (Hilbert-transformed) or baseband-demodulated (in-phase quadrature (IQ)) form acquired at time $t$, where $\mathbf{r}$ is the spatial position vector within the image plane. The function $p(\mathbf{r}, t + \tau)$ represents a pulse-echo frame acquired at a later time $t + \tau$, where $\tau$ is the inter-frame time. The image acquisition method is illustrated in Figure 1.3.

A spatio-temporal cross-correlation function between the two sequential complex pulse-echo image frames separated by time $\tau$ is defined as

$$R_{01}(\mathbf{r}, t) = \langle p(\mathbf{r}, t)p^*(\mathbf{r}, t + \tau) \rangle, \quad (1.2)$$
where \( \langle \cdot \rangle \) represents a two-dimensional convolution with a Gaussian mask

\[
\langle f(r) \rangle = f(r) \otimes e^{-|r|^2/2\delta^2},
\]

(1.3)

where \( \delta \) is the window width parameter.

Similarly, the autocorrelation functions \( R_{00}(r, t) \) and \( R_{11}(r, t) \) are defined here as

\[
R_{00}(r, t) = \langle |p(r, t)|^2 \rangle \quad \text{and} \quad R_{11}(r, t) = \langle |p(r, t + \tau)|^2 \rangle
\]

(1.4)

respectively, which can be regarded as maps of integrated backscattered energies at times \( t \) and \( \tau \). A integrated backscatter term can thus be defined as

\[
\beta(r, t) = \sqrt{R_{00}(r, t)R_{11}(r, t)}.
\]

(1.5)

An echo decorrelation map is then defined as

\[
\Delta(r, t) = 2 \frac{\beta^2(r, t) - |R_{01}(r, t)|^2}{\beta^2(r, t) + \overline{\beta^2(t)}},
\]

(1.6)

where the function \( \overline{\beta^2(t)} \) represents the spatial mean value of \( \beta^2(r, t) \) from Eq. (1.5). The echo decorrelation function was normalized by this denominator because normalization by \( \beta^2(r, t) \) alone was found to cause artifactually high decorrelation in the regions of low echogenicity, while normalization by the function \( \overline{\beta^2(t)} \) caused artifacts in regions of high echogenicity (Mast et al., 2008). The normalization in Eq. (1.6) results in a more uniform echo decorrelation map. The resulting echo decorrelation map is zero in regions where the image is unchanged and maximum in regions where local echo changes are greatest. This is demonstrated in Figure 1.4, where the top panel shows a segment of Hilbert-transformed,
demodulated (IQ) signals separated by $\Delta t$. The bottom panel shows the corresponding echo decorrelation. The echo decorrelation was small where the pulse-echo signals separated by $\Delta t$ remained relatively unchanged. The echo decorrelation was large where the large changes in pulse echo signals were observed. These changes in pulse-echo signals correspond to heat-induced changes in the scattering medium, which includes gas and vapor formation, structural changes, and thermal expansion as well as the changes in acoustic properties such as the speed of sound and attenuation (Damianou et al., 1997; Worthington and Sherar, 2001; Varghese et al., 2004; Nahirnyak et al., 2010; Gudur et al., 2012).

Finally, because the echo decorrelation map defined by Eq. (1.6) also varies stochastically in time, a temporal running average is used to provide a better estimate of local changes in the scattering medium (Mast et al., 2008). The temporal running average employed is given by

$$\bar{\Delta}(\mathbf{r}, t_i) = (1 - \epsilon)\bar{\Delta}(\mathbf{r}, t_{i-1}) + \epsilon \Delta(\mathbf{r}, t_i), \quad (1.7)$$

where $t_i$ is the time of the current ($i^{th}$) echo decorrelation image frame and $\epsilon$ is a user-defined parameter ($0 < \epsilon < 1$) that determines the effective length of temporal averaging, which is chosen based on the system frame rate.

### 1.1.6 Integrated backscatter imaging

In this dissertation, in order to assess the utility of echo decorrelation imaging for mapping heat-induced changes in tissue during thermal ablation, echo decorrelation imaging is compared to integrated backscatter imaging. The integrated backscatter imaging algorithm has previously shown potential for monitoring thermal lesioning in liver tissue during HIFU (Zhong et al., 2007). Previous studies have shown that the formation of gas bodies during HIFU exposures caused an increase in tissue backscatter, which is observed as an hyperecho (Zhong et al., 2007; Yu and Xu, 2008). The hyperechoic regions formed during HIFU have
been used to quantify the formation and growth of lesions in the tissue and can be tracked using integrated backscatter imaging for treatment monitoring (Zhong et al., 2007; Yu and Xu, 2008).

Integrated backscatter imaging was implemented on the same pulse echo data used to generate echo decorrelation images. To compute integrated backscatter images, the integrated backscatter term defined in Eq. 1.5 was smoothed in a manner similar to the echo decorrelation images. The relative integrated backscatter term was defined by determining the ratio between the cumulative integrated backscatter and the integrated backscatter computed at the start of treatment (Mast et al., 2008; Zhong et al., 2007; Thomas et al., 1989). The integrated backscatter map, used for comparison with echo decorrelation imaging, is defined as

$$\text{IBS}(r, t) = 10 \cdot \log_{10} \left( \frac{\bar{\beta}(r, t)}{\bar{\beta}(r, 0)} \right),$$  \hspace{1cm} (1.8)

where $\bar{\beta}(r, t)$ is the temporally averaged integrated backscatter at time $t$ and $\beta(r, 0)$ is the...
auto-correlation function defined by Eq. (1.5) at the start of the treatment (Mast et al., 2008). The integrated backscatter term computed here tracks changes in echo energy relative to the frame acquired at the start of treatment for the course of thermal ablation. This is unlike the echo decorrelation function, which tracks changes in the echo signals separated by millisecond time duration over the course of treatment.

1.2 Research Objectives

This study investigates the feasibility of using ultrasound echo decorrelation imaging as a treatment monitoring and control tool by formulating the following hypotheses,

1. Echo decorrelation is a predictor of thermal lesion formation in the liver tissue during \textit{in vitro} and \textit{in vivo} thermal ablation.
2. Echo decorrelation correlates with elevations in tissue temperature during \textit{in vitro} radio-frequency ablation.

The following specific aims were designed to test the hypotheses defined above,

1. Test prediction of thermal lesioning using echo decorrelation imaging during \textit{in vitro} RFA.
2. Test prediction of thermal lesioning using echo decorrelation imaging during \textit{in vivo} RFA and ultrasound ablation.
3. Test the dependence of ultrasound echo decorrelation on tissue temperature during \textit{in vitro} RFA.

1.3 Thesis Organization

In Chapter II, the feasibility of using ultrasound echo decorrelation imaging for the prediction of thermal lesioning during \textit{in vitro} RFA has been investigated. In this study, receiver
operating characteristic (ROC) curves were employed to assess the prediction ability of echo decorrelation imaging by quantitatively comparing echo decorrelation with gross tissue histology. For comparison, integrated backscatter is also computed and its predictive ability is assessed in a manner similar to that used to assess echo decorrelation imaging. This study used the data from the previously published experiments (Mast et al., 2008) and includes an updated analysis similar to the one published in Subramanian et al. (2014).

In Chapter III, the feasibility of using ultrasound echo decorrelation imaging for the prediction of thermal lesioning during \textit{in vivo} RFA and ultrasound ablation was investigated. Similar to Chapter II, the predictive ability of echo decorrelation imaging and integrated backscatter was assessed using ROC curves. The effect of tissue motion due to animal breathing on echo decorrelation has also been investigated. This study has been published in Ultrasound in Medicine and Biology (Subramanian et al., 2014).

In Chapter IV, tissue temperature is simulated in the entire image plane using finite element analysis (FEA) to assess the relationship between tissue temperature and echo decorrelation. In order to account for variability in tissue properties, simulations were generated using tissue parameters determined using an unscented Kalman filter (UKF). The UKF was implemented as an inverse solver to recover the specific heat, thermal conductivity, and electrical conductivity corresponding to the measured area of the ablated tissue region, as determined from gross tissue histology. The dependence of echo decorrelation on tissue temperature was determined using the Pearson correlation coefficient. The temperature prediction ability of echo decorrelation imaging is assessed using receiver operating characteristic (ROC) curves. A manuscript proposing the use of unscented Kalman filter for optimizing tissue parameters for simulating tissue temperature was submitted to the Physics in Medicine and Biology journal. Another manuscript assessing the dependence of echo decorrelation on tissue temperature will be submitted to Physics in Medicine and Biology.

Conclusions are presented in Chapter V. This chapter summarizes the results of the
dissertation as well as its strengths and limitations. It also lists future directions.
Chapter II

*In vitro* radiofrequency ablation monitoring using ultrasound echo decorrelation imaging

2.1 Introduction

Mast et al. (2008) previously investigated the ability of ultrasound echo decorrelation imaging to map tissue changes during *in vitro* RFA using ROC analysis and compared its ablation predictive ability against integrated backscatter. This chapter, in addition to the analysis performed in Mast et al. (2008), includes an updated analysis similar to the one performed for the *in vivo* RFA study reported in Chapter III and Subramanian et al. (2014). The goal of this study is to demonstrate the feasibility of using ultrasound echo decorrelation imaging for the visualization of thermal lesion formation during *in vitro* RFA.

In this chapter, an echo decorrelation imaging algorithm, slightly modified from the one published in Mast et al. (2008), described in Section 2.2.1 was implemented on the experimental data reported in Mast et al. (2008). In addition to the ROC analysis described in Mast et al. (2008), optimum echo decorrelation and integrated backscatter thresholds are obtained for prediction of ablation. Sensitivity and specificity values associated with the optimum echo decorrelation and integrated backscatter thresholds were determined to assess their predictive ability. The ablated area measured using the gross tissue histology...
is compared to the area predicted by the echo decorrelation and integrated backscatter thresholds, and the RMS error of prediction is computed. Additionally, the ability of echo decorrelation to delineate between ablated and unablated regions was tested. In order to assess the effect of tissue temperature on echo decorrelation, the Pearson product moment correlation was determined between log_{10}-scaled echo decorrelation and tissue temperature measured using a thermocouple placed near the RF electrode.

2.2 Materials and Methods

2.2.1 Echo Decorrelation Imaging Implementation

The echo decorrelation algorithm described in Chapter I was implemented on the pulse-echo data acquired during RFA. Ultrasound imaging was performed by the Iris 2 ultrasound imaging and ablation system (Guided Therapy Systems, Mesa, AZ) using the L7 ultrasound array (Barthe et al., 2004). In each acquisition, 384 pulse-echo signals were recorded, comprising of two adjacent complex pulse-echo frame pairs separated by 19.6 ms. Throughout each treatment, echo signals were recorded from the Iris system using a 14-bit, PC-based A/D converter (CompuScope CS 14200, Gage Applied Technologies, Montreal, Quebec, Canada) at a sampling rate of 33.3 MHz and stored. The acquired echo signals were then processed in MATLAB (The MathWorks, Natick, MA) to form B-mode, integrated backscatter, and echo decorrelation images as described below. For each recorded pulse-echo frame pair, echo signals were band-pass filtered using the Gaussian filter defined by

\[ G(f) = e^{-\frac{(f-f_0)^2}{2\alpha^2}}, \]  \hspace{1cm} (2.1)

with a center frequency \((f_0)\) of 7.36 MHz and a \(-6\) dB bandwidth \((\alpha)\) of 2.35 MHz, after zero padding the 1320 sample pulse-echo signals to 2048 samples. This filter also implicitly
performs a Hilbert transform to form complex analytic pulse-echo signals with real and imaginary parts. B-mode (brightness mode) images were obtained by logarithmically scaling the echo signal amplitudes (absolute value of the complex analytic pulse-echo signals) $|p(r, t)|$ with a displayed dynamic range of 60 dB (Mast et al., 2008).

To compute echo decorrelation and integrated backscatter images, the cross-correlation and auto-correlation functions $R_{01}(r, t)$, $R_{00}(r, t)$, and $R_{11}(r, t)$ were computed using Eqs. (1.2) and (1.4). Spatial integration was implemented by Eq. (1.3), using a Gaussian window with width parameter $\delta = 3.5$ mm. Choosing a very large $\delta$ results in excessive smoothing of the mapped echo decorrelation, reducing its spatial resolution. The choice of a very small $\delta$ would result in an echo decorrelation map that is sensitive to noise. Hooi et al. (2015) observed that the error between the mapped echo decorrelation and scattering medium decoherence was minimum for $\delta$ on the order of one-sixth of average lesion diameter, with relatively small error occurring up to window widths of about one-half the lesion width. The average diameter of the lesions produced during this series of RFA treatments was $\sim 7.57$ mm. Hence, the choice $\delta = 3.5$ mm would result in a relatively small error between the mapped echo decorrelation and actual decoherence of the scattering medium. The time- and position-dependent echo decorrelation was then computed using Eq. (1.6) and smoothed by the running average smoothing filter defined in Eq. (1.7) with $\epsilon = 0.05$. To form cumulative echo decorrelation maps, the temporal maximum of the resulting echo decorrelation was recorded at each pixel location.

To form integrated backscatter images, the integrated backscatter computed using Eq. (1.5) was smoothed temporally using a running-average smoothing filter similar to Eq. (1.7). Relative integrated backscatter maps were formed from the temporal maxima of $\text{IBS}(r, t)$ at each pixel location. Hybrid integrated backscatter maps were formed for display by overlaying these relative integrated backscatter maps over the B-mode image frames.
2.2.2 Experiments

The experimental configuration for the RFA procedures is shown in Figure 2.1. RFA was performed as described previously by Mast et al. (2008) in *ex vivo* bovine liver for \( N = 9 \) treatments. Fresh bovine livers were acquired from the local slaughterhouse and were sectioned into samples of dimensions 85 × 85 × 60 mm\(^3\). An acrylic box of dimensions 85 × 85 × 60 mm\(^3\) was used as the sample holder, with a side cut out and sealed with an acoustically transparent window (Tegaderm, 3M, St Paul, MN). A 7-MHz, 192-element linear ultrasound array (L7, Guided Therapy Systems, Mesa, AZ) was placed against the acrylic box in contact with the acoustically transparent window as shown in Figure 2.1(a).

An umbrella type RF electrode (LaVeen 2.0 needle electrode, Boston Scientific Corporation, Boston, MA) shown in Figure 2.2(a) was inserted into the tissue along with a low-noise 1-mm type K thermocouple (GKMQSS-040U-6, Omega Engineering Inc, Stamford, CT) as shown in Figure 2.1(a). The thermocouple was placed distal to the RF electrode at a distance of \( \sim 5 \) mm as observed in the B-mode images shown in Figure 2.2(b). A grounding pad was placed at the distal end of the tissue relative to the needle electrode as shown in Figure 2.1. For each treatment, the RF electrode was driven by a RF generator (RF 2000B, Radio Therapeutics) (Figure 2.2(b)) with initial power set at 20 W and a treatment duration of 6 min. The RF generator adjusts power throughout the treatment based on the tissue’s electrical impedance. Temperature was recorded at the thermocouple location for the duration of the treatment using a digital data logger (Omegaette HH306, Omega Engineering, Stamford, CT).

After each ablation trial, a tubular plastic marking was inserted in the needle track of the RFA probe. To maintain the tissue shape for accurate registration with B-mode images, the liver tissue was frozen in a \(-80\) °C freezer in an acrylic container with the same dimensions used as the sample holder for the experiments. The frozen tissue samples
Figure 2.1: Experimental configuration for in vitro RFA experiments. (a) A photo of the experimental setup used for performing the RFA experiments. (b) A B-mode ultrasound image showing the inserted RF electrode (red) and the thermocouple (yellow).
were then sectioned into 2-mm slices parallel to the ultrasound image plane. For direct comparison to echo decorrelation images, the tissue section corresponding to the image plane was registered to the ultrasound image based on the visible probe tracks indicated by the plastic tube markings. The lesion area was manually segmented based on gross discoloration of the tissue with all pixels within the lesion boundary defined as ablated and the remainder defined as unablated using ImageJ (ImageJ, National Institute of Health, Bethesda, MD) (Mast et al., 2008). The lesion area was quantified as the summed area of all pixels within the lesion boundaries.

