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Non-invasive estimation of hyperthermia temperatures with ultrasound

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Abstract

Ultrasound is an attractive modality for temperature monitoring because it is non-ionizing, convenient, inexpensive and has relatively simple signal processing requirements. This modality may be useful for temperature estimation if a temperature-dependent ultrasonic parameter can be identified, measured and calibrated. The most prominent methods for using ultrasound as a non-invasive thermometer exploit either (1) echo shifts due to changes in tissue thermal expansion and speed of sound (SOS), (2) variation in the attenuation coefficient or (3) change in backscattered energy from tissue inhomogeneities. The use of echo shifts has received the most attention in the last decade. By tracking scattering volumes and measuring the time shift of received echoes, investigators have been able to predict the temperature from a region of interest both theoretically and experimentally in phantoms, in isolated tissue regions *in vitro* and preliminary *in vivo* studies. A limitation of this method for general temperature monitoring is that prior knowledge of both SOS and thermal-expansion coefficients is necessary. Acoustic attenuation is dependent on temperature, but with significant changes occurring only at temperatures above 50°C, which may lead to its use in thermal ablation therapies. Minimal change in attenuation, however, below this temperature range reduces its attractiveness for use in clinical hyperthermia. Models and measurements of the change in backscattered energy suggest that, over the clinical hyperthermia temperature range, changes in backscattered energy are dependent on the properties of individual scatterers or scattering regions. Calibration of the backscattered energy from different tissue regions is an important goal of this approach. All methods must be able to cope with motion of the image features on which temperature estimates are based. A crucial step in identifying a viable ultrasonic approach to temperature estimation is its performance during *in vivo* tests.

Keywords: *Diagnostic ultrasound, hyperthermia, non-invasive thermometry*

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Introduction

Hyperthermia is a cancer treatment in which tumours are elevated to cytotoxic temperatures (41–45°C) in order to aid in their control [1, 2]. Hyperthermia has also been shown to be a viable adjunct to chemotherapy and radiotherapy [1–7]. Other types of thermal therapy, such as high temperature ablation therapies, are being investigated as well [8–12].

A major limitation of thermal therapies, however, is the lack of detailed thermal information available to guide the therapy [1, 2, 6, 13–17]. Temperatures are routinely measured invasively, but only sparse measurements can be made. The limited number of measurements may result in less information than is necessary to produce satisfactory temperature distributions in order to assess thermal dosimetry properly [6, 14]. With the advent of multi-element heating devices, there is increased need for temperature measurements that could provide detailed feedback about temperature distributions. This information in real time would considerably improve the ability to deliver consistently effective temperature distributions [18–22].

To meet the capability of present and forthcoming heating technologies for hyperthermia, a clinically useful method is needed to measure 3D temperature distributions to within 0.5°C in 1 cm^3 volumes. A non-invasive method for volumetrically determining temperature distribution during treatment would greatly enhance the ability to uniformly heat tumours at therapeutic levels in patients receiving hyperthermia treatment [23]. Many investigators have looked at ways of measuring temperature non-invasively. Possible methods include impedance tomography [24], microwave radiometry [25] and magnetic resonance imaging (MRI) [8, 26]. The required accuracy and spatial resolution can probably be achieved with MRI, but it is expensive and may be difficult to use along with some heating therapies [26]. Nevertheless, at present MRI is the most advanced clinical technology for non-invasive monitoring of thermal therapies [27, 28].

Ultrasound is a non-ionizing, convenient and inexpensive modality with relatively simple signal processing requirements. These attributes make it an attractive method to use for temperature estimation if an ultrasonic parameter, which is dependent on temperature, can be found, measured and calibrated. Methods for using ultrasound as a non-invasive thermometer fall into three categories: (1) Those based on echo-shifts due to changes in tissue thermal expansion and speed of sound (SOS), (2) Those that use the measurement of acoustic attenuation coefficient and (3) Those that exploit the change in backscattered energy (CBE) from tissue inhomogeneities.

