

# High-Intensity Focused Ultrasound Thermal Lesion Detection Using Entropy Imaging of Ultrasound Radio Frequency Signal Time Series

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## Abstract

**Background:** During the past few decades, high-intensity focused ultrasound (HIFU) modality has been gaining surging interest in various therapeutic applications such as non- or minimally-invasive cancer treatment. Among other attributes, robust and real-time HIFU treatment monitoring and lesion detection have become essential issues for successful clinical acceptance of the modality. More recently, ultrasound radio frequency (RF) time series imaging has been studied by a number of researchers. **Materials and Methods:** The objective of this study is to investigate the applicability of entropy parameter of RF time series of ultrasound backscattered signals, a. k. a. Entropy imaging, toward HIFU thermal lesion detection. To this end, five fresh *ex vivo* porcine muscle tissue samples were exposed to HIFU exposures with total acoustic powers ranging from 30 to 110 Watts. The contrast-to-speckle ratio (CSR) values of the entropy images and their corresponding B-mode images of pre-, during- and post-HIFU exposure for each acoustic power were calculated. **Results:** The novelty of this study is the use of Entropy parameter on ultrasound RF time series for the first time. Statistically significant differences were obtained between the CSR values for the B mode and entropy images at various acoustic powers. In case of 110 Watt, a CSR value 3.4 times higher than B-mode images was accomplished using the proposed method. Furthermore, the proposed method is compared with the scaling parameter of Nakagami imaging and same data which are used in this study. **Conclusion:** Entropy has the potential for using as an imaging parameter for differentiating lesions in HIFU surgery.

**Keywords:** Contrast-to-speckle ratio, entropy imaging, high intensity focused ultrasound, ultrasound radio frequency time series analysis

## INTRODUCTION

In recent years, a number of technological innovations have come to practice to reduce the level of invasiveness in various surgical procedures. High-intensity focused ultrasound (HIFU) is a notable example of such techniques applied in non- or minimally-invasive treatments in areas such as oncology, general surgery, and cosmetic surgery.<sup>[1-3]</sup>

In a typical HIFU treatment, a thermal lesion can be produced in a region of tissue where a tumor exists. It results in an irreversible tissue coagulation necrosis in the region of interest (ROI). Thus, monitoring the process of creating a thermal lesion is very important for controlling the position of the probe, coagulated volume, lesion size, and also estimating the degree of coagulation.

Some of the methods for monitoring and controlling the HIFU lesion creation process in tissue are using X-ray, computed tomography, and magnetic resonance imaging.<sup>[4]</sup> The latter provides high quality and high spatial resolution images. However, imaging by these methods is time-consuming and relatively expensive in comparison with ultrasound imaging. On the other hand, the real-time feedback for highly accurate positioning, heating control, high temporal resolution, low cost, and safety of the ultrasound imaging method have made it common and useful for HIFU treatment monitoring and control.<sup>[5]</sup>

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Generally, lesion detection during a typical HIFU thermal therapy is more feasible than after HIFU exposure. Creation and collapsing of microscopic bubbles in the focal region during thermal induction of HIFU is the cavitation effect in the tissue that provides an effective method<sup>[6]</sup> of HIFU focal region detection.

In the past few decades, ultrasound tissue characterization, in general, and HIFU lesion detection, in particular, have been active topics of research. The basis of most ultrasound-based tissue characterization methods is that the backscattered ultrasound radio frequency (RF) echoes carry tissue dependent information that can be used for detecting the type of tissue.

A few studies have been conducted for analyzing ultrasound RF data that made the basis of the method proposed in our study. Moradi *et al.*<sup>[7]</sup> separated different types of animal tissues using RF echo signals acquired from a tissue sample. Imani *et al.*<sup>[8]</sup> proved that ultrasound RF time series imaging could correctly distinguish the ablated from nonablated tissue.