2.2.3 Receiver operating characteristics curve analysis

In order to test the predictive ability of echo decorrelation and integrated backscatter imaging, receiver operating characteristic (ROC) curves were employed (Mast et al., 2008; Krzanowski and Hand, 2009). In this analysis, treatment outcomes were predicted using echo decorrelation and integrated backscatter thresholds, so that all the spatial points exceeding a threshold were predicted to be ablated, and the rest unablated. Using pixel-by-pixel compar-
ison of cumulative echo decorrelation and integrated backscatter images with corresponding
segmented tissue maps, prediction success was determined for each pixel as a function of the
threshold. ROC curves, defined as the true-positive rate (sensitivity) vs. the false-positive
rate (1—specificity), were then plotted for the prediction of ablation, where the true positive
and false positive rates are defined as

\[
\text{True Positive Rate} = \text{sensitivity} = \frac{\text{True Positives}}{\text{True Positives} + \text{False Negatives}},
\]

\[
\text{False Positive Rate} = 1 - \text{specificity} = \frac{\text{False Positives}}{\text{False Positives} + \text{True Negatives}},
\]

\[
\text{specificity} = \frac{\text{True Negatives}}{\text{False Positives} + \text{True Negatives}}.
\]

Area under the ROC curve (AUROC) was determined to assess the utility of echo decorrela-
tion and integrated backscatter for the prediction of ablation. An AUROC of 1 indicates
that the treated region was classified perfectly, while an AUROC of 0.5 means that the
classification was no better than chance.

For accurate prediction of ablation, the optimal threshold was chosen to be that yielding
predicted ablated regions (True Positives + False Negatives) with average area matching the
actual ablated regions (True Positives + False Positives). At this threshold, the number of
false positives would equal the number of false negatives. Hence, the echo decorrelation and
integrated backscatter thresholds yielding equal number of false positives and false negatives
were chosen as the optimum thresholds.

The positive predictive value (PPV) indicates the proportion of positive outcomes (lo-
cal tissue ablation) that were correctly classified, and the negative predictive value (NPV)
indicates the proportion of negative outcomes (tissue locally unablated) that were correctly

42
classified. The positive and negative predictive values are defined as

\[
PPV = \frac{\text{True Positives}}{\text{True Positives} + \text{False Positives}},
\]

(2.5)

\[
NPV = \frac{\text{True Negatives}}{\text{True Negatives} + \text{False Negatives}}.
\]

(2.6)

At the optimum threshold defined here, where the number of false positives equals the number of false negatives, the positive and negative predictive values should equal the sensitivity and specificity values respectively. Hence, only the sensitivity and specificity values were reported for this analysis.

Assessment of prediction success was performed by testing significance of the AUROC statistic using a general model for the AUROC standard error (Hanley and McNeil, 1982). In this analysis, effective sample sizes for each treatment outcome were conservatively estimated from the Gaussian window size (δ) used for the computation of echo decorrelation and integrated backscatter. For this calculation, the windows were considered independent when the spatial cross-correlation coefficient of two Gaussian windows, as defined in Eq. (1.3), was below 0.5. The distance between window centers for a correlation coefficient of 0.5 is \(2\sqrt{2\log(2)}\delta\), equivalent to full width at half maximum (FWHM) for a Gaussian curve. The effective number of treatment outcomes in each spatial region (ablated and unablated) was determined based on the maximum hexagonal packing density, which is given by \(\pi/\sqrt{12}\) unit-diameter circles per unit-area rectangle.

The significance of AUROC differences between echo decorrelation and integrated backscatter was computed by using DeLong’s method of comparing two correlated ROC curves using pROC statistical package in R (R Foundation for Statistical Computing, Vienna, Austria) (Hanley and McNeil, 1983; DeLong et al., 1988; Robin et al., 2011). The effective sample size \(N_{\text{effective}}\) for each outcome was estimated as described above from the Gaussian window size δ. To adjust the significance values, the Z-statistic obtained using the pROC package
in R was scaled for the effective sample size as defined below

\[ Z_{\text{effective}} = Z / \sqrt{N_{\text{total}} / N_{\text{effective}}}, \quad (2.7) \]

where \( Z \) is the Z-statistic obtained for all outcomes \( N_{\text{total}} \) and \( Z_{\text{effective}} \) is the scaled Z statistic for the effective sample size. The effective significance \( p_{\text{effective}} \) (two-tailed) for the difference between AUROC values determined using echo decorrelation and integrated backscatter was then obtained by

\[ p_{\text{effective}} = 2(1 - \text{cdf}(Z_{\text{effective}})), \quad (2.8) \]

where the \( \text{cdf} \) represents the cumulative distribution function.

### 2.2.4 Data Processing

To assess the ability of echo decorrelation to distinguish between the ablated and unablated regions, paired \( t \)-tests were performed between the mean (spatially averaged) cumulative \( \log_{10} \)-scaled echo decorrelation values within the ablated and unablated regions at the end of treatment. Differences in echo decorrelation were assessed for statistical significance using the criterion \( p < 0.05 \). One-tailed \( p \)-values were employed to assess the significance of any increase in echo decorrelation caused by tissue ablation. For comparison, similar analysis was performed using integrated backscatter imaging.

The time-dependent measured echo decorrelation at the thermocouple location during the RFA treatments was also compared with the temperature simultaneously measured by the thermocouple. The temporally averaged echo decorrelation measured at the thermocouple location was temporally interpolated to synchronize with the temperature recordings from the thermocouple. To determine whether echo decorrelation was correlated with tissue temperature, the Pearson correlation coefficient was computed between the measured temperature and the echo decorrelation, using all temporal data points from all the nine trials.
When testing statistical significance of the correlation between echo decorrelation and tissue temperature, the number of independent samples was conservatively estimated as the number of temporal data points multiplied by the running-average parameter $\epsilon = 0.05$ from Eq. (1.7).

To assess the ability of echo decorrelation and integrated backscatter to predict ablated area, absolute and normalized RMS errors were computed between the predicted and measured ablated areas. The absolute RMS error was computed as the root-mean-squared value of the difference between predicted and measured areas for all trials. The normalized RMS error was computed as the ratio of the absolute RMS error and the root-mean-squared value of the measured area, expressed as a percentage.

### 2.3 Results

Figure 2.3(a) shows hybrid echo decorrelation maps, comprising echo decorrelation and B-mode images, for all RFA treatments ($N = 9$). Similar hybrid images (Figure 2.3(b)) are also shown for integrated backscatter at the end of RFA treatment. Also shown are the corresponding segmented tissue sections (Figure 2.3(c)), with the segmented ablated regions enclosed by dashed black lines. Qualitatively, higher echo decorrelation and integrated backscatter values are observed in the ablated regions, while relatively lower echo decorrelation and integrated backscatter values are observed in the unablated regions.

Figure 2.4(a) shows a bar graph representing the mean and standard deviations of cumulative log$_{10}$-scaled echo decorrelation in the ablated and unablated regions for all RFA treatments. The cumulative log$_{10}$-scaled echo decorrelation in the ablated region ($-2.590 \pm 0.592$) was significantly greater than that in the unablated region ($-3.563 \pm 0.444$) ($t = 6.808$, $p = 6 \cdot 10^{-5}$, $N = 9$). Similarly, Figure 2.4(b) shows a bar graph representing the mean and standard deviations of cumulative integrated backscatter in the ablated and unab-
Figure 2.3: Hybrid echo decorrelation and integrated backscatter images for all radiofrequency ablation treatments ($N = 9$). (a) Echo decorrelation at the end of treatment with the yellow dashed lines representing the lesion boundary predicted by the optimum decorrelation threshold. (b) Integrated backscatter at the end of treatment with the yellow dashed lines representing the lesion boundary predicted by the optimum integrated backscatter threshold. (c) Tissue sections corresponding to the ultrasound image plane, with the ablated region enclosed by dashed black lines.
Figure 2.3: Continued from previous page.
Figure 2.4: Bar graphs illustrating the means and standard deviations of (a) cumulative echo decorrelation and (b) integrated backscatter in the ablated and unablated regions.
lated regions. The cumulative integrated backscatter in the ablated region (2.903±1.076) dB was also significantly greater when compared to that in the unablated region (1.959±1.232) dB ($t = 5.284, p = 3 \cdot 10^{-4}, N = 9$). This indicates that both echo decorrelation and integrated backscatter imaging algorithms are able to delineate between the ablated and unablated regions.

Computed ROC curves for the prediction of ablation using echo decorrelation and integrated backscatter imaging are shown in Figure 2.5. The results from the ROC analysis for prediction of ablation in the tissue are shown in Table 2.1. The AUROC was 0.820 for prediction of ablation using echo decorrelation ($p \ll 10^{-13}, N = 197$) and 0.668 using integrated backscatter ($p = 2 \cdot 10^{-5}, N = 197$). Echo decorrelation performed significantly better than integrated backscatter for the prediction of ablation ($p = 6.8 \cdot 10^{-4}, N = 197$).

Optimum thresholds for prediction of ablation using echo decorrelation and integrated backscatter imaging were −2.840 and 2.565 dB respectively. Both echo decorrelation and integrated backscatter performed better as a negative predictor than a positive predictor.
at the optimum threshold. Figures 2.3(a) and (b) shows the predicted lesion boundaries (represented by dashed yellow lines) using the optimum thresholds for both echo decorrelation and integrated backscatter imaging for all treatments.

Figures 2.6(a) and (b) show scatter plots of the ablated area predicted by the echo decorrelation and integrated backscatter thresholds plotted against the ablated area from gross tissue histology for all treatments. The ablated area for all treatments ($N = 9$)

Table 2.1: Results of ROC analysis for prediction of ablation for $N = 9$ in vitro RFA exposures.

<table>
<thead>
<tr>
<th></th>
<th>AUROC</th>
<th>Optimum threshold</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echo decorrelation</td>
<td>0.820</td>
<td>$-2.840$</td>
<td>0.668</td>
<td>0.819</td>
</tr>
<tr>
<td>($\log_{10}$-scaled)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Integrated backscatter</td>
<td>0.668</td>
<td>2.565 dB</td>
<td>0.514</td>
<td>0.740</td>
</tr>
</tbody>
</table>
was 449.3 ± 116.4 mm². The absolute and normalized RMS errors for the prediction of ablated area using the optimum echo decorrelation threshold were 197.0 mm² and 42.59% respectively. The absolute and normalized RMS errors for the prediction of ablated area using the optimum integrated backscatter threshold were marginally better, at 143.0 mm² and 30.93% respectively.

Figure 2.7(a) shows tissue temperature values plotted against the mean and standard deviation of the local running-average, \( \log_{10} \)-scaled echo decorrelation, measured at the thermocouple location throughout the RFA treatments. Similarly, Figure 2.7(b) shows tissue temperature values plotted against the mean and standard deviation of the local running-average, dB-scaled integrated backscatter, measured at the thermocouple location. Figure 2.7(a) indicates a nonlinear relationship between echo decorrelation and tissue temperature. Although there is an apparent monotonically increasing relationship between echo decorrelation and tissue temperature, the rate of increase in echo decorrelation is not the same for all treatments. This could be due to variability in tissue structure among the various tissue samples used for the RFA treatments. However, the instantaneous tissue temperature and echo decorrelation were correlated across all treatments with high statistical significance \( r = 0.396, p \ll 10^{-13}, N = 2671 \). Although Figure 2.7(b) also shows a non-linear relationship between measured tissue temperature and integrated backscatter, the relationship is not monotonically increasing. There also exists a positive correlation between local integrated backscatter and tissue temperature with high statistical significance \( r = 0.345, p \ll 10^{-13}, N = 2671 \).

2.4 Discussion

Radiofrequency ablation (RFA) is a standard minimally invasive treatment for unresectable liver cancer and other soft tissue tumors (Wong et al., 2010). The lesion size and
Figure 2.7: Mean and standard deviation of (a) log\(_{10}\)-scaled echo decorrelation, and (b) integrated backscatter values at the thermocouple position for all temperature measurements within 5 °C bands for all \( N = 9 \) RFA treatments.
shape depends strongly on the tissue structure and the location of blood vessels relative to the tumor site. Failure to ablate all the tumor cells may result in tumor recurrence. An inexpensive and reliable method for real-time evaluation of thermal necrosis remains an unmet need. In this chapter, the feasibility of using echo decorrelation imaging for the visualization of thermal lesion formation during \textit{in vitro} RFA has been investigated. The possible application of echo decorrelation imaging for use in treatment monitoring and its limitations are discussed below.

The mean echo decorrelation was significantly higher in the ablated region when compared to the unablated region, indicating that echo decorrelation was able to distinguish necrosis. Relatively high sensitivity and specificity values obtained at the optimum decorrelation threshold indicates a spatial match between the predicted lesion and the actual lesion. These results demonstrate the capability of using ultrasound echo decorrelation imaging for visualizing thermal lesioning in the tissue during \textit{in vitro} RFA.

Possible causes of echo decorrelation during thermal ablation may include structural changes, vaporization and dissolution of gas that occurs in tissue during coagulative necrosis (Nahirnyak et al., 2010; Gudur et al., 2012). Structural changes that occur in tissue during thermal ablation include cellular swelling, microvascular changes, denaturation of collagen and other proteins, and microstructural tissue damage due to vaporization (Kruskal et al., 2001; Wright and Humphrey, 2002; Bischof and He, 2006). These changes are related to variation in tissue properties such as attenuation, sound speed and stiffness (Worthington and Sherar, 2001; Sapin-de Brosses et al., 2010). To further the understanding of echo decorrelation imaging, the dependence of these parameters on echo decorrelation should be investigated.

At temperatures greater than 95 °C, microbubbles are formed near the RF electrode (Kruskal et al., 2001). These microbubbles are observed as a hyperechoic cloud in the B-mode ultrasound image. Although this hyperechoic region can be used to indicate if the
tissue is ablated, the size and location of the microbubble cloud is not well correlated with the extent of the lesion formed (Solbiati et al., 1999; Machi et al., 2001; Leyendecker et al., 2002). The microbubbles can spread to adjacent regions through portal and hepatic venules (Kruskal et al., 2001), further impairing their utility in treatment monitoring.

This hyperechoic cloud also affects the integrated backscatter measurements, which rely on changes in echo energy to track ablation. Acoustic shadowing associated with microbubbles leads to loss of information in the shadowed region (Zhong et al., 2007). This also results in a decrease in echo energy as observed in Figure 2.7(b). The formation of microbubbles could also negatively impact echo decorrelation imaging. However, from Figure 2.3, it has been shown that echo decorrelation can map tissue ablation over large spatial regions, including regions affected by acoustic shadowing. The temperature threshold for protein denaturation is estimated to be 60 °C (Wright and Humphrey, 2002). As echo decorrelation imaging has been shown to map lesioning occurring well below the temperature threshold for the formation of microbubbles, the temperature feedback loop already present in most clinical RFA systems could be employed to prevent any potential degradation of the echo decorrelation map.

A limitation of this study was that the comparison of echo decorrelation with tissue temperature was made only at the thermocouple location. As the thermocouple was placed near the RF electrode where rapid heating occurred, this analysis did not take into consideration the regions with slow heating rates. For a complete assessment of the relationship between echo decorrelation and tissue temperature, comparison needs to be made in the entire image plane. Hence, the dependence of echo decorrelation imaging on tissue temperature is investigated in Chapter IV.

Tissue motion is a major confounding factor for most ultrasound imaging methods. Ultrasound imaging methods relying on tracking displacements are severely affected by echo decorrelation due to respiratory and cardiac motion (Cespedes et al., 1999). Investigation
of the effect of tissue motion on echo decorrelation would be crucial for the assessment of
the utility of echo decorrelation imaging as a clinical RFA treatment monitoring and control
tool. Hence, in vivo testing performed in Chapter III of echo decorrelation imaging is an
important step for testing the feasibility of using ultrasound echo decorrelation for clinical
applications.

2.5 Conclusion

This in vitro study investigated the capability of echo decorrelation imaging algorithm to
identify thermal lesions formed during ablation. Significantly higher echo decorrelation was
observed in the ablated region than in the unablated region, implying that echo decorrela-
tion is able to distinguish between ablated and unablated regions. Echo decorrelation had
higher correlation to the ablated area when compared to integrated backscatter imaging.
Also, higher AUROC values were obtained for echo decorrelation imaging when compared
to integrated backscatter. A weak but significant correlation was observed between echo
decorrelation and tissue temperature at the thermocouple location. Together, these results
indicate that echo decorrelation is a better predictor of heat induced tissue changes than
integrated backscatter.
Chapter III

_In vivo_ thermal ablation monitoring using ultrasound echo decorrelation imaging

3.1 Introduction

In the previous chapter the feasibility of using ultrasound echo decorrelation imaging for visualization of thermal lesioning using RFA in _ex vivo_ tissue has been demonstrated. However, echo decorrelation imaging is more challenging _in vivo_ because of potential decorrelation artifacts caused by respiratory motion, cardiac motion, and perfusion. Hence, to test the feasibility of using ultrasound echo decorrelation imaging as a treatment monitoring tool, the ability of echo decorrelation to distinguish between ablated and unablated regions in the presence of tissue motion should be assessed.