This study explores ongoing efforts in temperature estimation using shifts in echo position, variations in ultrasonic attenuation and changes in backscattered energy that occur due to thermal effects. It concentrates on approaches that appear to have the greatest potential for monitoring temperatures in the hyperthermia (41–45°C) range.

Thermal effects on backscattered ultrasound

As tissue is interrogated with ultrasound during heating in the hyperthermia range, at least two effects are easily seen in both backscattered signals and in pulse-echo images. They are a shift in apparent position of scattering regions and changes in signal strength from those regions. These changes are associated with thermal effects on SOS in tissue and on tissue attenuation and backscatter properties.

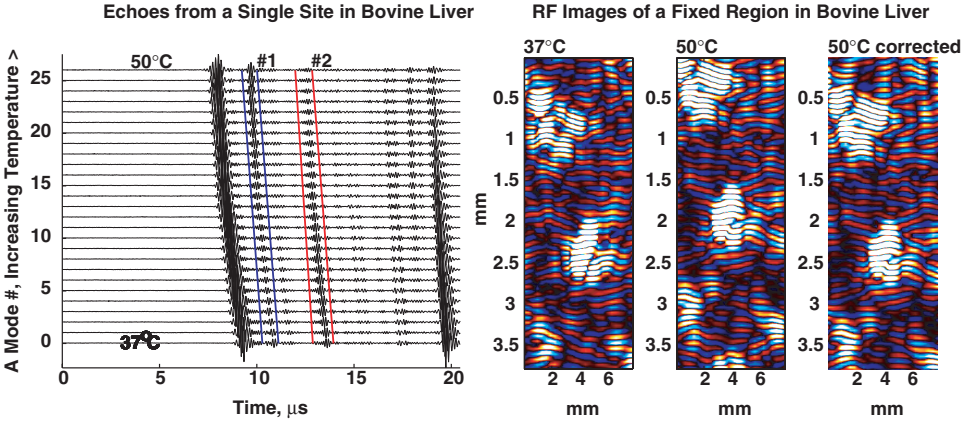

Figure 1. Changes in backscattered ultrasound with temperature. (Left) Echoes measured from a single site in a 1 cm thick sample of fresh bovine liver at temperatures from 37–50°C. The two delineated echoes (indicated by bands marked #1 and #2) shift with temperature have energies that appear to change with temperature (similar to Figure 4 in [29]). (Right) RF images of a fixed region in bovine liver showing apparent motion from 37–50°C. The right panel shows the image at 50°C after motion compensation.

Echo shifts and changes in signal strength

Backscattered signals and images from samples of bovine liver, homogeneously heated in a water bath, are shown in Figure 1. As temperature was increased, the position of the tissue interface and scattering regions within the tissue changed in echo signals from the specimen. Apparent motion occurs in part because SOS changes with temperature. It was, however, assumed fixed at $1540\,\mathrm{m\,s^{-1}}$ by the imaging system. There were also clear changes in signal strength with temperature. The rectangular region in the RF images of Figure 1 highlights an image feature that appears to move as the specimen was heated. Movement in the axial direction in images is similar to the shifts in echo signals. Apparent motion towards the transducer is consistent with the change in SOS in the water bath. The images show, however, that there is also an apparent lateral movement, presumably due to changes in the tissue.

Apparent image motion and tracking echo shifts

Quantifying the time dependence of echo positions is important because the echo shift is the basis for much of the recent work on temperature estimation. In addition, in order to compare signal strengths under consistent conditions, apparent motion of scattering regions must be tracked so that compensation for apparent motion can be applied. Echo tracking is also important for any temperature estimation method because a key challenge for *in vivo* studies is measurement of thermal effects in the presence of real motion in the tissue of a living system in addition to apparent and actual motion from thermal effects.