In two articles authored by Hughes,<sup>[9,10]</sup> he verified that ultrasound signals could be analyzed with the use of entropy to characterize the changes in the microstructures of scattering media such as biological tissue. If the HIFU thermal lesion is formed, the structures of backscattered RF echoes in the same point at pre- and post-HIFU exposures are become significantly different. The main purposes of this study were (i) examining the entropy parameter of the backscattered RF echoes to estimate the location of the lesion, and (ii) comparing the contrast-to-speckle ratio (CSR) of the B-Mode and entropy-generated images. Entropy was measured in three situations: pre-HIFU, during- HIFU and post-HIFU (after 10 min) exposures. Considering post- and pre-HIFU exposures and entropy results, the lesion location was estimated for different acoustic powers of 30, 50, 70, 90, and 110 Watts.

## MATERIALS AND METHODS

### Image-guided high-intensity focused ultrasound system

A full description of the custom-built image-guided HIFU system used in this study has been given elsewhere.<sup>[11,12]</sup> A 192-element confocal endocavity convex array probe (EC9-5/10, Ultrasonix) of the ultrasound imaging system (Sonix RP, Ultrasonix, Richmond, BC, Canada) operating at a center frequency of 6.5 MHz with a bandwidth of 3 MHz, was fixed in a confocal configuration in a hole in the center of the HIFU transducer to perform real-time imaging and RF echo data collecting. The HIFU transducer is a single-element concave piezo-composite transducer operating at 1 MHz with an aperture diameter of 125 mm and focal depth of 100 mm. The lateral width and axial length of the HIFU focal volume were measured in water to be 2 and 8 mm at full width at half maximum, respectively.<sup>[12]</sup> Considered size of the ROI in this study is based on the focal depth. The considered size of ROI includes the lesion and its surrounding area.

### Data collection

Five fresh *ex vivo* porcine muscle tissue samples were exposed to HIFU ablation at different total acoustic powers of 30, 50, 70, 90, and 110 W, as described in a previous publication.<sup>[11]</sup> At each acoustic power, the RF echo data and B-Mode images were recorded in three different instances of before-, during- and 10 min after HIFU exposure by a frame rate of 16 Hz. During HIFU exposure, the RF data were recorded when the HIFU transducer was briefly turned off for 120 ms to avoid acoustic and electrical interference between the HIFU transducer and the ultrasound imaging probe. The postexposure data were recorded 10 min after the end of exposure to remove the effect of cavitation microbubbles that may be generated during the HIFU exposure in the focal region.

Each acquired RF data frame contained 192 lines with 4680 samples per line. The axial step size between two consecutive data points is about 0.0192 mm which results in the overall tissue depth of 90.1 mm in this study. The sampling rate of the RF echo data was 40 MHz and two neighboring scan lines were 0.33 mm apart.<sup>[11]</sup>

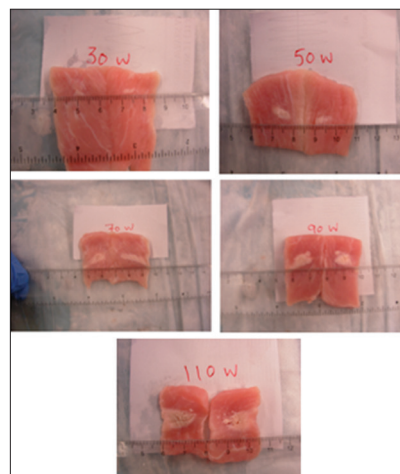
### High-intensity focused ultrasound experiments

The results of this study were obtained from five *ex vivo* porcine muscle tissue samples. Figure 1 shows the tissue samples after HIFU ablation when they were cut open to show the induced thermal lesions.<sup>[11]</sup>

### Radio frequency time series analysis

A time series is a sequence of data points, typically consisting of successive measurements made over a time interval. Time series analysis comprises methods for analyzing time series data to extract meaningful statistics and other characteristics of the data.<sup>[8,13]</sup>

In this study, it is hypothesized that if a specific region of the tissue undergoes to structural changes due to HIFU energy exposure, the time series of backscattered RF echo signals from the region would carry the information pertinent to



**Figure 1:** Tissue samples after high-intensity focused ultrasound ablation at different acoustic powers of 30, 50, 70, 90, and 110 W

tissue structural properties. This information differs for the coagulated and noncoagulated regions of tissue.<sup>[7,14]</sup>

In RF signal time series analysis, the values of RF echo signals measured over time from a fixed point of tissue in three instances of pre-HIFU, during-HIFU and post-HIFU (after 10 min) exposures were used to form the time series signal of each section. The length of time series signal related to each instance of data collection is equal to the corresponding frame number. Figure 2 shows the definition of time series used in this study.