In this chapter, echo decorrelation imaging is tested _in vivo_ for both RFA and ultrasound ablation treatments. The predictive ability of echo decorrelation imaging in the presence of tissue motion is assessed by quantitatively comparing echo decorrelation with gross tissue histology using receiver operating characteristic (ROC) curves. For comparison, the integrated backscatter is also computed (Arthur et al., 2005; Zhong et al., 2007), and its predictive ability is assessed in a manner similar to that used to assess echo decorrelation imaging (Mast et al., 2008).
Motion gating was performed by excluding severely uncorrelated image frames. The effect of tissue motion on echo decorrelation was tested by comparing echo decorrelation values in the ablated and unablated tissue regions with or without motion gating. To assess the effect of tissue temperature on echo decorrelation, the Pearson product moment correlation was determined between log_{10}-scaled echo decorrelation and tissue temperature measured using a thermocouple placed near the RF electrode.

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3.2 Materials and Methods

Echo decorrelation imaging was tested using pulse-echo data recorded during in vivo RFA and ultrasound ablation experiments. Methods used for the experiments and data analysis are detailed below for RFA experiments performed in porcine liver and for ultrasound ablation experiments performed using image-ablate arrays in rabbit liver with a VX2 tumor model. All animal experiments were performed according to protocols approved by the University of Cincinnati Institutional Animal Care and Use Committee (IACUC).

3.2.1 Radiofrequency Ablation

RFA experiments were performed within a normal porcine liver in vivo for $N = 5$ treatments. The experimental setup for the treatments is shown in Figure 3.1. The swine was anesthetized and its liver was exposed via laparotomy. RFA was performed using a 2-cm RF needle electrode (LaVeen, Boston Scientific, Boston, MA), which was inserted into the liver. Treatments were performed in the left, medial, and right lobes of the liver. Two grounding pads were placed on the back of the pig. A low-noise 1-mm thermocouple
Figure 3.1: Experimental setup for radiofrequency ablation experiments. (a) Experimental configurations of radiofrequency ablation of porcine liver. The ultrasound probe is shown resting on the liver, with the thermocouple and RF probe inserted into the liver in the ultrasound image. (b) B-mode ultrasound image showing the inserted RFA probe shaft and thermocouple. The red circle indicates the tip of the RF electrode and the yellow circle indicates the tip of the thermocouple.
Table 3.1: Exposure conditions for $N = 5$ in vivo RFA treatments performed in a porcine liver.

<table>
<thead>
<tr>
<th>Treatment number</th>
<th>Liver lobe</th>
<th>Power (W)</th>
<th>Duration (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Left</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>Medial</td>
<td>31</td>
<td>170</td>
</tr>
<tr>
<td>3</td>
<td>Right</td>
<td>25</td>
<td>175</td>
</tr>
<tr>
<td>4</td>
<td>Left</td>
<td>25</td>
<td>343</td>
</tr>
<tr>
<td>5</td>
<td>Right</td>
<td>26</td>
<td>165</td>
</tr>
</tbody>
</table>

(GKMQSS, Omega Engineering, Stamford, CT) was also inserted near (~5 mm) the RF needle electrode to record local tissue temperature during treatment. For each treatment, the RF needle electrode was driven by an RF generator (RF 2000B, Radio Therapeutics, Mountain View, CA). The power and time duration settings used for all RFA treatments are outlined in Table 3.1.

A 192-element, 7-MHz linear ultrasound array (L7, Guided Therapy Systems, Mesa, AZ) was positioned on the porcine liver such that its image plane included the RF needle electrode and the thermocouple. The ultrasound array position on the liver was marked using an electrocautery device. In each acquisition, 384 echo signals, comprising a pulse-echo image frame pair, were acquired at intervals of $0.85 \pm 0.05$ s. These echoes were filtered by the Gaussian bandpass filter from Eq. (2.1) with a center frequency of 7.36 MHz and a bandwidth of 1 MHz, resulting in a pair of complex analytic pulse-echo image frames with dimensions $42.2 \times 30.5$ mm$^2$, separated by an inter-frame time of 19.6 ms (inverse of the system frame rate, 51 Hz). For treatment 1, pre-treatment data (ultrasound imaging only) were acquired immediately before RFA treatment at the same position. Echo decorrelation, integrated backscatter and B-mode images were formed as described in Section 2.2.1. Here, spatial integration was implemented using Eq. 1.3, with the Gaussian
width parameter $\delta$ defined as 2.5 mm. To compare echo decorrelation images with and without ablation treatment, the pre-treatment data were analyzed over a duration equal to the subsequent RFA treatment.

After all treatments were performed, the liver was excised and the animal was sacrificed. To maintain tissue shape for accurate registration with B-mode images, the excised liver lobes were frozen in a $-80^\circ$C freezer and then sectioned parallel to the image plane as indicated by the electrocautery marks. Tissue sections were scanned on a flatbed scanner (CanoScan 8800F, Canon, Tokyo, Japan) at 800-dpi (32-$\mu$m) resolution. For direct comparison with echo decorrelation and integrated backscatter images in each case, scanned tissue sections were oriented and registered to ultrasound images using tissue boundaries and visible probe tracks as spatial references. To test the utility of echo decorrelation and integrated backscatter imaging in predicting ablation, the treated region was segmented based on gross discoloration of the tissue (ImageJ, National Institute of Health, Bethesda, MD), with all pixels within the lesion boundary defined as ablated and the rest defined as unablated.

To assess the effect of tissue motion on echo decorrelation imaging, echo decorrelation images were recomputed using motion gating. To this end, a $5 \times 5$ mm$^2$ region of interest (ROI) was selected for each trial from an unablated region where minimal echo decorrelation was observed. The first frames within all acquired frame pairs were selected for analysis. The Pearson product moment correlation was used to compute the correlation coefficient of the echo signals within the ROI for all the selected frames sequentially. Figure 3.2 is a representative plot of the Pearson product-moment correlation performed between echoes within the ROI for sequentially selected frames separated by $0.85 \pm 0.05$ s. The temporal interval between two peaks of the correlation coefficient plot was found to be $\sim 6$ s. The correlation coefficient plot suggests that the pulse-echo frames are correlated
for a portion of the respiratory cycle and severely uncorrelated for the remainder.

To perform motion gating, echo decorrelation was computed using only frame pairs containing selected frames with correlation coefficients greater than 0.6. This threshold choice omitted only the frames that were severely uncorrelated because of substantial tissue motion. Similar to the computations of echo decorrelation without motion gating, a temporal running average was performed using Eq. 1.7 and cumulative echo decorrelation maps were formed from the temporal-maximum echo decorrelation at each pixel location.

To assess the ability of echo decorrelation to differentiate between ablated and unablated regions, paired $t$-tests were performed between the mean (spatially averaged) cumulative log$_{10}$-scaled echo decorrelation within the ablated and unablated regions at the end of treatment, with and without motion gating. Differences in echo decorrelation were assessed for statistical significance using the criterion $p < 0.05$. Holm adjustment was used to counteract
the effect of multiple testing on \( p \)-values (Holm, 1979). One-tailed \( p \)-values were employed to assess the significance of any increase in echo decorrelation caused by tissue ablation, as well as any decrease in echo decorrelation caused by motion gating. Similarly, to test the ability of integrated backscatter to differentiate between the ablated and unablated regions, paired \( t \)-tests were performed between the mean cumulative integrated backscatter within the ablated and unablated regions at the end of treatment.

The time-dependent measured echo decorrelation and integrated backscatter during the RFA treatments were compared with the temperature simultaneously measured by thermocouple. As the precise location of the thermocouple was not known in all cases, for comparison of tissue temperature with echo decorrelation and integrated backscatter, the spatial maximum of the running-average echo decorrelation and integrated backscatter was determined at each time point. The spatial maximum of the echo decorrelation and integrated backscatter was then temporally interpolated to synchronize with the temperature recordings from the thermocouple. To determine whether echo decorrelation and integrated backscatter were correlated with tissue temperature, Pearson correlation coefficients were computed between the measured temperature and the log\(_{10}\)-scaled, spatial-maximum echo decorrelation and integrated backscatter, using all temporal data points from the five trials. When statistical significance of the correlation between echo decorrelation and tissue temperature was tested, the number of independent samples was conservatively estimated as the number of temporal data points multiplied by the running-average parameter \( \epsilon = 0.05 \) from Eq. 1.7. The statistical significance of the correlation between integrated backscatter and tissue temperature was similarly tested.
3.2.2 Ultrasound Ablation

Ultrasound ablation and imaging were performed using a 3-mm-diameter, 32-element miniaturized image-ablate array probe on a rabbit liver with implanted VX2 tumors for \(N = 2\) treatments, within a series of \textit{in vivo} experiments described previously (Mast et al., 2011). VX2 tumor fragments were implanted in separate liver lobes 11 d before the experiment was performed. At the time of the ablation experiments, the tumors had grown to about 1 cm diameter.

For the ablation experiments, the rabbit was anesthetized and its liver exposed. The image-ablate array was inserted into a balloon through which cooling water was circulated. The probe assembly was placed on the liver lobe surface proximal to the VX2 tumor
Table 3.2: Exposure conditions for \( N = 2 \) \textit{in vivo} ultrasound ablation experiments performed in a rabbit liver with VX2 tumor.

<table>
<thead>
<tr>
<th>Treatment number</th>
<th>Liver lobe</th>
<th>Intensity (W/cm(^2))</th>
<th>Duration (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Left</td>
<td>38.5</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>Right</td>
<td>38.5</td>
<td>120</td>
</tr>
</tbody>
</table>

and fixed by a 3D positioning arm, as illustrated in Figure 3.3. Acoustic coupling was implemented between the probe and liver surface using phosphate-buffered saline (PBS) and confirmed using ultrasound imaging from the image-ablate array. Continuous-wave, 4.8-MHz ultrasound was fired from the entire 32-element array in an unfocused beam with spatial-average, temporal-average intensity 38.5 W/cm\(^2\). Treatment cycles, consisting of 8.5 s continuous-wave sonication followed by 1.5 s of imaging by the same array, were repeated for exposure durations of 1.5–2.0 min. The exposure conditions used for the ultrasound ablation treatments are shown in Table 3.2.

In each acquisition, 32 echo signals were acquired at a frame rate of 16 Hz. The echoes were then filtered by the Gaussian bandpass filter from Eq. 2.1 with a center frequency 4.8 MHz and a bandwidth of 0.3 MHz to form complex analytic echo signals. To assess the effect of disturbances such as tissue motion on echo decorrelation imaging, pre-treatment pulse-echo data were similarly acquired immediately before each ablation treatment, at the same probe position. Cumulative echo decorrelation images were computed from pre-treatment data with durations matching the corresponding ablation treatments.

Echo decorrelation and integrated backscatter were computed using Eqs. 1.5 and 1.6 from consecutive frames of pulse-echo data, with an inter-frame time of 60 ms, obtained during the 1.5-s quiescent periods between each sonication cycle. A temporal running average was performed using Eq. 1.7.
After the treatments were completed, the animal was sacrificed. The liver was then excised, sectioned along the image plane at the array location, and stained with triphenyl tetrazolium chloride (TTC) vital stain. Tissue sections were scanned and registered in a manner similar to the RFA treatments. Tissue sections were segmented, mapping regions of treatment based on the local TTC uptake and registered to ultrasound images using visible tissue boundaries and anatomic landmarks.

To test whether echo decorrelation imaging could delineate between the ablated and unablated regions in the ultrasound ablation experiments, a paired \( t \)-test was performed between \( \log_{10} \)-scaled mean cumulative echo decorrelation values for the ablated and unablated regions (\( N=2 \) trials). The ability of integrated backscatter imaging to delineate between the ablated and unablated region was similarly tested.

### 3.2.3 Receiver operating curve analysis

In order to test prediction of ablation by echo decorrelation imaging and integrated backscatter, for both RFA and ultrasound ablation, receiver operating characteristic (ROC) curves were employed (Mast et al., 2008; Krzanowski and Hand, 2009) as described in Section 2.2.3. In this analysis, treatment outcomes were predicted using echo decorrelation and integrated backscatter thresholds, so that all the spatial points exceeding a threshold were predicted to be ablated, and the rest unablated. Using pixel-by-pixel comparison of cumulative \( \log_{10} \)-scaled echo decorrelation and integrated backscatter images with corresponding segmented tissue maps, prediction success was determined for each pixel as a function of the threshold. ROC curves were then plotted for prediction of ablation. Area under the ROC curve (AUROC) was determined to assess the utility of echo decorrelation and integrated backscatter to predict ablation. Similar to the *in vitro* analysis, optimal decorrelation and integrated backscatter thresholds for prediction of local ablation were selected by using the thresholds yielding equal false positives and
Assessment of prediction success was performed for both RFA and ultrasound ablation by testing significance of the AUROC statistic using a general model for the AUROC standard error previously employed in Section 2.2.3 (Hanley and McNeil, 1982). To compare predictions using echo decorrelation with those using integrated backscatter, the significance of AUROC differences between echo decorrelation and integrated backscatter was also computed for both RFA and ultrasound ablation using the DeLong’s method of comparing two correlated ROC curves as described in Section 2.2.3 (Hanley and McNeil, 1983; DeLong et al., 1988). The significance of AUROC differences between echo decorrelation and integrated backscatter was computed by using DeLong’s method of comparing two correlated ROC curves. The significance value was adjusted for the effective sample size as described previously in Section 2.2.3.

To assess the ability of echo decorrelation and integrated backscatter to predict ablated area, the absolute RMS and percent error was computed between the predicted and measured ablated areas.

3.3 Results

Figure 3.4 shows hybrid echo decorrelation maps, comprising log_{10}-scaled echo decorrelation and B-mode images, for all \( N = 5 \) \textit{in vivo} RFA treatments. For each case, hybrid echo decorrelation maps are shown at the end of RFA treatment at the same location. Similar hybrid images are also shown for integrated backscatter at the end of RFA treatment. Also shown are the corresponding segmented tissue sections, with the segmented ablated regions enclosed by dashed black lines. Qualitatively, higher echo decorrelation and integrated backscatter is observed in the ablated regions, while relatively lower echo
Figure 3.4: Hybrid echo decorrelation and integrated backscatter images for all RFA treatments. (a) Log_{10}-scaled echo decorrelation at end of treatment, with the yellow lines encircling the ablated area predicted using the optimum decorrelation threshold. (b) Integrated backscatter at end of treatment, with the dashed yellow lines encircling the ablated area predicted by the optimum integrated backscatter threshold. (c) Tissue sections corresponding to the ultrasound image plane, with the ablated region enclosed by dashed black lines. Results for treatment numbers 1 through 4 are shown in rows (1) through (4), respectively.
decorrelation and integrated backscatter is observed in the unablated regions.

The temporal evolution of $\log_{10}$-scaled echo decorrelation during RFA treatment is illustrated by Figure 3.5. Panel 3.5(a) shows the hybrid echo decorrelation maps plotted at 40 s into pretreatment, matching the duration of RFA treatment 1. Panels 3.5(b)–(f) show the hybrid echo decorrelation maps plotted after 20, 25, 30, 35 and 40 s of RFA treatment, in the same image plane where the pretreatment data were acquired. While echo decorrelation was minimal in the ablated region, echo decorrelation due to tissue motion was elevated near the liver lobe boundaries during pretreatment. As the RFA treatment progressed, echo decorrelation increased in the ablated region. Echo decorrelation due to tissue motion similarly increased; however, it was largely concentrated at the liver lobe boundaries.