In ultrasonic imaging, techniques for motion estimation, that is for estimation of the displacement between two image regions, comprise an active field of research [30–34] and have been used successfully for elasticity imaging, phase aberration correction, blood velocity estimation and other applications. In these areas, motion estimation is typically called speckle tracking or time-delay estimation. Work based on exploiting thermal effects

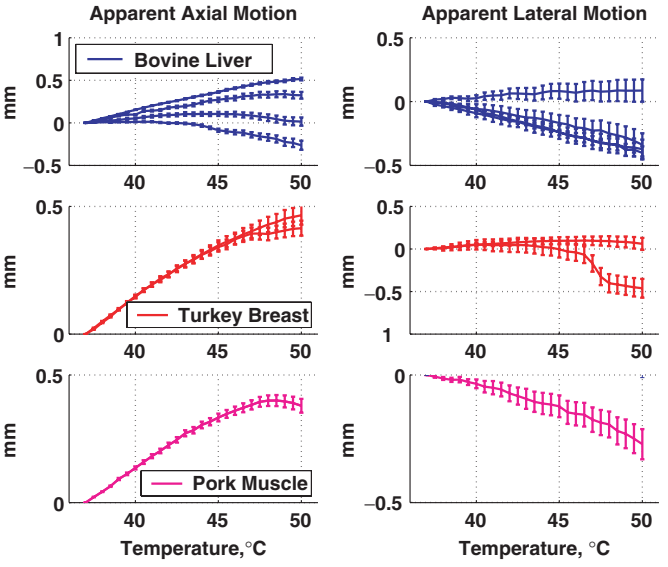

Figure 2. Apparent motion of tissue in the axial and lateral dimensions due to temperature. Each plot is the mean of motion in eight regions ± the standard error of the mean for each tissue specimen. Results from four bovine liver samples are shown in the upper panels, for two turkey breast and one pork muscle samples in the lower panels.

that induce tissue strain has primarily been aimed at guiding focused ultrasound therapies rather than at accurate estimation of temperatures [35–38].

Measurement of echo shifts and tracking of apparent motion has been based on correlation techniques. Employing RF signals permits the use of cross-correlation as a similarity measure for automatic tracking of regions as a function of temperature. The result of maximizing 2D cross-correlation to estimate displacement and then shifting and resampling images to apply the displacement is shown in the images of Figure 1.

Apparent tissue motion in both axial and lateral directions from eight overlapping regions in 10×40 mm images of four specimens of bovine liver, two of turkey breast and one of pork-rib muscle is shown in Figure 2. Tissue features appear to move closer to the transducer in all but two of the liver specimens, which is consistent with the increase in the SOS in the water path between the tissue and transducer. In those two specimens presumably non-uniform thermal effects in tissue were larger than the changes due to SOS changes in the water bath.

The non-uniform component of tissue motion is indicated by the lateral changes. That tissue-dependent component also contributed to the axial motion, as seen particularly at temperatures above 47°C. Note too the difference in the apparent lateral motion in the two specimens of turkey breast. In the one that exhibited nearly constant lateral motion, tissue fibres were parallel to the array of transducer elements. In the one that showed a change of several tenths of a millimetre near 47°, striations were perpendicular to the array.

Potential pitfalls with motion-estimation techniques involve (1) propagation of errors in displacement estimation over the temperature range and (2) non-rigid image motion, i.e. apparent motion over temperatures that cannot be compensated by a simple shift of the images. Errors in displacement estimation depend on multiple factors, including: quantization errors that depend on the image sampling rate (or pixel size); decorrelation

of the RF signals due to small changes in the underlying scattering structure; signal-to-noise ratio and size of the region; and artifacts or features that appear in only one of the images.

The maximum apparent motion across all specimens in Figure 2 was ~0.5 mm in both the axial and lateral directions. This finding means that on average, tissue movement was <20 μm per 0.5°C step. This small change is consistent with visual observation of echo shift and apparent motion in images. That displacement is at least an order of magnitude less than motion tracking and compensation methods based on correlation would be able to handle in this application. Displacements for which we compensated took place in ~1 minute. Because the typical frame interval for conventional ultrasound imagers is 30 ms, it is expected that motions at rates several orders of magnitude faster than encountered in *in vitro* studies could be compensated using correlation methods. Frame rates for motion tracking are likely to be much higher than the rate at which temperature estimates are updated.