### Shannon entropy

The present study considered entropy parameter to enhance the HIFU lesion detection in the tissue. In the information theory, the measurement of the average uncertainty of time-series in a signal is considered an entropy function.<sup>[9]</sup> To this end, the Shannon Entropy  $H$ , as given in Equation (1), is defined as a negative summation of the probability of a given random amplitude ( $p_i$ ) multiplied by the base 2 logarithm of ( $p_i$ ).<sup>[9]</sup>

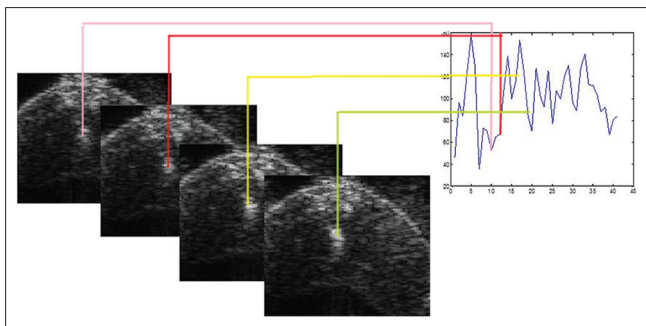
$$H = - \sum_{i=1}^N p_i \log_2 p_i \quad (1)$$

In signal analysis theory, the entropy is a measure of similarity of the sample values of a signal. When all amplitude values in time series signals are the same, the value of entropy is zero and when every amplitude value is unique, the value of entropy is 1.<sup>[15]</sup>

It is well-accepted that the distribution of the ultrasound RF echo time series signals conform to the Rayleigh distribution.<sup>[16]</sup> In this research, the entropies of time series before-, during- and 10-minute after HIFU exposure were calculated in each point of the selected tissue region individually. The entropy results produced a 2D matrix with dimensions representing the ROI in tissue which is shown as a 2D image. The resulting matrix values of during-and post-exposures were divided by corresponding resulting matrix values of pre-exposure to improve the image contrast.

### Contrast-to-speckle ratio

The accuracy of the HIFU lesion detectability can be quantified using the CSR parameter as proposed by Patterson *et al.*<sup>[17]</sup> CSR measurements are used to make a comparison between B-mode



**Figure 2:** Samples of radio frequency echo signals, collected over time from a fixed spot of tissue under continuous emission of ultrasound, form one radio frequency signal time series

images and the results of the proposed method. The CSR is calculated by defining two equal sized regions of interest as given by equation (2):

$$CSR = \frac{(S_0 - S_i)/S_0}{\sqrt{(\sigma_0^2 + \sigma_i^2)}} \quad (2)$$

Where  $S_0$  and  $\sigma_0^2$  are the average and variance of the signal values outside the thermal lesion, respectively.  $S_i$  and  $\sigma_i^2$  are the average and variance of the signal values inside the thermal lesion at the same window size, respectively.

### Nakagami distribution

In previous studies, it has been demonstrated that the Nakagami parameter and the scaling parameter of the Nakagami distribution can be effectively used to detect HIFU induced thermal lesions.<sup>[18,19]</sup> In addition, it was reported that the scaling parameter of the Nakagami distribution led to better results in lesion detection compared with the Nakagami parameter.<sup>[19]</sup> To compare our method in estimating the location and dimension of the thermal lesion, in this study, we computed the scaling parameter of the Nakagami distribution for the first frame of the post-HIFU and pre-HIFU exposures for each acoustic power. Equation (3) gives the Nakagami probability density function.<sup>[20]</sup>

$$f(r) = \frac{2m^m r^{2m-1}}{\Gamma(m)\Omega^m} \exp\left(-\frac{mr^2}{\Omega}\right) \quad (3)$$

$$r \geq 0, m \geq \frac{1}{2}, \Omega \geq 0$$

Where the symbol  $r$  denotes possible values for the random variable  $R$  of the envelope of the backscattered signal,  $\Gamma(\cdot)$  is the gamma function,  $m$  is the Nakagami parameter, and  $\Omega$  is the scaling parameter.  $m$  and  $\Omega$  are given by the following equations:

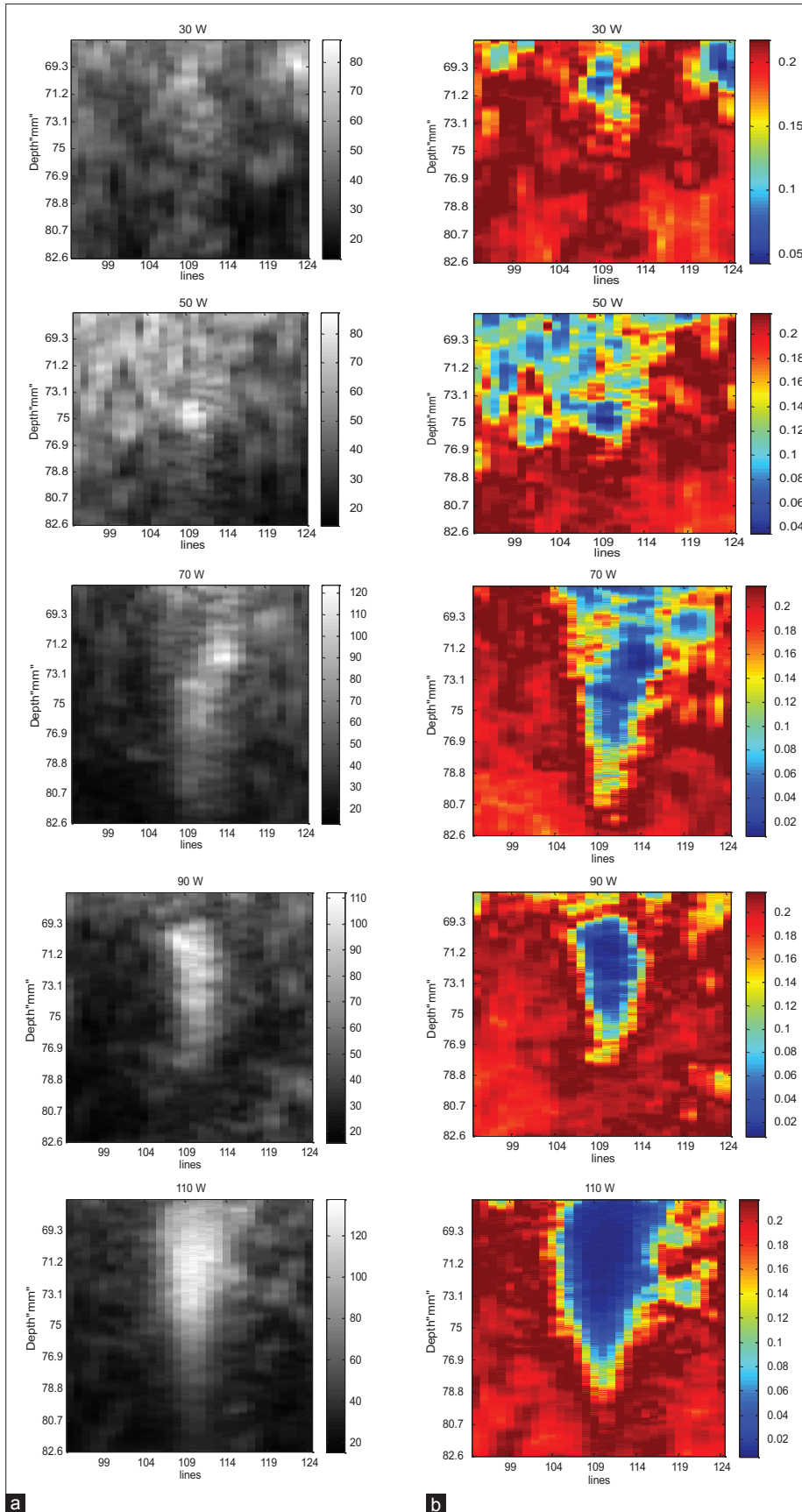
$$m = \frac{[E(R^2)]^2}{E[R^2 - E(R^2)]^2} \quad (4)$$