For the ultrasound ablation trials, Figure 3.6 shows hybrid echo decorrelation maps formed during at the end of pre-treatment imaging and at the end of ultrasound ablation treatment. Also shown are the corresponding segmented tissue sections, with segmented ablated regions enclosed by dashed black lines. The B-mode ultrasound images, produced
Figure 3.5: Hybrid echo decorrelation images for RFA treatment 1. (a) After 40 s pretreatment. (b) After 20 s treatment. (c) After 25 s treatment. (d) After 30 s treatment. (e) After 35 s treatment. (f) After 40 s treatment.
Figure 3.6: Echo decorrelation images for all ultrasound treatments. (a) End of pre-treatment imaging. (b) End of the ultrasound ablation treatment with the dashed yellow lines representing the lesion boundary predicted by the optimum decorrelation threshold. (c) Tissue sections corresponding to the ultrasound image plane, with the ablated region enclosed by dashed black lines. Results for treatment numbers 4 and 6 are shown in rows (1) and (2), respectively.

during ultrasound ablation using the 32-element image-ablate array, were of low resolution compared to those produced using the 192-element L7 diagnostic array used for RFA experiments. At the end of pre-treatment imaging, some echo decorrelation is observed in the echo decorrelation images, possibly due to tissue motion. Similarly, Figure 3.7 shows the hybrid integrated backscatter maps formed at the end of pre-treatment imaging and at the end of each ultrasound ablation treatment, along with corresponding segmented tissue sections.

Mean cumulative log_{10}-scaled echo decorrelation values in the ablated and unablated regions for all RFA treatments are given in Table 3.3. Figure 3.8(a) shows the mean and stan-
Figure 3.7: Integrated backscatter images for all ultrasound treatments. (a) End of pre-treatment imaging. (b) End of the ultrasound treatment with dashed yellow lines encircling the lesion area predicted using the integrated backscatter threshold. (c) Tissue sections corresponding to the ultrasound image plane, with the ablated region enclosed by dashed black lines. Results for treatment numbers 4 and 6 are shown in rows (1) and (2), respectively.

The standard deviation of the cumulative log_{10}-scaled echo decorrelation in the ablated and unablated regions of the tissue at the end of RFA treatment, with and without motion gating. For RFA, the mean cumulative log_{10}-scaled echo decorrelation in the ablated region ($-1.215 \pm 0.257$) was significantly greater than the unablated region ($-2.174 \pm 0.831$) at the end of treatment ($t = 3.498, p = 0.036, N = 5$). With motion gating, the mean echo decorrelation in the unablated region ($-2.651 \pm 0.752$) at the end of treatment ($-1.520 \pm 0.304$) was significantly reduced ($t = 5.173, p = 0.013, N = 5$). The mean cumulative echo decorrelation in the ablated region at the end of treatment was also significantly reduced relative to the ungated case ($t = 3.526, p = 0.036, N = 5$). Still, after motion gating, the mean cumulative echo decorrelation
### Table 3.3: Log$_{10}$-scaled echo decorrelation values for $N = 5$ *in vivo* RFA treatments in a porcine liver.

<table>
<thead>
<tr>
<th>Treatment number</th>
<th>End treatment Unablated</th>
<th>End treatment Ablated</th>
<th>End treatment (gated) Unablated</th>
<th>End treatment (gated) Ablated</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-2.174</td>
<td>-1.293</td>
<td>-2.578</td>
<td>-1.547</td>
</tr>
<tr>
<td>2</td>
<td>-1.524</td>
<td>-1.145</td>
<td>-1.802</td>
<td>-1.348</td>
</tr>
<tr>
<td>3</td>
<td>-3.757</td>
<td>-1.444</td>
<td>-3.860</td>
<td>-1.538</td>
</tr>
<tr>
<td>4</td>
<td>-2.230</td>
<td>-1.390</td>
<td>-2.643</td>
<td>-1.990</td>
</tr>
<tr>
<td>5</td>
<td>-2.110</td>
<td>-0.801</td>
<td>-2.371</td>
<td>-1.176</td>
</tr>
</tbody>
</table>

Mean: -2.174 -1.2154 -2.651 -1.520
Std. dev. 0.831 0.257 0.752 0.304

### Table 3.4: Log$_{10}$-scaled echo decorrelation values for $N = 2$ *in vivo* ultrasound ablation treatments in rabbit liver with VX2 tumor.

<table>
<thead>
<tr>
<th>Treatment number</th>
<th>Pre-treatment Unablated</th>
<th>Pre-treatment Ablated</th>
<th>End treatment Unablated</th>
<th>End treatment Ablated</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-1.888</td>
<td>-1.354</td>
<td>-1.552</td>
<td>-1.227</td>
</tr>
<tr>
<td>2</td>
<td>-2.412</td>
<td>-1.851</td>
<td>-1.866</td>
<td>-1.323</td>
</tr>
</tbody>
</table>

Mean: -2.150 -1.602 -1.709 -1.275
Std. dev. 0.370 0.350 0.222 0.067

decorrelation in the ablated region was significantly greater than in the unablated region, ($t = 3.474$, $p = 0.036$, $N = 5$).

Figure 3.8(b) shows the mean and standard deviation of the cumulative integrated backscatter values in the ablated and unablated regions of the tissue at the end of RFA treatment. The mean cumulative integrated backscatter in the ablated region (5.958 ± 2.571 dB) was significantly greater than the unablated region (2.161 ± 0.585 dB) at the end of treatment ($t = 3.883$, $p = 0.008$, $N = 5$).

For ultrasound ablation, Figure 3.9(a) shows the mean and standard deviation of the
Figure 3.8: Bar graphs showing the mean and standard deviation of cumulative $\log_{10}$-scaled echo decorrelation and integrated backscatter values in ablated and unablated regions for RFA treatment. (a) Decorrelation at the end of RFA treatment, with and without motion gating. (b) Integrated backscatter at the end of RFA treatment without motion gating.
Figure 3.9: Bar graphs showing the mean and standard deviation of cumulative \( \log_{10} \)-scaled echo decorrelation and integrated backscatter values in ablated and unablated regions for ultrasound ablation. (a) Decorrelation for ultrasound ablation, at the end of pre-treatment imaging and at the end of ultrasound ablation treatment. (b) Integrated backscatter at the end of ultrasound ablation treatment.
cumulative log_{10}-scaled echo decorrelation in the ablated and unablated tissue regions at the end of pre-treatment imaging and at the end of ablation treatment for each case. The mean cumulative log_{10}-scaled echo decorrelation in the ablated and unablated regions of the tissue for all treatments are given in Table 3.4. Similar to the RFA trials, the mean cumulative log_{10}-scaled echo decorrelation at the end of ablation treatment was greater in the ablated region ($-1.275 \pm 0.067$) than in the unablated region ($-1.709 \pm 0.222$), but this was not a statistically significant difference ($t = 3.978, \ p = 0.222, \ N = 2$). At the end of pre-treatment imaging, the mean cumulative echo decorrelation within the ablated region ($-1.275 \pm 0.067$) was significantly greater than in the unablated region ($-2.150 \pm 0.370$) ($t = 39.97, \ p = 0.031, \ N = 2$). The abnormally high t value could be attributed to small sample size.

The mean cumulative log_{10}-scaled echo decorrelation at the end of treatment was greater in the ablated region when compared to the mean cumulative echo decorrelation in the same region after pre-treatment imaging of matching duration, but this difference was not statistically significant ($t = 1.634, \ p = 0.222, \ N = 2$). Similarly, the mean echo decorrelation in the unablated region at the end of treatment was not significantly higher than at the end of pre-treatment imaging ($t = 4.206, \ p = 0.222, \ N = 2$). Though the mean cumulative integrated backscatter in the ablated region ($2.476 \pm 2.228 \text{ dB}$) was greater than the mean cumulative integrated backscatter in unablated region ($2.149 \pm 1.780 \text{ dB}$) at the end of treatment ($t = 1.029, \ p = 0.245, \ N = 2$), the difference is not statistically significant.

Computed ROC curves for the prediction of ablation are shown for both the RFA and ultrasound ablation experiments in Figure 3.10. AUROC for RFA exposures was 0.833 for prediction of ablation using echo decorrelation ($p \ll 10^{-13}, \ N = 214$) and 0.733 using integrated backscatter ($p = 4 \cdot 10^{-9}, \ N = 214$). AUROC for ultrasound exposures was 0.776 using echo decorrelation ($p = 0.004, \ N = 20$) and 0.494 using integrated backscatter ($p = 0.515, \ N = 20$) for prediction of ablation. Although these AUROC statistics show com-
Figure 3.10: Receiver operating characteristic curves for accuracy of ablation prediction. (a) RFA. (b) Ultrasound ablation.
Table 3.5: Results of ROC analysis for prediction of ablation for $N = 5$ in vivo RFA and $N = 2$ in vivo ultrasound ablation exposures.

<table>
<thead>
<tr>
<th></th>
<th>AUROC</th>
<th>Optimum threshold</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>log$_{10}$-scaled</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echo decorrelation</td>
<td>0.833</td>
<td>$-1.295$</td>
<td>0.600</td>
<td>0.844</td>
</tr>
<tr>
<td>(RFA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Integrated backscatter</td>
<td>0.733</td>
<td>4.230 dB</td>
<td>0.521</td>
<td>0.815</td>
</tr>
<tr>
<td>(RFA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>log$_{10}$-scaled</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echo decorrelation</td>
<td>0.776</td>
<td>$-1.452$</td>
<td>0.801</td>
<td>0.571</td>
</tr>
<tr>
<td>(Ultrasound Ablation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Integrated backscatter</td>
<td>0.494</td>
<td>0.515 dB</td>
<td>0.704</td>
<td>0.364</td>
</tr>
<tr>
<td>(Ultrasound Ablation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

parable prediction performance for both sets of experiments for echo decorrelation imaging, statistical significance for the ultrasound exposures is lower because of the smaller effective sample size, with a conservative estimate of 19 independent predictions of treatment outcome, compared to 214 independent predictions for RFA exposures. AUROC values were significantly higher for ablation prediction using echo decorrelation imaging, compared to prediction using integrated backscatter, for RFA ($p = 0.004$, $N = 214$) but not ultrasound ablation ($p = 0.099$, $N = 20$) cases.

Optimal echo decorrelation thresholds for ablation prediction, were $-1.295$ for RFA and $-1.453$ for ultrasound ablation. Optimal integrated backscatter thresholds for ablation prediction were 4.23 dB for RFA and 0.515 dB for ultrasound ablation respectively.

Figures 3.11 (a) and (b) shows scatter plots of the ablated area predicted by the echo decorrelation and integrated backscatter thresholds plotted against the ablated area estimated using gross tissue histology for all RFA treatments ($N = 5$). The ablated area for all treatments was $358.5 \pm 141.2$ mm$^2$. The absolute and normalized RMS errors for prediction
Figure 3.11: Scatter plots representing the ablated area predicted by the optimum thresholds plotted against the measured lesion area from the tissue histology using (a) echo decorrelation imaging for RFA. (b) integrated backscatter imaging for RFA. (c) echo decorrelation imaging for ultrasound ablation. (d) Integrated backscatter imaging for ultrasound ablation.
Figure 3.12: (a) Scatter plot of spatial maximum, temporal running-average echo decorrelation map vs. simultaneous thermocouple-measured tissue temperature for all time points from 5 RFA trials. (b) Scatter plot of spatial maximum, temporal running-average integrated backscatter threshold map vs. simultaneous thermocouple-measured tissue temperature for all time points from 5 RFA trials.
of ablated area using the optimum echo decorrelation threshold were 218.5 mm$^2$ and 57.50% respectively. The absolute and normalized RMS errors for the prediction of ablated area using the optimum integrated backscatter threshold were marginally better, at 144.0 mm$^2$ and 37.89% respectively.

Figures 3.11 (c) and (d) shows scatter plots of the ablated area predicted by the echo decorrelation and integrated backscatter thresholds plotted against the ablated area estimated using the gross tissue histology for the two ultrasound ablation treatments ($N = 2$). The mean and standard deviation of ablated area for the two ultrasound ablation treatments was $204.8 \pm 19.88$ mm$^2$. The absolute and normalized RMS errors for the prediction of ablated area using the optimum echo decorrelation threshold were $106.22$ mm$^2$ and 51.74% respectively. The absolute and normalized RMS errors for the prediction of ablated area using the optimum integrated backscatter threshold were higher, at $171.4$ mm$^2$ and 83.46% respectively.

Figure 3.12 (a) and (b) shows a scatter plot of the thermocouple-measured tissue temperature versus the spatial-maximum, running-average, log$_{10}$-scaled echo decorrelation and integrated backscatter, measured simultaneously throughout the RFA treatments respectively. This scatter plot indicates a nonlinear relationship between echo decorrelation and tissue temperature. Although there is an apparent monotonically increasing relationship between echo decorrelation and tissue temperature, the rate of increase in echo decorrelation is not the same for all treatments. However, the instantaneous tissue temperature and echo decorrelation were correlated across all treatments with high statistical significance ($r = 0.322$, $p = 5 \cdot 10^{-23}$, $N = 890$). The modest correlation between echo decorrelation and temperature may be partially due to the lack of precise knowledge of the thermocouple location. Also, nonthermal factors such as gas activity and tissue motion may cause substantial echo decorrelation, complicating any relationship between local
echo decorrelation and tissue temperature. The integrated backscatter and the measured temperature had lower but still significant correlation ($r = 0.171$, $p = 2 \cdot 10^{-7}$, $N = 890$).

### 3.4 Discussion

Echo decorrelation imaging has previously shown potential for monitoring thermal ablation *in vitro* in studies reported by Mast et al. (2008). The feasibility of ultrasound echo decorrelation imaging as a treatment monitoring tool for *in vivo* thermal ablation and its possible limitations are discussed below. Echo decorrelation during thermal ablation may be caused due to structural changes, vaporization, and dissolution of gas that occur in tissue during coagulative necrosis. In the case of ultrasound ablation, another possible source of echo decorrelation is bubble activity associated with acoustic cavitation. Performing thermal ablation *in vivo* introduces possible sources of artifactual echo decorrelation, including unsteady perfusion, tissue motion and respiration-induced tissue motion.

Respiratory tissue motion is an important source of error for ultrasound-based treatment monitoring methods, including echo decorrelation imaging. The relative importance of tissue motion as a source of artifactual echo decorrelation can be assessed from the motion gating test reported here. For thermal monitoring of *in vivo* RFA, motion gating significantly reduced the mean cumulative echo decorrelation in both ablated and unablated regions. However, with or without motion gating, the mean cumulative echo decorrelation in the ablated region was significantly greater than in the unablated region. This suggests that for the imaging configuration employed here, with pulse-echo image frames separated by about 20 ms, ablation-induced echo decorrelation dominated any artifactual decorrelation caused by tissue motion alone. Uncertainty caused by tissue motion could be reduced by use of a higher imaging frame rate, potentially eliminating the need
While the effect of tissue motion was mitigated using motion gating, motion induced decorrelation may mask some heat induced decorrelation. Effects of tissue motion and electronic noise could potentially be compensated by the method described in Hooi et al. (2015). This method separates the decorrelation caused by motion, electronic noise, and heat induced tissue changes, allowing compensation for measured artifactual decorrelation. This method was shown to substantially reduce motion-induced decorrelation artifacts during the treatment 1 of the in vivo RFA experiments described in this chapter (Hooi et al., 2015).

The ROC curves (Figure 3.10) plotted for both RFA and ultrasound ablation are indicative of the ability of echo decorrelation imaging to classify ablated and unablated tissue regions. The relatively high AUROC values obtained for both ultrasound ablation and RFA indicate the utility of echo decorrelation imaging for prediction of local ablation. Integrated backscatter imaging showed less predictive power than echo decorrelation for both RFA and ultrasound ablation. In the case of ultrasound ablation, integrated backscatter performed no better than chance and the AUROC obtained for integrated backscatter was not statistically significant. For RFA, AUROC values for echo decorrelation imaging were significantly greater than those for integrated backscatter. This is consistent with previous results on prediction of ex vivo tissue ablation by RFA (Mast et al., 2008). These results suggest potential for echo decorrelation imaging to predict thermal lesioning in the tissue in the presence of tissue motion.