Non-thermal and unwanted thermal effects

To eliminate non-thermal sources in backscattered signals and images, changes in ultrasonic signals and images must be determined over the duration of a measurement paradigm when no heating occurs. Unwanted thermal effects include those on the measurement system itself. Spurious thermal effects may be seen in tissue as well. For example, in echo shift measurements the heated region has a tendency to cause a 'thermal lens' effect that distorts the image of the tissue beyond the heated region, where this effect can cause artifacts in temperature estimation [39].

Ultrasonic measurement of temperature

Temperature dependence of ultrasonic tissue parameters has been reported extensively from *in vitro* analyses of ultrasonic tissue characteristics [40–50]. These early investigators looked at changes in tissue characteristics with temperature in order to evaluate thermal errors in tissue characterization. Nevertheless, some investigators did consider the possibility of using temperature dependence of tissue properties as a means to track temperature changes [42, 43, 51].

The primary ultrasonic parameter examined for its dependence on temperature in early work on measurement of temperature was SOS [43, 46, 51]. In these initial studies, investigators tried to obtain SOS maps of the medium from which to infer temperature distributions. This approach, however, has never been instituted clinically [52]. Perhaps this approach has not been implemented because, in order to measure SOS, it is necessary to measure both distance and time, to image an identifiable target from two directions or to use a crossed-beam (multiple beams) method [53]. Such measurement is further complicated by the fact that ultrasonic windows do not always exist *in vivo* to allow insonification of a region of interest from two views. Another problem is that the temperature dependence of SOS differs depending on the tissue type, e.g. whether tissue has high water or fat content.

Recently, the use of ultrasonic parameters as a guide for thermal therapy has been revisited with several different parameters being considered. In particular, papers by Sun and Ying [23], Seip, Simon, Ebbini and coworkers [54–56], Maass-Moreno, Damianou and coworkers [57–59] and this group [29, 60, 61] have reported the changes in received ultrasonic signals due to changes in ultrasonic tissue characteristics with temperature. These changes have been investigated both theoretically and *in vitro* with an eye towards

using these signals for non-invasive monitoring of thermal therapy. Most of these investigators have looked at changes in SOS and thermal expansion with temperature that cause echo shifts in the backscattered ultrasonic signal.

Echo shifts

Of the ultrasonic thermometry methods explored to date, the use of echo shifts has received the most attention in the last decade. Most of these efforts have been geared towards high intensity focused ultrasound (HIFU) therapy, which typically heats small volumes of tissue to above 60°C.

In investigations by Ebbini and coworkers, tracking echo shifts from scattering volumes was shown to be promising, as was the work of other investigators looking at the echo shifts [56]. Maass-Moreno and coworkers investigated the ability to predict temperature in HIFU therapy from echo shifts in turkey breast muscle [57, 58]. They found that results were consistent with their theoretical predictions.

Sun and Ying have also found some success in being able to predict temperatures using time-gated echo shifts, but they acknowledge the difficulty of using this method for general temperature monitoring because prior knowledge of both SOS and thermal expansion coefficients is necessary [23]. Obtaining *a priori* knowledge of both SOS and thermal expansion coefficients is a formidable problem for the *in vivo* case, as demonstrated by a quick look at the earlier tissue-characterization literature that shows that SOS can vary greatly in different types of tissues. In fact the speed change due to temperature in lipid tissue is opposite in direction to the SOS change in aqueous tissue. These complications could cause difficulties in trying to determine temperature in complicated inhomogeneous tissues, as found in an *in vivo* situation.

Apparent and actual displacements of scattering regions are produced by changes in SOS and thermal expansion, respectively. Temperature estimation using these effects is based on measuring displacements in the direction of propagation z, which can be related to changes in temperature $\triangle T(z)$ according to [39, 55, 56, 62]

$$\Delta T(z) = c_0/2(\alpha - \beta) \times \delta t(z)/\delta z \tag{1}$$

where $t(z)$ is the estimated time-shift at depth z, c_0 is the SOS before heating, α is the linear coefficient of thermal expansion and the coefficient $\beta = (1/c_0)(\delta c/\delta t)$ describes the change in SOS with temperature. In this approach, variation in SOS with temperature is assumed to be linear up to ~45°C. The term $(\alpha - \beta)$ depends on tissue type and its fat content [35].