$$\Omega = E(R^2) \quad (5)$$

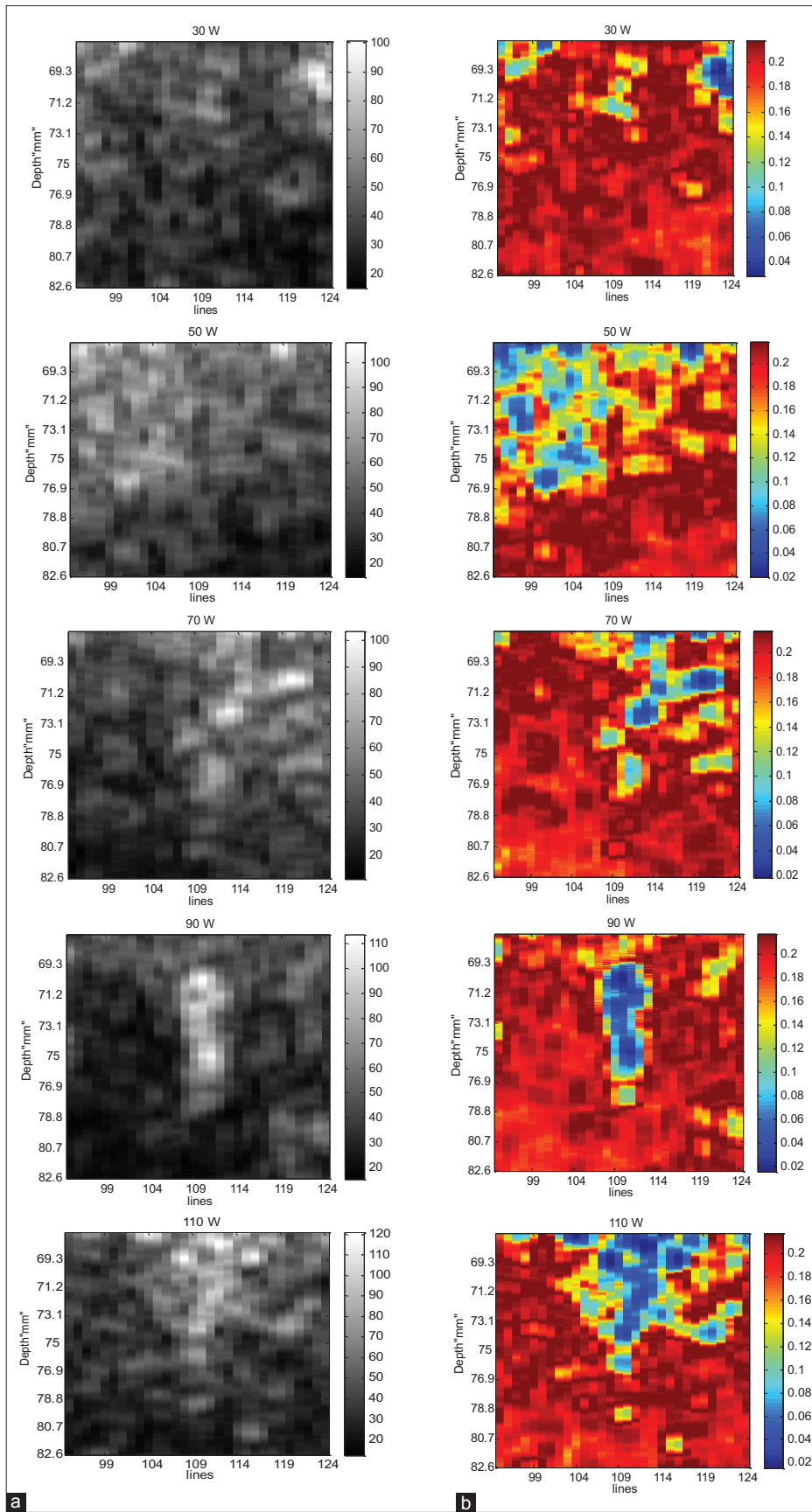
In equations (4) and (5),  $E(\cdot)$  is the statistical average and  $R$  represents the envelope of the backscattered signal.