### 3.5 Conclusion

The results shown in this chapter demonstrate the utility of echo decorrelation imaging for predicting tissue thermal damage during in vivo thermal ablation. Significantly higher
mean cumulative echo decorrelation was observed in ablated tissue regions compared to unablated regions for RFA, indicating the ability of echo decorrelation to delineate between ablated and unablated regions. For in vivo RFA, motion gating reduced the mean echo decorrelation significantly. However, with or without motion gating, the mean cumulative echo decorrelation was significantly greater in the ablated than in the unablated region. This result suggests that echo decorrelation can delineate between ablated and unablated regions in presence of motion related artifacts. Higher AUROC values were obtained for both RFA and ultrasound ablation using echo decorrelation imaging than using relative integrated backscatter, despite limitations including tissue motion and the low resolution of the image-ablate array used for ultrasound ablation. Together, these results indicate the feasibility of echo decorrelation imaging as a tool for monitoring in vivo thermal ablation.
Chapter IV

Dependence of ultrasound echo decorrelation on local tissue temperature during *in vitro* radiofrequency ablation

4.1 Introduction

Echo decorrelation imaging has previously shown potential for prediction of thermal lesioning in tissue during *in vitro* RFA (Chapter II) and *in vivo* thermal ablation (Chapter III) (Mast et al., 2008; Subramanian et al., 2014). As discussed in Section 1.1.2, thermal damage caused during RFA is directly related to the degree of temperature rise and treatment duration (Sapareto and Dewey, 1984). Monitoring temperature rise in tissue could aid in ablation monitoring and control. The FDA also requires that the temperature be measured during thermal therapies (Rivens et al., 2007). Use of temperature sensors such as thermocouples are undesirable because they are invasive and can only measure temperature at the sensor location. Hence, they cannot provide enough information if the treatment region is large. Electromagnetic interference also restricts thermocouple use and placement, as placing thermocouples near the RF probe causes them to act as a heat source. Hence, a noninvasive method to assess the temperature rise throughout the treated region would be
useful.

In this chapter, the feasibility of using the echo decorrelation imaging algorithm for mapping tissue temperature during RFA is tested. To this end, 2-D echo decorrelation maps generated during RFA are compared to tissue temperature in the same plane. The temperature rise in the tissue can be simulated by solving the Pennes bioheat transfer equation (BHTE) (Pennes, 1948). However, these simulations are usually limited by uncertainty in tissue physical parameter measurements, location of blood vessels, and other sample-specific properties. Most RFA simulation studies have used measured values of tissue physical properties, reported in the literature, to simulate temperature elevation, resulting in substantial uncertainty (Tungjitkusolmun et al., 2000; Schutt and Haemmerich, 2008; dos Santos et al., 2009). Because tissue parameter values vary among individuals or tissue samples, these values need to be estimated individually for accurate simulation of tissue temperature.

Sample-specific tissue properties can be estimated using iterative inverse techniques (Fuentes et al., 2013; Audigier et al., 2014), which typically require a large number of computations before convergence. As a typical 3D FEM simulation of RFA requires about 1 h to complete, these methods can be computationally expensive (dos Santos et al., 2009). Also, there is no guarantee that convergence to a global minimum will be achieved, as the initial guess needs to be close to the optimal solution (Fuentes et al., 2013).

The unscented Kalman filter (UKF) developed by Julier and Uhlmann (2004) is a computationally inexpensive technique commonly used for state estimation and system identification problems. In this chapter, an inverse solver based on UKF is proposed for optimization of tissue parameters to accurately simulate tissue temperature during RFA. In this approach, the unscented transform is used to approximate the statistics of the ablated tissue area through a nonlinear transformation of known statistics of tissue parameters (dos Santos et al., 2009). The mean-square error between simulated and measured ablated areas is minimized to recover a set of tissue parameters for accurate temperature simulation. To
validate the simulated temperature profile, the temperature measured using thermocouple is compared against simulated tissue temperature at the thermocouple location.

To determine the correlation between echo decorrelation and tissue temperature in the image plane, the Pearson correlation coefficient was estimated. The temperature prediction ability of echo decorrelation imaging was then assessed using receiver operating characteristics (ROC) curves by performing pixel-by-pixel comparison between echo decorrelation and simulated temperature profiles. For comparison, the temperature prediction ability of integrated backscatter is also assessed. Optimum echo decorrelation and integrated backscatter thresholds for the prediction of tissue temperatures greater than 40, 60, and 80 °C were determined. Sensitivity and specificity values associated with the optimum echo decorrelation and integrated backscatter thresholds were determined to assess their predictive ability.

4.2 Methods

Below, methods are presented for accurate finite element (FE) simulation of temperature elevations from a series of \textit{ex vivo} RFA experiments, formation of echo decorrelation images and analysis of temperature prediction ability of echo decorrelation imaging. For the geometry and exposure conditions of each experiment, a fixed number of FE simulations were performed using deterministic sampling of the specific heat, thermal conductivity, and electrical conductivity parameters. These simulations were used to approximate statistics of the simulation outcome (area of the ablated tissue region) as well as a nonlinear mapping between the input tissue parameters and the ablated area. The Kalman filter was implemented to recover a set of tissue parameters minimizing the mean-square error between measured and simulated ablated areas. Sensitivity of simulated tissue temperature to systematic errors was also assessed.

The echo decorrelation imaging algorithm is applied on the pulse-echo data acquired
during RFA treatments. Echo decorrelation in the image plane was compared against the temperature estimated with FE simulations using ROC curves to assess its temperature prediction ability. ROC curves were plotted for prediction of tissue temperatures greater than 40, 60, and 80 °C. Optimum echo decorrelation and integrated backscatter thresholds for the prediction of tissue temperatures greater than 40, 60, and 80 °C were determined. Sensitivity and specificity values associated with the optimum echo decorrelation and integrated backscatter thresholds were determined to assess their predictive ability.

The following sections describe methods for the RFA experiments, FE simulation, UKF implementation, echo decorrelation image formation, and assessment of temperature prediction ability of echo decorrelation.

4.2.1 Experimental Setup

The experimental setup used in Chapter II for the in vitro RFA experiments was modified to perform the RFA experiments described in this study. The clinical RF generator (RF 2000B, Radio Therapeutics, Mountain View, CA) used in Chapter II and Chapter III adjusted the output voltage supplied to the RF electrode based on electrical impedance of the tissue using a proprietary control algorithm. To simulate the tissue temperature with acceptable accuracy, the voltage supplied to the tissue via the RF electrode must be known. To this end, the RF electrode previously used in conjunction with the clinical RF generator was replaced with the custom-made needle electrode shown in Figure 4.1(a). The needle electrode was powered using a signal generator (33220A, Agilent, Santa Clara, CA) coupled to a 50 dB gain RF power amplifier (3100L, ENI, Rochester, NY), so that the voltage applied to the tissue was known.

In addition, to ensure precise comparison of the echo decorrelation map to both corresponding simulated tissue temperature and gross tissue histology in the same image plane, placement of ultrasound array (L7, Guided Therapy Systems, Mesa, AZ) must be precisely
known. To this end, a custom ultrasound array holder (Figure 4.1(c)) was designed such that when the ultrasound array was placed in the holder, the image plane position relative to the benchtop would be known. Similarly, for precise knowledge of thermocouple and RF needle electrode position relative to the ultrasound array, a custom needle guide (Figure 4.1(b)) was designed. The guide was used for positioning the RF needle electrode along with the thermocouples such that they were angled perpendicular to the benchtop and positioned at the same distance relative to each other for all experiments.
Figure 4.2: (a) Schematic diagram for the in vitro RFA experiments. (b) Photo of the experimental setup of RFA experiments. (c) Ultrasound B mode image representing the image plane with RF electrode (yellow circle) and two thermocouples (red circles).
4.2.2 Experiments

The experimental setup used for the in vitro RFA treatments is shown in Figure 4.2(a). Fresh bovine livers were acquired from a local slaughterhouse and were cut into samples of dimensions matching the sample holder $85 \times 85 \times 60 \text{ mm}^3$ and stored in a bag filled with phosphate buffered saline (PBS), then stored in ice at $0^\circ \text{C}$. All treatments were performed within 12 hours postmortem. A side was cut out of the sample holder and sealed with an acoustically transparent window (Tegaderm, 3M, St Paul, MN). A 192-element 7-MHz ultrasound array (L7, Guided Therapy Systems, Mesa, AZ) was placed against the acoustically transparent window as shown in Figure 4.2(b). The ultrasound array was placed on the custom made holder as shown in Figure 4.2(b) to ensure that the array was aligned parallel to the benchtop.

Two 1-mm diameter thermocouples and a 1.4-mm diameter needle electrode with an exposed length of 22 mm were inserted into the liver sample though a custom made guide such that all were aligned parallel to each other. The thermocouples were placed at a distance of $\sim 8 \text{ mm}$ from the RF electrode. A grounding pad was placed at the distal end of the tissue relative to RF probe as shown in Figure 4.2(b).

A 500 kHz sine wave was produced by a signal generator (33220A, Agilent, Santa Clara, CA) with voltage amplitude 280–320 mVpp, amplified using a 50 dB gain RF power amplifier (3100L, ENI, Rochester, NY), and supplied to the needle electrode. 15 RFA treatments were performed with $31–34 \text{ V}_{\text{RMS}}$ input voltage and treatment durations 1–6 min. For each experiment, the treatment was stopped when the impedance near the RF probe increased due to tissue vaporization at very high temperatures ($> 100^\circ \text{C}$), as indicated by large fluctuations of the built-in power meter.

Ultrasound imaging was performed as described in Section 2.2.1, with ultrasound pulse-echo frame pairs acquired at a faster time interval of $0.222 \pm 0.031 \text{ s}$ compared to Chapter 90.
II. Echo decorrelation, integrated backscatter and B-mode images were formed as described in Section 2.2.1, with the Gaussian window width parameter $\delta = 1.5$ mm, equivalent to one-sixth of the average lesion diameter ($\sim 6.45$ mm) (Hooi et al., 2015). As demonstrated in Hooi et al. (2015), this choice of $\delta$ would result in a relatively small error between the mapped echo decorrelation and actual decoherence of the scattering medium. The time- and position-dependent echo decorrelation and integrated backscatter were then computed using Equation 1.7, with the running-average parameter $\epsilon = 0.02$ to account for the faster image acquisition rate. Cumulative echo decorrelation and integrated backscatter images were formed by recording the temporal maximum of the resulting echo decorrelation and integrated backscatter at each pixel location.

After completion of each treatment, the liver specimen was frozen in a $-80$ °C freezer, to retain shape for the purpose of accurate image registration (Mast et al., 2008). The tissue was then sectioned parallel to the image plane. Tissue sections were scanned using a flatbed scanner (V600, Epson, Long Beach, CA) at 600 dpi. The tissue section corresponding to the image plane was selected by choosing the tissue section at the height closest to the ultrasound image plane, based on the known distance between the benchtop and the ultrasound array. For direct comparison to temperature profiles and echo decorrelation images, the tissue section corresponding to the image plane was registered to the ultrasound image using visible probe tracks. The lesion area was manually segmented based on gross discoloration of the tissue with all the pixels within the lesion boundary defined as ablated. The ablated area was then quantified as the total area of all pixels within the segmented lesion boundaries (Mast et al., 2008).

4.2.3 Finite element simulations

Tissue temperature was simulated using ABAQUS software (Hibbit, Karlsson and Sorensen, Inc., Pawtucket, RI), where 3D models of the needle electrode and liver tissue sample were
created to match the geometry of each RFA experiment. A fine mesh was created near the electrode, where the temperature gradient is largest, while a coarser mesh was created near the tissue boundary. Convergence tests were performed to ensure a sufficient mesh size.

To estimate tissue temperature, FEM simulations solved the Pennes bio-heat transfer equation (Pennes, 1948) without perfusion, given by

$$\rho c \frac{\partial T}{\partial t} = \nabla \cdot k \nabla T + Q,$$

where $T$ is the tissue temperature, $\rho$ is the tissue mass density, $k$ is the tissue thermal conductivity, $c$ is the tissue specific heat, and $Q$ is the heating power per unit volume generated by the RF electrode,

$$Q = J \cdot E,$$

where $E$ is the electric field intensity and $J$ is the current density. The electrical field intensity and current density vectors were determined at each time step by solving the Laplace equation

$$\nabla \cdot \varepsilon \nabla V = 0,$$

independent of the thermal equation, where $V$ is the voltage and $\varepsilon$ is the electrical conductivity.

The initial tissue temperature was set to the average starting temperature measured by the two thermocouples in the corresponding experiment. A constant voltage, equal to the RMS value of the experimentally applied input voltage, was set at the RF electrode. An insulated boundary condition was implemented for both the thermal and electrical problems, except at the position of the grounding pad, where the electrical boundary condition was set to 0 V.

The ablated area was computed using a MATLAB (The MathWorks, Natick, MA) script,
Table 4.1: Relationships between literature-reported liver tissue properties and temperature, the mean and standard deviation of the coefficients, and the values of thermal and electrical properties of the custom stainless steel needle electrode.

<table>
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<th>Relationship</th>
<th>$k$ (Wm$^{-2}$C$^{-1}$)</th>
<th>$c$ (Jkg$^{-1}$C$^{-1}$)</th>
<th>$e$ (Sm$^{-1}$)</th>
<th>$\rho$ (kgm$^{-3}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k = k_0 + 0.001265T$</td>
<td></td>
<td></td>
<td>$e = c_0 1.02^{T-37}$</td>
<td>1060</td>
</tr>
<tr>
<td>$0 &lt; T &lt; 100^\circ$C</td>
<td>$c = c_0$, $T &lt; 63.5^\circ$C</td>
<td>$c = c_0 + c_1(T - 63.5)$, $T \geq 63.5^\circ$C</td>
<td>$e_0(\text{mean} = 0.3$, Std. dev. = 0.075)</td>
<td></td>
</tr>
<tr>
<td>Coefficients</td>
<td>$k_0(\text{mean} = 0.4882$, Std. dev. = 0.1221)</td>
<td>$c_0(\text{mean} = 3399.9$, Std. dev. = 522.34), $c_1 = 28.9</td>
<td>$e_0(\text{mean} = 0.3$, Std. dev. = 0.075)</td>
<td></td>
</tr>
<tr>
<td>Electrode</td>
<td>18</td>
<td>840</td>
<td>$1 \times 10^8$</td>
<td>6450</td>
</tr>
</tbody>
</table>

in which the simulated temperature within the image plane was first spatially interpolated to a resolution of 0.1 mm. The thermal dose parameter (Sapareto and Dewey, 1984) approximating the thermal damage in the tissue was then determined as

$$EM_{43} = \sum R^{T(r,t)-43}\delta t/60,$$

(4.4)

where $\delta t$ is the time step in seconds, $R = 2$ for $T \geq 43^\circ C$, and $R = 4$ for $T < 43^\circ C$. The thermal lesion within the image plane was defined by assigning pixels exceeding $EM_{43} = 200$ min as ablated, and the ablated area was estimated as the total area of these pixels.

4.2.4 Unscented transform

The unscented transform is implemented here to propagate literature-reported values for the mean and standard deviation of specific heat (Haemmerich et al., 2005; dos Santos et al., 2009), thermal conductivity (Valvano et al., 1985), and electrical conductivity (Gabriel et al., 1996) listed in table 4.1 through a nonlinear transformation, resulting in estimated statistics of the ablated tissue area. The standard deviation of the thermal conductivity measurements was not reported in Valvano et al. (1985), hence an uncertainty of 25% was assumed for this analysis. The electrical conductivity of liver has previously been assumed to increase 2%
with every degree rise in tissue temperature (Berjano, 2006), which can be expressed using
\[ e = e_0 1.02^{T-37}, \]
where \( e_0 \) is the electrical conductivity value measured at 37°C.