The echo shift occurring between two successive RF images is estimated using the speckle tracking technique described above in one dimension, in this case along the propagation axis. Repeating this process along adjacent beams generates a 2D map of the shifts in a region of interest. A temperature map based on differentiating the shifts along the propagation direction is then generated using the relation given above.

Varghese et al. [62] investigated the spatial distribution of heating using echo shifts in studies that included *in vivo* measurements. Temperature estimates were obtained using cross-correlation methods described previously and Equation (1). Resulting temperature maps were used to display the initial temperature rise and to continuously update a thermal map of the treated region that was simultaneously monitored using thermosensors.

Temperature estimation based on echo shifts has been successful in calibrated, homogeneous tissue phantoms [56] and in small regions where shifts can be separated from behaviour of surrounding tissue [39, 62]. By tracking scattering volumes and measuring the time shift of received echoes, investigators have been able to estimate the temperature of a region of interest both theoretically and experimentally, including preliminary *in vivo* results, but this approach has not as yet been reduced to a practical ultrasonic thermometer that can be applied to an extended tissue region.

Attenuation

Attenuation changes with temperature appear to be more pronounced at temperatures above 50°C than in the hyperthermia range. In a study of inter-costal tissues from rats and pigs by Towa et al. [63], there was a statistically significant, but slight, change in attenuation coefficient from 22–37°C. They concluded that attenuation measures at 22°C, rather than at body temperature, were sufficient for accurate estimates of acoustic levels at pleural surfaces.

Several groups have investigated the temperature dependence of tissue characteristics at temperatures above 50°C [59, 64, 65]. In measurements of insertion loss at room temperature before and after heating, increases in attenuation of up to $2.4\,\mathrm{dB\,cm^{-1}}$ at 3.5 MHz were found in porcine liver after heating to 80°C in 300 s [65].

Damianou et al. [59] investigated the temperature and frequency dependence of ultrasonic attenuation and absorption in soft tissues. They found that attenuation was highly dependent on temperature, but only at temperatures >50°C. Techavipoo et al. [66] measured attenuation of canine tissue from 25–95°C with different tissue samples heated to different target temperatures to reduce cumulative tissue degradation. They found that attenuation at 3, 4 and 5 MHz was relatively unchanged from 40–60°C, but increased sharply above 60°C.

Ribault et al. [67] also looked at the effect of temperature rise on frequency-dependent attenuation and found that tissue damage (lesion formation) caused a change in attenuation in porcine liver *in vitro*. This effect was found by looking at the backscattered signal over the volume of the lesion and comparing the power received before and after high intensity focused ultrasound (HIFU). Other investigators have observed similar effects in the past [68]. Thus, attenuation is of interest for thermometry, but probably only at temperatures above 50°C. This range, however, is not suitable for clinical hyperthermia because hyperthermia temperatures usually do not exceed 50°C.

Change in backscattered energy

In a search for an ultrasonic parameter that changed monotonically with temperature, the backscattered energy was modelled from individual scatterers [60]. According to that model, the backscattered energy from scatterers could change by as much as 5 dB over the temperature range from 37–50°C, the relevant clinical hyperthermia range. Changes in backscattered energy were modelled assuming that the scattering potential of the volume was proportional to the scattering cross-section of sub-wavelength scatterers. It was predicted with this model that the change in backscattered energy could increase or decrease depending on what type of inhomogeneity caused the scattering. These calculations suggested that the change in backscattered energy could vary greatly depending on the type of scatterers in a given tissue region.