## RESULTS

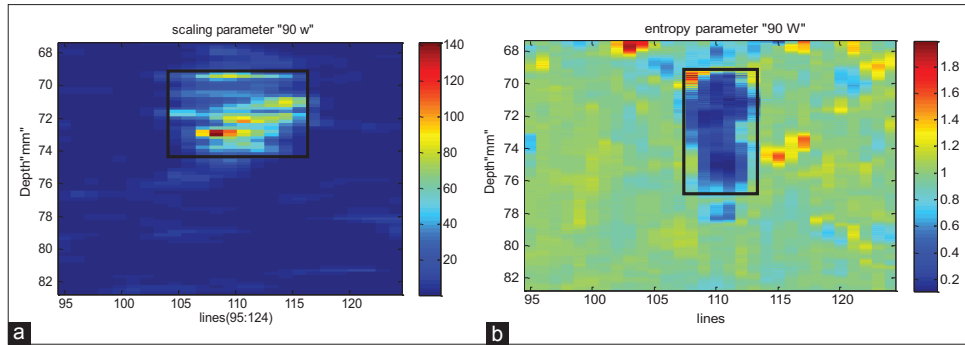
Figures 3 and 4 show the results of B-mode images and their corresponding entropy images in two instances of during- and post-exposure, respectively. According to Figures 3 and 4 in the ablated region of both during- and post-exposure, decreasing the amount of entropy is seen. The lower value of entropy could be due to the changed tissue structure in effect of HIFU exposure. Furthermore, it can be said that as the tissue temperature increases, tissue particles get more dependent and becomes more homogeneous. Hence, backscattered RF echo amplitudes become more uniform in comparison to before exposure when backscattered RF echo amplitudes are more random in nature.



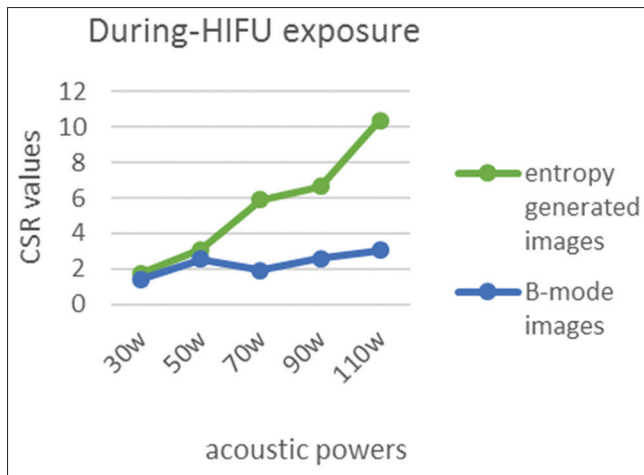
**Figure 3:** During high intensity focused ultrasound exposure images (a) B-mode images of selected region of interest at different acoustic powers of 30, 50, 70, 90, and 110 W. (b) Generated images based on the Shannon entropy



**Figure 4:** Post high intensity focused ultrasound exposure images (a) B-mode images of selected region of interest at different acoustic powers of 30, 50, 70, 90, and 110 W. (b) Generated images based on the Shannon entropy



**Figure 5:** The ratio of the estimated post- to pre-values of selected region of interest and their corresponding size of lesion at acoustic power of 90 W. (a) Scaling parameter and (b) entropy parameter maps



**Figure 6:** Contrast-to-speckle ratio values of B-mode images and entropy images at different acoustic powers of 30, 50, 70, 90, and 110 W

To prepare data for analyzing the scaling parameter, the Hilbert transform of each scan line was taken to obtain the envelope image. The scaling parameter of the first frame of pre- and post-HIFU exposure for each acoustic power was calculated using equation (5). The scaling images were constructed using a rectangular moving window whose axial length was equal to the wavelength of the 4 MHz ultrasound beam (0.385 mm), and the lateral width spans three scan lines (3 mm × 0.33 mm). RF time series data were used in generating the entropy image. In other words, all data frames of pre-, during-, and post-HIFU instances were used to construct a unique image at each acoustic power separately. Figure 5 shows the result of the entropy and the scaling parameter images. Figure 5a is the map of the average ratio of the post-exposure scaling parameter divided by the pre-exposure value, and Figure 5b is the map of the post-exposure entropy value divided by the pre-exposure value. As it is seen in Figure 5, the scaling parameter did not properly detect the location of the lesion.