The unscented transform was implemented similarly to dos Santos et al. (2009). In this
implementation, let the \( n \)-dimensional random variable \( \mathbf{x} \) represent tissue parameters with
mean \( \mathbf{x} \) and covariance \( \mathbf{P}_x \), related to ablated tissue area \( \mathbf{y} \) through a nonlinear transfor-
mation \( \mathbf{y} = g(\mathbf{x}) \). A set of tissue parameter values called sigma points \( \mathcal{X} \), with associated
weights \( w \), are then deterministically chosen such that application of the nonlinear trans-
formation \( g \) to these points completely captures the first two moments of the ablated area
(expected value and variance),
\[ \mathcal{Y} = \sum_i w_i g(\mathcal{X}_i) \quad \text{and} \quad \mathbf{P}_y = \sum_i w_i (g(\mathcal{X}_i) - \mathcal{Y})(g(\mathcal{X}_i) - \mathcal{Y})^T. \]  

Selection of sigma points and associated weights is performed using a Taylor series ex-
pansion of the transforming function to form a set of equations (De Menezes et al., 2008)
\[ \sum_i w_i = 1 \quad \text{and} \quad \sum_i w_i \mathcal{X}_i^m = \mathbb{E}\{u^m\}, \quad (4.6) \]
where \( u \) is a zero-mean random variable and \( m \) is the order of a central moment for this
random variable. Using the known mean and covariance of the input random variables,
the weights and sigma points can be determined by solving equation 4.6 up to the fourth
moment. For \( n \)-dimensional input random variables, minimum required number of sigma
points is \( 2n + 1 \) (De Menezes et al., 2008). However, for multivariate inputs, the effect of
interdependence between input random variables should be considered. To this end, the
sigma points are considered to be located at the edges, main axis, and center of an \( n \-
dimensional cube, resulting in a set of \( 2^n + 2n + 1 \) sigma points (De Menezes et al., 2008).
The weights and sigma points obtained using equation 4.6 for the case $n = 3$ are

\[
\begin{align*}
    w_{\text{edges}} &= \frac{1}{48}; \quad w_{\text{axis}} = \frac{1}{36}; \quad w_{\text{center}} = \frac{2}{3} \\
    \mathcal{X}_{\text{edges}} &= (\bar{x}_1 \pm \sigma_1 \sqrt{3}, \bar{x}_2 \pm \sigma_2 \sqrt{3}, \bar{x}_3 \pm \sigma_3 \sqrt{3}) \\
    \mathcal{X}_{\text{axis}} &= \begin{cases} 
        (\bar{x}_1 \pm \sigma_1 \sqrt{3}, \bar{x}_2, \bar{x}_3) \\
        (\bar{x}_1, \bar{x}_2 \pm \sigma_2 \sqrt{3}, \bar{x}_3) \\
        (\bar{x}_1, \bar{x}_2, \bar{x}_3 \pm \sigma_3 \sqrt{3})
    \end{cases} \\
    \mathcal{X}_{\text{center}} &= (\bar{x}_1, \bar{x}_2, \bar{x}_3),
\end{align*}
\]  

(4.7)

where $\bar{x}_1$, $\bar{x}_2$, $\bar{x}_3$, $\sigma_1$, $\sigma_2$, and $\sigma_3$ are the mean and standard deviation of the specific heat, thermal conductivity, and electrical conductivity listed in table 4.1.

These sigma points listed in Table 4.2 were used as inputs to the FE model for each RFA treatment and the simulated tissue temperature data was saved at 5 s time steps. Tissue parameters were updated during the simulations according to the temperature dependencies given in table 4.1. Changes in the electrical conductivity for temperatures greater than 100 °C, due to tissue vaporization (Berjano, 2006), were not implemented, as the RFA treatments were ceased when sudden increases in electrical impedance were observed. The ablated tissue area was then estimated for all sets of sigma points listed in table 4.2 using equation 4.4.

### 4.2.5 Unscented Kalman Filter

The UKF was implemented as an inverse solver, similarly to Wan and Van der Merwe (2000). In this approach, the goal is to determine a set of input tissue parameters minimizing the mean-square error between predicted and measured ablated areas. This minimization is achieved through a series of iterations where the mean and covariance of input random variables are updated until acceptable error (within 2%) is achieved. To avoid the compu-
Table 4.2: The 15 sets of sigma points determined using unscented transform to be used as inputs to the finite element model for all 15 RFA treatments.

<table>
<thead>
<tr>
<th>Simulation number</th>
<th>$k_0$ (Wm$^{-2}$K$^{-1}$)</th>
<th>$c_0$ (Jkg$^{-1}$K$^{-1}$)</th>
<th>$e_0$ (Sm$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.6995</td>
<td>4304</td>
<td>0.4299</td>
</tr>
<tr>
<td>2</td>
<td>0.2768</td>
<td>2495</td>
<td>0.1700</td>
</tr>
<tr>
<td>3</td>
<td>0.6995</td>
<td>2495</td>
<td>0.1700</td>
</tr>
<tr>
<td>4</td>
<td>0.2768</td>
<td>4304</td>
<td>0.4299</td>
</tr>
<tr>
<td>5</td>
<td>0.6995</td>
<td>4304</td>
<td>0.1700</td>
</tr>
<tr>
<td>6</td>
<td>0.2768</td>
<td>2495</td>
<td>0.4299</td>
</tr>
<tr>
<td>7</td>
<td>0.2768</td>
<td>4304</td>
<td>0.1700</td>
</tr>
<tr>
<td>8</td>
<td>0.6995</td>
<td>2495</td>
<td>0.4299</td>
</tr>
<tr>
<td>9</td>
<td>0.6995</td>
<td>3399</td>
<td>0.3000</td>
</tr>
<tr>
<td>10</td>
<td>0.4882</td>
<td>4304</td>
<td>0.3000</td>
</tr>
<tr>
<td>11</td>
<td>0.4882</td>
<td>3399</td>
<td>0.4299</td>
</tr>
<tr>
<td>12</td>
<td>0.2768</td>
<td>3399</td>
<td>0.3000</td>
</tr>
<tr>
<td>13</td>
<td>0.4882</td>
<td>2495</td>
<td>0.3000</td>
</tr>
<tr>
<td>14</td>
<td>0.4882</td>
<td>3399</td>
<td>0.1700</td>
</tr>
<tr>
<td>15</td>
<td>0.4882</td>
<td>3399</td>
<td>0.3000</td>
</tr>
</tbody>
</table>

The computational expense of FEM simulations for each iteration, a mapping between the input tissue parameters $x_1$, $x_2$ and $x_3$ and the ablated area $y$ is approximated using a second-order Taylor series expansion (dos Santos et al., 2009)

$$y = g(x_1, x_2, x_3)$$

$$= a_0 + a_1 x_1 + b_1 x_2 + c_1 x_3 + c_{12} x_1 x_2 + c_{13} x_1 x_3 + c_{23} x_2 x_3 + a_2 x_1^2 + b_2 x_2^2 + c_2 x_3^2.$$

The coefficients of the mapping function (equation 4.9) defining the second order mapping between the tissue parameters and the ablated area were determined using the Moore-Penrose pseudo-inverse method (dos Santos et al., 2009).

Initial estimates for the mean $\mathbf{X}_0$ and covariance $\mathbf{P}_{x_0}$ were determined using the weighted
mean and covariance of the sigma points as

\[
\overline{X}_k = \sum_i w_{i,k} X_{i,k} \quad \text{and} \quad P_{x_k} = \sum_i w_{i,k} (X_{i,k} - \overline{X}_k)(X_{i,k} - \overline{X}_k)^T.
\] (4.9)

At the \( k \)th iteration, the output variables can be determined for corresponding tissue parameters and sigma points using the mapping function \( g \) as

\[
y_k = g(x_k) \quad \text{and} \quad Y_k = g(X_k).
\] (4.10)

The updates are performed by first computing the innovation \( P_{y_k y_k} \) and cross \( P_{x_k y_k} \) covariances, which are defined as

\[
P_{y_k y_k} = \sum_i w_i (Y_{i,k} - \overline{Y}_k)(Y_{i,k} - \overline{Y}_k)^T \quad \text{and} \quad P_{x_k y_k} = \sum_i w_i (X_{i,k} - \overline{X}_k)(Y_{i,k} - \overline{Y}_k)^T.
\] (4.11)

The Kalman gain \( K \) is defined as

\[
K_k = P_{x_k y_k} P_{y_k y_k}^{-1}.
\] (4.12)

The update equations for the mean \( \overline{x}_k \), and the input covariance \( P_{x_k} \) are

\[
\overline{x}_{k+1} = \overline{X}_k + K_k (y_{\text{meas}} - \overline{Y}_k) \quad \text{and} \quad P_{x_k} = P_{x_k} - K_k P_{y_k y_k} K_k^T.
\] (4.13)

where \( y_{\text{meas}} \) is the ablated area determined from gross tissue histology. The percent error between the measured ablated area \( y_{\text{meas}} \) and the estimated area \( y_k \) was determined (equation 4.10) for each iteration. If the percent error was greater than 1\%, new sigma points were determined using equation 4.7 with the mean defined as \( \overline{X}_k \) and standard deviation defined as the square root of \( P_{x_k} \) (equation 4.13), which was determined via Cholesky de-
composition. These sigma points were then iterated from equations 4.9–4.13 to predict the new ablated area and to estimate new tissue parameters, until the percent error fell below 1% or converged to a constant value, which was below 2% in all cases.

Optimized tissue parameters listed in Table 4.3 for a given experiment were then used in the corresponding FE model to estimate tissue temperature profiles in the image plane. Figure 4.3 shows the treatment volume generated by the finite element model for a representative treatment. To verify the accuracy of the simulated temperature, time-dependent temperatures recorded by the two thermocouples were compared to temperatures simulated at the thermocouple locations and the RMS error of temperature prediction was determined for all treatments.

### Table 4.3: Tissue parameter values determined by the UKF for all 15 RFA treatments.

<table>
<thead>
<tr>
<th>Treatment Number</th>
<th>$k_0$ (Wm$^{-2}$K$^{-1}$)</th>
<th>$c_0$ (Jkg$^{-1}$K$^{-1}$)</th>
<th>$e_0$ (Sm$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.410</td>
<td>2878</td>
<td>0.495</td>
</tr>
<tr>
<td>2</td>
<td>0.353</td>
<td>2891</td>
<td>0.537</td>
</tr>
<tr>
<td>3</td>
<td>0.364</td>
<td>2945</td>
<td>0.512</td>
</tr>
<tr>
<td>4</td>
<td>0.364</td>
<td>2948</td>
<td>0.508</td>
</tr>
<tr>
<td>5</td>
<td>0.415</td>
<td>3093</td>
<td>0.421</td>
</tr>
<tr>
<td>6</td>
<td>0.452</td>
<td>3165</td>
<td>0.377</td>
</tr>
<tr>
<td>7</td>
<td>0.398</td>
<td>2987</td>
<td>0.472</td>
</tr>
<tr>
<td>8</td>
<td>0.407</td>
<td>3032</td>
<td>0.441</td>
</tr>
<tr>
<td>9</td>
<td>0.471</td>
<td>3285</td>
<td>0.336</td>
</tr>
<tr>
<td>10</td>
<td>0.358</td>
<td>2828</td>
<td>0.557</td>
</tr>
<tr>
<td>11</td>
<td>0.458</td>
<td>3224</td>
<td>0.362</td>
</tr>
<tr>
<td>12</td>
<td>0.395</td>
<td>2986</td>
<td>0.457</td>
</tr>
<tr>
<td>13</td>
<td>0.415</td>
<td>3140</td>
<td>0.405</td>
</tr>
<tr>
<td>14</td>
<td>0.379</td>
<td>2861</td>
<td>0.531</td>
</tr>
<tr>
<td>15</td>
<td>0.377</td>
<td>2841</td>
<td>0.536</td>
</tr>
</tbody>
</table>
4.2.6 Sensitivity Analysis

To estimate the uncertainty in temperature maps simulated for comparison with echo decorrelation, sensitivity analysis was performed. Possible sources of error for this assessment include inaccuracy in estimating thermocouple positions, irregular sectioning of tissue, and error in temperature measurements due to electromagnetic interference. In addition, sensitivity of the simulation outcomes to its input parameters and to variations in thermal lesion size between nearby tissue sections was also assessed.

4.2.6.1 Uncertainty in simulated temperature

Thermocouple positions within the image plane were determined from B-mode images using the hyperechoic spots (enclosed by red circles in Figure 4.2(c)) caused by the thermocouples. Thermocouple positions were estimated to be accurate within a radius of 2 mm.
(average radius of these bright spots) in the image plane and an out-of-plane distance of ±2 mm (the average tissue-slice thickness). To determine the effect of this uncertainty on tissue temperature, standard deviations of the final simulated temperatures within two cylinders of 2 mm radius and 4 mm length around the two thermocouples were determined for all treatments. The uncertainty in temperature due to inaccuracy in estimating thermocouple positions and irregular sectioning was then determined by calculating the mean of these standard deviations across the simulations corresponding to all 15 treatments.

Uncertainty caused by electromagnetic interference to thermocouple measurements was usually observed as a dip in the measured temperature when the RF signal was switched on. This uncertainty was determined by estimating the RMS value of the apparent change in temperature observed at the two thermocouple locations at the beginning of all treatments. The combined uncertainty in the simulated tissue temperature \( \sigma_{\text{sim}} \) due to uncertainty in thermocouple position \( \sigma_{\text{TC}} \) and electromagnetic interference \( \sigma_{\text{EM}} \) was determined using

\[
\sigma_{\text{sim}} = \sqrt{\sigma_{\text{TC}}^2 + \sigma_{\text{EM}}^2}.
\]  

(4.14)

4.2.6.2 Uncertainty in simulation outcomes

To estimate the effect of uncertainty in tissue parameters (specific heat, thermal conductivity and electrical conductivity) on simulation outcomes (ablated area and tissue temperature), we utilized the values of ablated area and tissue temperature simulated using the sigma points defined in Equation 4.7 and listed in Table 4.2 across all RFA treatments \( N = 15 \). These sigma points were selected at the axis, edges and center of a 3D cube, representing the tissue parameter space. Percentage uncertainty in ablated area \( g(\mathcal{X}_i) \) (equation 4.9) for the \( i^{\text{th}} \) sigma point \( \mathcal{X}_i \) was calculated with respect to the sigma point located at center \( \mathcal{X}_{\text{center}} \) of
the 3D cube, for all $N = 15$ RFA treatments using
\[
\% \text{ difference} = \frac{\sum_{j=1}^{N} g(\mathcal{X}_i) - g(\mathcal{X}_{\text{center}})}{\sum_{j=1}^{N} g(\mathcal{X}_{\text{center}})} \times 100\%.
\] (4.15)

The RMS difference in tissue temperature for the $i^{\text{th}}$ sigma point $\mathcal{X}_i$ due to variations in tissue parameters was estimated using the final simulated temperature at the end of treatment, across all $N = 15$ RFA treatments. Let $T(\mathcal{X}_i, j)$ represent the final simulated temperature estimated at the thermocouple location using the $i^{\text{th}}$ sigma point for the $j^{\text{th}}$ RFA treatment. Let $T(\mathcal{X}_{\text{center}}, j)$ represent the final simulated temperature estimated using the sigma point $\mathcal{X}_{\text{center}}$ located at center of the 3D cube for the $j^{\text{th}}$ RFA treatment. The RMS difference denoting the uncertainty in tissue temperature due to variations in input parameters (thermal conductivity, specific heat and electrical conductivity) for $N = 15$ RFA treatments is calculated using
\[
\text{RMS difference} = \sqrt{\frac{\sum_{j=1}^{N} (T(\mathcal{X}_i, j) - T(\mathcal{X}_{\text{center}}, j))^2}{N}}.
\] (4.16)

To estimate the uncertainty associated with variations in thermal lesion size, the tissue sections adjacent to the previously chosen tissue section corresponding to the ultrasound image plane were selected. The ablated area was determined for these tissue sections based on the gross discoloration of tissue as described in Section 4.2.2 and corresponding tissue parameters were determined using the UKF (Equation 4.13). The newly estimated tissue parameters were used as inputs to the finite element simulations as described in Section 4.2.3 and corresponding tissue temperature at the thermocouple location was determined for the duration of treatment. The RMS difference in simulated tissue temperature at the thermocouple location between the sections immediately below $T_-$, above $T_+$, and at the
originally selected tissue section $T_0$ was determined for a RFA treatment as

$$\text{RMS difference} = \sqrt{\frac{\sum_{l=1}^{n}(T_-(l) - T_0(l))^2 + \sum_{l=1}^{n}(T_+(l) - T_0(l))^2}{2n}}, \quad (4.17)$$

where $n$ is the treatment duration. The uncertainty associated with variations in thermal lesion shape and size between nearby tissue sections on simulated tissue temperature across all 15 RFA treatments was then determined as the mean of all 15 RMS differences.

### 4.2.7 Data Analysis

To test the interdependence of the treatment duration, voltage applied on the RF electrode, ablated area, and the spatial maximum of the cumulative echo decorrelation, correlation coefficients were determined among them.