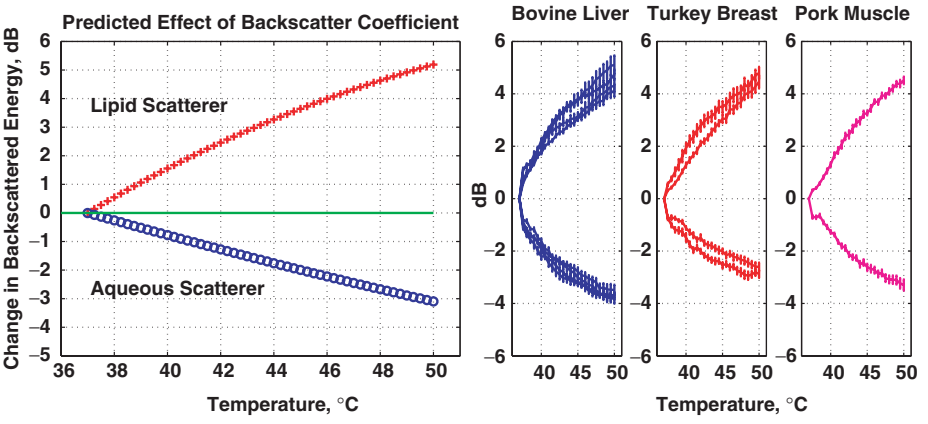

Figure 3. Predicted and measured CBE. (Left) Predicted CBE for single, sub-wavelength lipid and aqueous scatterers in an aqueous medium (similar to Figure 5 in [60]). (Right) Means of measured CBE in positive and negative regions of backscattered-energy images in four specimens of bovine liver, two of turkey breast, and one of pork muscle. The error bar is the standard error of the mean estimated from eight regions of interest in each of the tissue specimens [61].

In 1D studies, it was shown that it is possible to isolate and measure backscattered energy from individual scattering regions and that measured CBE was nearly monotonically dependent on temperature [29]. In the studies of CBE in images, apparent motion of image features has been tracked and compensated for automatically as described above, so that CBE can be measured at each pixel in motion-compensated images [61]. This approach allows use of the whole ultrasonic image rather than just the signals from selected scattering regions, but at the price of possibly increasing noise in estimates of CBE.

After compensating for apparent motion in images of bovine liver, turkey breast and pork muscle, the change in backscattered energy at each pixel over eight image regions in all tissue specimens was calculated with respect to a reference temperature (37°C). As temperature increased, for some scattering regions the CBE was positive, for others it was negative, as seen in Figure 3. This kind of change was predicted by the model of the CBE for a single scatterer. Because the means of CBE from pixels with positive and negative relative backscattered energy changed nearly monotonically, CBE is a suitable parameter for temperature estimation. Its accuracy and spatial resolution, however, have not been determined.

Discussion and conclusions

The use of echo shifts and changes in backscattered energy are the most promising techniques for estimating temperatures in the hyperthermia (41–45°C) range. In this brief review of ultrasonic methods for estimating hyperthermia temperatures with ultrasound, the preprocessing step that is common to these methods has been emphasized, namely the tracking of apparent and actual motion of scattering regions. Motion detection takes on even more importance in *in vivo* studies because of the addition of possible motion of the subject.

Time shift as a function of depth is the basis for temperature estimation using echo shifts. Motion must be tracked and correction applied before temperature can be estimated using changes in backscattered energy. Given the importance of determining tissue motion for estimating temperature with ultrasound, it is likely that more sophisticated methods for motion tracking are likely to be applied to this problem. If temperature estimation based on both echo-shift and CBE continue to show promise, the accuracy and reliability

of temperature estimation with ultrasound may be enhanced by a technique that combines both approaches.

Both echo-shift and CBE methods depend on being able to accurately calibrate the tissue being heated. The echo-shift method, in addition to precise knowledge of the echo shift with tissue depth, requires a knowledge of α, the linear coefficient of thermal expansion, and β, a descriptor of the change in SOS with temperature. Similarly, calibration of the CBE method requires a knowledge of how backscattered energy changes for a given type of tissue. The sensitivity to noise for these calibration data has yet to be fully determined for either method. That sensitivity will determine the temperature accuracy that is possible for a given spatial resolution for either method. A crucial step in identifying a viable ultrasonic approach to temperature estimation remains careful evaluation of its performance during *in vivo* tests.

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