Figures 6 and 7 compare the CSR values of B-mode and entropy images at two instances of during- and post-HIFU exposures, respectively. The CSR is calculated by defining two regions of the same size inside and outside the thermal lesion in each instance. During- and post-HIFU window sizes

are 51 pixels axially and 3 lines laterally equal to at each stage in the ROI. Figures 6 and 7 demonstrate the improvement of CSR values using an entropy imaging method over the B-mode imaging during- and post-HIFU exposure. The proposed method provided better CSR in each acoustic power. In the acoustic power of 110 W, for example, the CSR value during ablation in entropy images was 10.3489, almost 3.4 times greater than B-mode images with a CSR value of 3.0536.

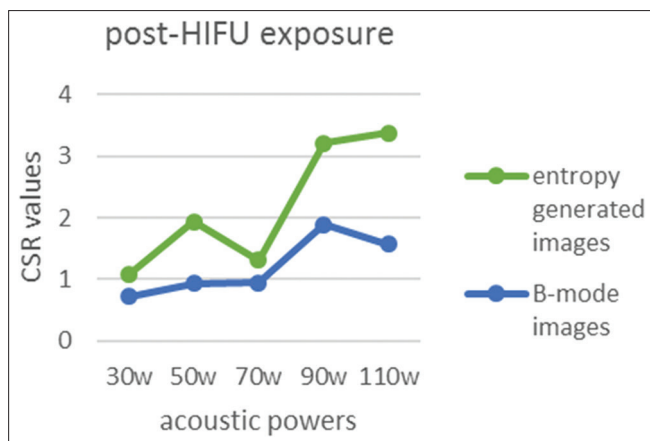
## DISCUSSION

Results obtained in this study, demonstrate that the entropy imaging method could result in higher CSR values over the standard B-mode images and the Nakagami scaling images reported by Rangraz *et al.*<sup>[19]</sup> In entropy imaging, the thermal lesions were fairly well detectable both during- and post-HIFU exposure. As mentioned earlier, in equation (1) entropy is a negative summation of the probability of a signal multiplied by the base 2 logarithm of the probability. This means that unlike the standard B-mode and Nakagami imaging, the amplitude value of the signal does not have any effect on the outcome. However, in this study, to construct the B-mode and Nakagami images, the envelope of the temporal signal obtained by calculating the Hilbert transform of each scan line. In addition, the effect of different acoustic powers in tissue coagulation could be assessed in entropy generated images.

The main reason for studying the 10 min post exposure was minimizing the effects of cavitation, tissue degassing and boiling bubbles that are typically generated in the focal region during the HIFU exposure, especially at higher acoustic power levels. The induced gas bodies will scatter, reflect or distort the HIFU beam and could lead to a false determination of the exposed region position during HIFU exposure.

## CONCLUSION

In this study, a new method of RF echo signal time series analysis using the entropy parameter was presented. The main objective of this study was to detect HIFU-induced thermal lesions in an *ex vivo* tissue model at different total acoustic powers. Based on the results obtained, the generated entropy images provide higher contrast in detecting HIFU



**Figure 7:** Contrast-to-speckle ratio values of B-mode images and entropy images at different acoustic powers of 30, 50, 70, 90, and 110 W

thermal lesions in comparison with the B-mode images at each acoustic power. Moreover, the proposed entropy method yields higher thermal lesion detectability comparing to the Nakagami imaging.

Further studies are suggested to evaluate the effect of temperature by adding a quantitative thermometry method such as thermocouples. Moreover, extending the study to *in vivo* animal studies which includes blood flow and tissue motion effects is proposed.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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