For comparison of ultrasound echo decorrelation with tissue temperature, both the echo decorrelation and temperature profiles were interpolated spatially and temporally. In this analysis, spatial and temporal sampling intervals were chosen to ensure the independence of echo decorrelation values for each sampled location and time from the Gaussian window size used for the computation of echo decorrelation. For this calculation, the windows were considered independent when the spatial cross-correlation coefficient of two Gaussian windows as defined in Eq. (1.3), was below 0.5. The distance between window centers for a correlation coefficient of 0.5 is $2\sqrt{2\log(2)\delta}$, where $\delta$ is the Gaussian window width parameter. Similarly, the effective temporal sample size was determined by selecting the data points at an interval of $1/\epsilon$ corresponding a effective time length of $\sim 5$ s, where, $\epsilon$ is the running average parameter from Eq. (1.7). Similar analysis was performed for the corresponding temperature profiles and integrated backscatter maps.

To test the dependence of echo decorrelation on tissue temperature, Pearson correlation coefficients were determined between log$_{10}$-scaled echo decorrelation and simulated tissue
temperature for the entire treatment duration for all treatments and for all spatial points in the image plane. Linear regression was performed between the tissue temperature and echo decorrelation parameter to test the ability of echo decorrelation to map tissue temperature. To determine the accuracy of temperature predictions made using the linear fit, the standard deviation of the prediction error was determined. For comparison, this analysis was repeated using the cumulative integrated backscatter maps to test the ability of integrated backscatter imaging to map tissue temperature. To assess the significance of the difference between correlation coefficients obtained for integrated backscatter and echo decorrelation, the Fisher $r$-to-$z$ transformation was applied to compute normalized $z$-scores. The difference between these $z$ values was normalized using the RMS value of the two individual standard errors. The significance of this difference was then assessed based on the cumulative distribution function of the normal distribution.

Dynamic compression was applied to the echo decorrelation data to assess if the resulting transformation could result in a better correlation between echo decorrelation and tissue temperature. Dynamic compression of the form $\Delta^a$ was applied to the echo decorrelation values, where $a$ is the exponential power. The exponential power parameter $a$ was varied through a range of values and corresponding transformed echo decorrelation values were determined. Pearson correlation coefficient values were determined between the transformed echo decorrelation and tissue temperature data. A value of $a$ corresponding the maximum correlation coefficient was selected for further analysis.

In order to test prediction of tissue temperatures greater than 40, 60, and 80° C by echo decorrelation and integrated backscatter imaging, receiver operating characteristic (ROC) curves were employed (Mast et al., 2008; Krzanowski and Hand, 2009). In this analysis, temperature elevations were predicted using echo decorrelation and integrated backscatter thresholds, so that all the spatial points exceeding a threshold were predicted to have exceeded certain temperature, and the rest lower. Using pixel-by-pixel comparison of cumu-
lative echo decorrelation and integrated backscatter images with corresponding segmented
temperature profiles, prediction success was determined for each pixel as a function of the
threshold. ROC curves were created by plotting the true-positive rate (sensitivity) against
the false-positive rate (1−specificity) for prediction of tissue temperature. Area under the
ROC curve (AUROC) was determined to assess the utility of echo decorrelation and in-
tegrated backscatter to predict temperature elevations. Assessment of prediction success
was performed by testing significance of the AUROC statistic using a general model for
the AUROC standard error (Hanley and McNeil, 1982). To compare predictions using echo
decorrelation with those using integrated backscatter, the significance of AUROC differences
between echo decorrelation and integrated backscatter was also computed for the three tem-
perature thresholds using DeLong’s method of comparing two correlated ROC curves (Hanley
and McNeil, 1983; DeLong et al., 1988).

Optimal echo decorrelation and integrated backscatter thresholds for prediction of tissue
temperatures were selected by using the threshold yielding equal false positives and false
negatives as described in Section 2.2.3. Sensitivity and specificity values were computed for
optimal decorrelation and integrated backscatter thresholds for prediction of tissue temper-
atures exceeding 40, 60, and 80° C.

To determine the thermal ablation prediction ability of echo decorrelation and integrated
backscatter imaging, ROC curves were employed in a manner similar to Chapter II and III.
The optimal echo decorrelation and integrated backscatter thresholds for the prediction of
thermal lesioning were selected by choosing the thresholds yielding equal false positives and
false negatives. The absolute RMS and percent error were computed between the predicted
and measured ablated areas.
4.3 Results

4.3.1 Temperature Simulations

Figure 4.4(a) shows a scatter plot of the measured area of ablation as a function of input voltage. Similarly, Figures 4.4(b) and (c) show scatter plots of the treatment time (time until treatment was ceased due to a large increase in tissue impedance) and the spatial maximum of the cumulative log$_{10}$-scaled echo decorrelation plotted against the applied voltage. Figures 4.4(d) and (e) show scatter plots of the spatial maximum log$_{10}$-scaled cumulative echo decorrelation plotted against the treatment time and ablated area. Applied voltage was insignificantly correlated with ablated area ($r = -0.046$, $p = 0.868$, $N = 15$) and treatment time ($r = -0.135$, $p = 0.630$, $N = 15$). The spatial maximum log$_{10}$-scaled echo decorrelation was not significantly correlated with applied voltage ($r = 0.345$, $p = 0.206$, $N = 15$), treatment time ($r = -0.144$, $p = 0.606$, $N = 15$), or ablated area ($r = -0.180$, $p = 0.519$, $N = 15$). These correlations were weak and insignificant possibly due to variability in the tissue properties and structure. However, a high correlation ($r = 0.940$, $p = 1 \cdot 10^{-7}$, $N = 15$) was observed between measured area and treatment time.

Figures 4.5(a)–(c) show the mean and standard deviation of the specific heat, thermal conductivity and electrical conductivity respectively estimated using UKF for $N = 15$ treatments as a function of tissue temperature. The mean and standard deviation of the coefficients ($k_0$, $c_0$ and $e_0$) used to produce the plots and corresponding coefficients of variation are listed in Table 4.4. Notably, while the mean values of thermal conductivity and specific heat were within the range of literature-reported measurements (Table 4.1), the electrical conductivity was higher than this range. This could be due to the addition of saline during the RFA experiments.

The temperature uncertainty due to imprecise knowledge of the thermocouple position was estimated as 3.32 °C. The uncertainty caused by electromagnetic interference on tem-
Figure 4.4: Scatter plots representing interdependence of various experimental parameters
(a) Ablated area plotted against applied voltages. (b) Treatment time plotted against applied voltage. (c) Spatial maximum of cumulative log₁₀-scaled echo decorrelation plotted against applied voltage. (d) Treatment time plotted against ablated area. (e) Spatial maximum of cumulative log₁₀-scaled echo decorrelation plotted against ablated area. (f) Spatial maximum of cumulative log₁₀-scaled echo decorrelation plotted against treatment time.
Figure 4.5: Mean and standard deviation of (a) Specific heat (b) Thermal conductivity (c) Electrical conductivity for $N = 15$ simulations, as estimated using UKF as a function of tissue temperature.

Table 4.4: Mean and standard deviation of UKF-estimated tissue properties for 15 RFA treatments.

<table>
<thead>
<tr>
<th></th>
<th>$k_0$ (W/m$^2$/°C)</th>
<th>$c_0$ (J/kg/°C)</th>
<th>$e_0$ (S/m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Values estimated from UKF</td>
<td>0.401 ± 0.037</td>
<td>3007 ± 145</td>
<td>0.463 ± 0.070</td>
</tr>
<tr>
<td>Coefficient of variation</td>
<td>9.22%</td>
<td>4.83%</td>
<td>15.35%</td>
</tr>
</tbody>
</table>
Table 4.5: Sensitivity of simulation outcomes (ablated area and tissue temperature) to changes in tissue parameters. The tissue parameters listed here correspond to the sigma points located at the edges and axis of the 3D cube representing the tissue parameter space.

<table>
<thead>
<tr>
<th>Thermal Conductivity (%)</th>
<th>Specific heat (%)</th>
<th>Electrical Conductivity (%)</th>
<th>Ablated Area (%)</th>
<th>Temperature °C</th>
</tr>
</thead>
<tbody>
<tr>
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<td>+43.30</td>
<td>+19.28</td>
<td>1.56</td>
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<td>-86.62</td>
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<td>-68.28</td>
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</tr>
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<td>+89.40</td>
<td>3.71</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>-43.30</td>
<td>-78.52</td>
<td>5.54</td>
</tr>
</tbody>
</table>

Temperature measurements was determined to be 0.53 °C. The combined uncertainty of the aforementioned effects on simulated tissue temperature was 3.36 °C. The sensitivity of simulation outcomes, i.e. ablated area and tissue temperature to input parameters is listed in Table 4.5. From the values reported in the table, an increase in thermal conductivity or specific heat resulted in a smaller ablated area. However, an increase in electrical conductivity resulted in a larger ablated area. The uncertainty associated with variations in thermal lesion size between nearby tissue sections on simulated tissue temperature was estimated to be 2.23 °C.

Figure 4.6(a) shows a scatter plot of ablation areas estimated by the finite element simulation vs. areas measured from gross tissue histology for all \((N = 15)\) treatments. The RMS error between the measured and simulated ablated area is 5.21 mm². To assess the
Figure 4.6: (a) Measured area vs. simulated areas for $N = 15$ RFA treatments. (b) Mean and standard deviation of simulated tissue temperature for all temperatures measured using thermocouples within 1 °C bands for all $N = 15$ experiments.

accuracy of temperature simulations, the measured tissue temperature was divided into bins with 1 °C width. The mean and standard deviation of the corresponding simulated temperature at the thermocouple location for each measured temperature bin was determined. Figure 4.6(b) shows the mean (solid line) and standard deviation (shaded area) of the simulated temperature plotted against the measured temperature at the thermocouple location. The RMS error between the simulated tissue temperatures and the measured temperature at the thermocouple position was 3.75 °C, which was only marginally greater than the combined uncertainty of 3.36 °C.

4.3.2 Echo Decorrelation Imaging

Figure 4.7(a) shows the instantaneous echo decorrelation measured during a representative RFA treatment at a single point ~ 1 mm from the RF electrode. Figure 4.7(b) shows
Figure 4.7: (a) Instantaneous echo decorrelation for a location near the RF probe for a representative treatment. Plotted in red is the result of applying the temporal running average filter on the data. (b) Corresponding cumulative $\log_{10}$-scaled echo decorrelation. (c) Simulated tissue temperature at the same location for a representative treatment.
the corresponding temporally averaged \( \log_{10} \)-scaled echo decorrelation parameter computed using Eq. 1.7. Also shown in the same figure is the cumulative \( \log_{10} \)-scaled echo decorrelation. Shown in Figure 4.7(c) is a plot of simulated tissue temperature for the treatment duration at the same location. Figure 4.7(a) shows an increase in decorrelation activity at high temperatures.

Figure 4.8(a) shows hybrid echo decorrelation images comprising B-mode and echo decorrelation maps for three representative treatments. The dashed lines show the ablation boundaries predicted by the optimal decorrelation thresholds at 40, 60, and 80 °C. Figure 4.8(b) shows corresponding hybrid integrated backscatter images for the same three treatments with the dashed lines depicting the ablation boundaries predicted by the optimal integrated backscatter thresholds estimated at 40, 60, and 80 °C. Figures 4.8(d) and (c) show the tissue section and temperature profile simulated using the UKF estimated tissue parameters. The dashed black lines in Figure 4.8(d) represent the ablation boundary determined using the gross discoloration of tissue. Qualitatively, higher echo decorrelation is observed in the ablated region compared to unablated regions.

Figure 4.9 shows the temporal evolution of \( \log_{10} \)-scaled echo decorrelation and corresponding tissue temperatures at 15 s, 20 s, and 60 s into treatment and at the end of treatment (90 s). Echo decorrelation is seen to increase as the treatment progressed, with a corresponding increase in tissue temperature.

Figure 4.10(a) shows the \( \log_{10} \)-scaled echo decorrelation plotted against the temperature simulated using tissue parameters estimated by the UKF. Echo decorrelation was significantly correlated with tissue temperature with a Pearson correlation coefficient of 0.516 (\( p \ll 10^{-14}, N = 60580 \)). The best linear fit between \( \log_{10} \)-scaled echo decorrelation and tissue temperature is given by

\[
T = 7.018 \cdot \log_{10}(\Delta) + 55.92. \tag{4.18}
\]
Figure 4.8: (a) The hybrid echo decorrelation images of three representative RFA treatments with dashed lines representing lesion boundaries predicted using optimum decorrelation thresholds for prediction of tissue temperatures greater than 40, 60, and 80 °C. (b) The hybrid integrated backscatter images with dashed lines representing lesion boundaries predicted using optimum integrated backscatter thresholds for prediction of temperatures greater than 40, 60, and 80 °C. (c) Corresponding temperature profiles simulated using the tissue physical parameters estimated by UKF. (d) Corresponding tissue sections with dashed black lines representing lesion boundaries.
Figure 4.9: Hybrid echo decorrelation images and tissue temperature for a representative RFA treatment. (a) After 15 s treatment. (b) After 20 s treatment. (c) 60 s treatment. (d) End treatment.
Figure 4.10: Scatter plots of (a) log_{10}-scaled echo decorrelation plotted against tissue temperature, (b) integrated backscatter plotted against tissue temperature.

The standard deviation of the difference between the simulated tissue temperature and the temperature estimated from the linear fit defined in Equation 4.18 is 12.23 °C. Similarly, Figure 4.10(b) shows a scatter plot of dB-scaled integrated backscatter plotted against the temperature simulated using tissue parameters estimated by the UKF. The line of best fit between integrated backscatter and tissue temperature is defined as

\[ T = 2.524 \cdot \text{IBS} + 24.01. \]  

(4.19)

The correlation coefficient between integrated backscatter and simulated tissue temperature is 0.567 \((p \ll 10^{-14}, N = 60580)\). The standard deviation of the difference between the simulated tissue temperature and the tissue temperature estimated from the linear fit defined in Equation 4.19 is 11.76 °C. These results indicate that both echo decorrelation and integrated backscatter are able to map tissue temperature with poor accuracy. However, integrated backscatter performed significantly better as a linear predictor of tissue temperature when compared to echo decorrelation \((z = -12.57, p \ll 10^{-14}, N = 60580)\).
Figure 4.11: Scatter plots of (a) echo decorrelation, (b) log\textsubscript{10}-scaled echo decorrelation, and (c) echo decorrelation with dynamic compression of the form $\Delta^{0.24}$ plotted against temperature simulated using the tissue parameters estimated using UKF.
Other forms of dynamic compression were attempted to improve the low correlation between echo decorrelation and tissue temperature. Figures 4.11(a) and (b) show the raw and log$_{10}$-scaled echo decorrelation data plotted against tissue temperature simulated using the tissue parameters estimated by the UKF. Figure 4.11(c) shows the raw echo decorrelation data transformed by $\Delta^a$, with $a = 0.24$ corresponding to the maximum correlation coefficient value plotted against tissue temperature. The correlation coefficient value between echo decorrelation data and tissue temperature was only marginally improved with this transformation ($r = 0.603$, $p \ll 10^{-14}$, $N = 60580$). The standard deviation of the difference between the simulated tissue temperature and the temperature estimated from the linear fit was 11.41 °C.

Results for the prediction of elevations in tissue temperatures greater than 40, 60, and 80 °C by echo decorrelation and integrated backscatter imaging using ROC analysis are listed in Table 4.6. Figures 4.12 (a and b) show ROC curves for prediction of tissue temperatures greater than 40, 60, and 80 °C using echo decorrelation and integrated backscatter imaging. Echo decorrelation imaging performed significantly better than integrated backscatter for prediction of tissue temperatures greater than 40, 60, and 80 °C ($p = 0.019$, $p \leq 10^{-14}$, $p \leq 10^{-14}$, $N = 60580$). Echo decorrelation imaging had better sensitivity and specificity values for prediction of tissue temperatures greater than 40, 60, and 80 °C compared to integrated backscatter imaging, implying that echo decorrelation performed better than integrated backscatter for prediction of ablative temperatures.

Figure 4.12(c) shows the ROC curves computed for the prediction of thermal lesioning in the tissue for both echo decorrelation and integrated backscatter imaging. AUROC values for prediction of thermal lesioning using echo decorrelation and integrated backscatter imaging were 0.919 and 0.893. The optimal decorrelation threshold for the prediction of thermal lesioning was −1.604. The optimal integrated backscatter threshold for prediction of thermal lesioning was 9.408 dB. Echo decorrelation performed significantly better than integrated
Figure 4.12: (a) ROC curves for prediction of tissue temperatures greater than 40, 60, and 80 °C using echo decorrelation. (b) ROC curves for prediction of tissue temperatures greater than 40, 60, and 80 °C using integrated backscatter. (c) ROC curves for prediction of lesion boundaries as observed from the gross tissue histology.
Table 4.6: Results of ROC analysis for prediction of tissue temperatures greater than 40, 60, and 80 °C for \( N = 15 \) in vitro RFA exposures.

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Echo Decorrelation Imaging</th>
<th>Integrated Backscatter Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUROC</td>
<td>Optimum threshold (log(_{10})-scaled)</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>40</td>
<td>0.871</td>
<td>−3.008</td>
</tr>
<tr>
<td>60</td>
<td>0.948</td>
<td>−1.988</td>
</tr>
<tr>
<td>80</td>
<td>0.966</td>
<td>−1.398</td>
</tr>
</tbody>
</table>

Table 4.7: Results of ROC analysis for prediction of ablation for \( N = 15 \) in vitro RFA exposures.

<table>
<thead>
<tr>
<th></th>
<th>AUROC</th>
<th>Optimum threshold (dB)</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echo decorrelation</td>
<td>0.919</td>
<td>−1.604</td>
<td>0.537</td>
<td>0.947</td>
</tr>
<tr>
<td>(log(_{10})-scaled)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Integrated backscatter</td>
<td>0.893</td>
<td>9.408 dB</td>
<td>0.469</td>
<td>0.940</td>
</tr>
</tbody>
</table>
Figure 4.13: (a) Scatter plot of the area predicted by the echo decorrelation. (b) Scatter plot of the area predicted by the integrated backscatter threshold.

backscatter for prediction of ablation with higher AUROC values \( p = 0.03, \ N = 495 \).

Figure 4.13 (a) and (b) show scatter plots of ablated areas predicted by the optimum echo decorrelation and integrated backscatter thresholds vs. ablated areas estimated using gross tissue histology for all 15 RFA experiments. The mean and standard deviation of ablated area for 15 RFA treatments was 131.67 \pm 77.85 \text{ mm}^2. The absolute RMS error for prediction of ablated area using the optimum echo decorrelation threshold was 96.42 \text{ mm}^2. The normalized RMS error between ablated area predicted by the optimum decorrelation threshold and measured ablated area was 63.40\%. Similarly, the absolute and normalized RMS errors for the prediction of ablated area using the optimum integrated backscatter threshold were marginally better with 48.34 \text{ mm}^2 and 31.78\% respectively.
4.4 Discussion

The feasibility of using ultrasound echo decorrelation imaging for predicting elevations in tissue temperature during radiofrequency ablation was investigated in this study. To this end, tissue temperature within the image plane must be known. Numerical methods such as finite element simulations are often used to understand, reproduce and predict experimental outcomes during RFA. These simulations are usually limited by uncertainty in tissue physical parameter measurements, location of blood vessels, and other sample-specific properties. Most RFA simulation studies have used measured values of tissue physical properties, reported in the literature, to simulate temperature elevation, resulting in substantial uncertainty (dos Santos et al., 2009). The UKF implementation proposed in this chapter allowed for the optimization of tissue parameters resulting in good agreement between simulation and experimental measurements, in the absence of precise knowledge of tissue physical parameters.

Previous studies focusing on optimization of RFA simulations for accurate computations have been performed for the purpose of patient specific treatment planning (Audigier et al., 2014; Chen et al., 2009). Optimization was performed using classical gradient-based (Chen et al., 2009) or gradient-free (Audigier et al., 2014) techniques, where a series of computations were performed until convergence to a minimum error was achieved. In contrast, the UKF-based optimization method presented here requires a fixed number of up-front computations to approximate the relationship between tissue physical parameters and the resulting ablated tissue area. This second-order polynomial approximation (Equation 4.9) between tissue parameters and ablated area allowed for minimization of the mean-squared error without further FEM simulations, reducing the computational cost. Use of GPU-based processing could further increase the speed of these computations. This method could also be applied to patient-specific treatment planning, allowing for prediction of thermal lesion formation.
and thus aiding in treatment guidance.

A major limitation of the present FEM implementation was the assumption of a homogeneous tissue medium. However, the liver is heterogeneous in nature, with structure including hepatic arteries and veins. The presence of large arteries and veins in the liver samples caused some non-uniform heating due to trapped blood and PBS, as observed in the tissue sections shown in Figure 4.8. As this heating is often directional, for simplicity these effects were ignored while performing temperature simulations. This simplification was a significant source of error in the temperature estimations, and thus contributed to the RMS error observed between simulation and measurements and thus affects the comparisons with echo decorrelation and integrated backscatter maps. Another limitation of the present model is that only one constraint was placed on this model, i.e the ablated area. Hence, the results converged to a small tolerance value. Adding additional constraints could result in more robust estimation of the tissue parameters, but could also possibly cause the solution not to converge within the small errors (< 2%) reported in this paper.

Figure 4.7 shows increased echo decorrelation activity at ablative tissue temperatures and relatively little echo decorrelation at sub-ablative tissue temperatures. Echo decorrelation imaging performed significantly better than integrated backscatter for prediction of temperatures greater than 40, 60, and 80 °C with greater AUROC, sensitivity, and specificity values at the optimum threshold. Although the sensitivity values remained low at the optimum threshold, the specificity values were high. At the optimum decorrelation threshold, where the number of false positives equals the number of false negatives, the positive and negative predictive values should equal the sensitivity and specificity values respectively (Section 2.2.3). The high specificity and negative predictive values obtained at this threshold are due in part to the relatively large number of instances where tissue temperature fell below 40, 60, and 80 °C. Still, the high AUROC values show capability for accurate prediction of regions where tissue temperature exceeds 40, 60, and 80 °C, which is useful for treatment
Elevations in tissue temperature are positively, but weakly correlated with echo decorrelation ($r = 0.51$). Although both echo decorrelation and integrated backscatter imaging methods were only able to map tissue temperature with low accuracy, both echo decorrelation and integrated backscatter were significantly correlated with tissue temperature. The low correlation coefficient value ($r = 0.51$) between echo decorrelation and tissue temperature could be due to movement of gas and vapor bubbles trapped in tissue. These potentially cause high decorrelation values in the unablated regions. Hence, for the development of echo decorrelation as a treatment monitoring tool, the effect of gas and vapor bubble formation in tissue needs to be characterized.

Figure 4.8 shows increased echo decorrelation in the ablated region and in the region with elevated tissue temperatures. The lesion area became increasingly hyperechoic at the end of treatment due to the formation of microbubbles at high tissue temperatures ($> 95 ^\circ\text{C}$) (Kruskal et al., 2001). The formation of microbubbles causes attenuation to increase dramatically, causing shadowing directly below it, resulting in loss of information in the shadowed region. Integrated backscatter is shown to be greatly affected by this effect. Figure 4.12(c) shows that although integrated backscatter showed a general trend of increasing with tissue temperature, it was also shown to decrease at ablative temperatures with negative IBS values. This could be attributed to shadowing. However, echo decorrelation is shown to map tissue temperatures below the threshold for microbubble formation ($> 95 ^\circ\text{C}$) as demonstrated in Figure 4.9. Also, high echo decorrelation was observed in the shadowed region corresponding to tissue ablation (Figure 4.8), implying that echo decorrelation can map ablation in spite of the formation of microbubble clouds.

Although integrated backscatter had a smaller prediction error when compared to echo decorrelation, integrated backscatter performed poorly at predicting ablative tissue temperatures, with lower AUROC for prediction of tissue temperatures greater than 40, 60, and
80 °C, when compared to ultrasound echo decorrelation. This could be attributed to acoustic shadowing. The higher sensitivity and specificity values for echo decorrelation indicate a better spatial correspondence with the ablated region. The smaller sensitivity and specificity values for integrated backscatter might indicate that integrated backscatter was sensitive to gas formation that might not always correspond to ablation (Gudur et al., 2012). Together with higher AUROC values for prediction of ablation, this implies that echo decorrelation imaging performs better than integrated backscatter imaging for both the prediction of ablation and ablative temperatures.

4.5 Conclusion

Significantly higher AUROC values were obtained for prediction of tissue temperatures greater than 40, 60, and 80 °C, using echo decorrelation when compared to integrated backscatter imaging. Although both echo decorrelation and integrated backscatter imaging methods were only able to map tissue temperature with low accuracy, both echo decorrelation and integrated backscatter were significantly correlated with tissue temperature. The higher sensitivity and specificity values obtained for the optimum decorrelation thresholds indicate a better spatial correspondence between the mapped echo decorrelation and regions where tissue temperature exceeded 40, 60, and 80 °C. Consistent with previous studies reported in Chapters II and III, sensitivity and specificity values for prediction of the ablated region were greater for echo decorrelation, indicating a better spatial correspondence. Together, these results indicate that echo decorrelation imaging performs better than integrated backscatter for prediction of ablation and ablative temperatures.
Chapter V

Conclusion

5.1 Results Summary

The overall goal of this dissertation was to investigate the feasibility of using ultrasound echo decorrelation imaging as a real-time ablation monitoring tool. To this end, the ability of echo decorrelation imaging to predict thermal lesion formation and temperature elevations in tissue was tested. The results of these studies and their possible limitations are summarized below.

To test the utility of ultrasound echo decorrelation as a predictor of thermal lesioning in tissue, echo decorrelation maps generated during thermal ablation were directly compared to gross tissue histology. For both in vitro and in vivo RFA experiments performed, significantly higher echo decorrelation values were observed in the ablated region when compared to the unablated region. This result suggests that echo decorrelation can differentiate between ablated and unablated regions. The high AUROC values obtained during the in vitro RFA treatments performed in Chapter II and IV (AUROC = 0.820, 0.919) and the in vivo RFA (AUROC = 0.833) and ultrasound ablation (AUROC = 0.776) treatments performed in Chapter III, demonstrate the utility of echo decorrelation imaging as a predictor of thermal lesion formation in tissue. Echo decorrelation imaging also performed significantly better
than integrated backscatter imaging for both in vitro and in vivo RFA experiments.

For accurate prediction of ablation, the optimum threshold was chosen such that the average predicted ablated area would equal the average measured ablated area. The optimum echo decorrelation thresholds predicted ablated area with higher sensitivity and specificity values compared to integrated backscatter thresholds, indicating a greater spatial correspondence with the thermal lesion formed. Both echo decorrelation and integrated backscatter thresholds generally had higher specificity values, but lower sensitivity values. Based on clinical need, a threshold with custom sensitivity and specificity can be applied for prediction of ablation. Increasing the echo decorrelation threshold would increase the number of negative predictions, thus increasing the specificity and decreasing the sensitivity. Decreasing the decorrelation threshold would increase the number of positive predictions, thereby decreasing the specificity and increasing the sensitivity.

A future goal of this project is to create a treatment algorithm for clinical use, where a treatment end-point would be for echo decorrelation in an ROI to exceed a decorrelation threshold chosen to predict ablation. Once the echo decorrelation in the entire ROI exceeded the decorrelation threshold, the ROI would be considered to be ablated and the treatment would be stopped. Clinically, it is desirable to have fewer false positives and false negatives. A false positive value indicates that the echo decorrelation threshold predicted an unablated region as ablated, while a false negative value indicates that the echo decorrelation threshold predicted an ablated region as unablated. Large numbers of false positives would cause the clinician to falsely predict ablation in unablated regions within the ROI, causing the treatment to stop prematurely, resulting in incomplete ablation. Hence, a threshold with high specificity value implying fewer false positive values (Eq 2.4), would be more useful for prediction of ablation clinically. Similarly, high specificity values are more useful for prediction of tissue temperatures greater than 40, 60, and 80° C.

However, this assessment does not take into consideration whether all the cells within the
segmented ablated region are dead. Use of vital staining techniques such as triphenyl tetrazolium chloride (TTC) and hematoxylin and eosin (H&E) assays could allow for an accurate assessment of echo decorrelation as a predictor of cell death (Karunakaran et al., 2012). Furthermore, the use of 4’,6-diamidino-2-phenylindole (DAPI) and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assays would allow for the detection of cell viability and apoptosis (Netto et al., 2006; Karunakaran et al., 2012). Echo decorrelation thresholds for prediction of viable and non-viable tissue could be estimated using the ROC analysis in a manner similar to the ones described in Chapters II, III and IV. The goal for such a study would be to develop a predictive model using echo decorrelation imaging to classify regions of irreversible cell death and viable tissue for real time treatment monitoring and control. Decorrelation thresholds estimated this way could potentially be used as end points for the prediction of thermal lesioning in the tissue. Although the results from the ROC analysis employing histological staining to assess for cell viability are not expected to be substantially different from the results reported in this dissertation, they could provide more accurate estimation of echo decorrelation thresholds for the prediction of ablation.

The high AUROC values obtained from the ROC analysis performed in Chapter IV demonstrate the capability of ultrasound echo decorrelation imaging for prediction of tissue temperatures greater than 40, 60, and 80 °C. Although both echo decorrelation imaging and integrated backscatter imaging methods were only able to map tissue temperature with low accuracy, both echo decorrelation and integrated backscatter were significantly correlated with tissue temperature. The movement of trapped gas and vapor bubbles causes high echo decorrelation values in unablated regions, resulting in a low correlation coefficient between echo decorrelation and tissue temperature. Hence, the effect of gas and vapor formation on echo decorrelation should be investigated.

Respiratory motion is an important source of error for most ultrasound treatment monitoring methods reported in literature. The relative importance of tissue motion as a source
of artifactual echo decorrelation was assessed by implementing the motion gating algorithm reported in Chapter III during \textit{in vivo} RFA experiments. Motion gating significantly reduced the echo decorrelation in both ablated and unablated regions. Still, echo decorrelation in the ablated region was significantly greater than in the unablated region. Although the effect of tissue motion was mitigated using motion gating, motion induced decorrelation may mask some heat induced decorrelation. Effects of tissue motion and electronic noise could potentially be compensated by the motion compensation algorithm described in Hooi et al. (2015). This algorithm allows for accurate estimation of motion induced decorrelation based on the imaging system’s beam functions, which can be simulated or measured (Hooi et al., 2015). However, this method relies on \textit{a priori} knowledge of motion induced echo decorrelation. Echo decorrelation due to in-plane and out-of-plane motion, strain and electronic noise can be estimated directly from pulse-echo image data taken prior to ablation, and can be compensated using the method described in Hooi et al. (2015). The feasibility of this method has been demonstrated during \textit{in vitro} and \textit{in vivo} ultrasound ablation studies reported by Fosnight et al. (2014a,b).

For the utility of ultrasound echo decorrelation imaging as a treatment monitoring and control tool, physical mechanisms behind echo decorrelation imaging must be well understood. Hooi et al. (2015) demonstrated through simulations that echo decorrelation approximates the decoherence spectrum of local tissue reflectivity, providing means to quantify heat induced changes in the scattering medium. These changes include structural changes in the tissue that can be directly related to degree of temperature rise in the tissue, dissolution of gas, and tissue vaporization (Nahirnyak et al., 2010; Gudur et al., 2012). Structural changes that occur in tissue during thermal ablation include cellular swelling, microvascular changes, denaturation of collagen and other proteins, and microstructural tissue damage due to vaporization (Kruskal et al., 2001; Wright and Humphrey, 2002; Bischof and He, 2006). These changes directly affect tissue properties such as attenuation, sound speed, and its elasticity.
Knowledge of the effect of these sources on echo decorrelation would be useful for treatment monitoring and control.

5.2 Future Directions

An important future step toward clinical thermal ablation monitoring is implementation of echo decorrelation imaging in real time. The high specificity values obtained for RFA show the potential of echo decorrelation imaging for real-time prediction of heat-induced thermal damage, with applications in thermal ablation monitoring. Computation of echo decorrelation images requires only a few arithmetic and filtering operations applied to beamformed ultrasound echo signals, comparable to processing performed by current imaging systems for conventional B-mode and color Doppler imaging. Thus, implementation of real-time echo decorrelation imaging on clinical pulse-echo scanners would require no additional hardware and relatively few software modifications.

As thermal ablation is an intrinsically three-dimensional problem requiring precision for the destruction of a tumor in its entirety, a 3D treatment guidance and monitoring modality is desirable. Because echo decorrelation images are computed directly from the same pulse-echo data used for 3D B-mode imaging, the echo decorrelation imaging algorithm can potentially be implemented on any 3D ultrasound imaging system with sufficiently high frame rate with low computational cost. This would ultimately allow detailed real-time, 3D monitoring and control of any clinical thermal ablation procedure.
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