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Measurements of The Relationship Between CT Hounsfield Units and Acoustic Velocity and How it Changes with Photon Energy and Reconstruction Method

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Abstract

Transcranial magnetic resonance guided focused ultrasound continues to gain traction as a non-invasive treatment option for a variety of pathologies. Focusing ultrasound through the skull can be accomplished by adding a phase correction to each element of a hemispherical transducer array. The phase corrections are determined with acoustic simulations that rely on speed of sound estimates derived from CT scans. While several studies have investigated the relationship between acoustic velocity and CT Hounsfield units (HU), these studies have largely ignored the impact of x-ray energy, reconstruction method, and reconstruction kernel on the measured HU, and therefore the estimated velocity, and none have measured the relationship directly. In this study 91 *ex-vivo* human skull fragments from two skulls are imaged by 80 CT scans with a variety of energies and reconstruction methods. The average HU from each fragment is found for each scan and correlated with the speed of sound measured using a through transmission technique in that fragment. As measured by the R-squared value, the results show that CT is able to account for 23-53% of the variation in velocity in the human skull. Both the x-ray energy and the reconstruction technique significantly alter the R-squared value and the linear relationship between HU and speed of sound in bone. Accounting for these variations will lead to more accurate phase corrections and more efficient transmission of acoustic energy through the skull.

I. Introduction

The potential applications of transcranial magnetic resonance guided focused ultrasound (tcMRgFUS) have grown tremendously in the last several years. This is due, in part, to its ability to impact the brain through several different mechanisms. Ablation with tcMRgFUS has been successfully used to treat Parkinsonian tremor [1, 2], essential tremor [3], neuropathic pain [4], and obsessive-compulsive disorder [5]. Interest in neuromodulation with tcMRgFUS has continued to grow, with several initial studies showing successful neuromodulation in animals [6–14] and humans [15–17]. In addition, microbubble mediated blood brain barrier opening as a means to deliver various drugs to the brain has been demonstrated in many different animal models and is progressing towards the clinic [18–21].

All of these applications require focusing acoustic energy through the skull but traversing the skull results in a blurring of the acoustic beam. This deformation of the beam results from both the high attenuation of the bone [22] and the heterogeneity of the skull with respect to velocity and thickness. The blurring that results from the heterogeneity of the skull can be partially corrected using an array of transducers by applying phase corrections to each element of the array [23, 24]. Computing these corrections requires estimating the acoustic path length between each element and the desired focal spot, which in turn requires knowledge of the speed of sound in the intervening tissue, especially the skull.

Early efforts to characterize the acoustic velocity of skull [25, 26] were augmented by Fry *et al.* [27] who demonstrated significant differences between the velocity in the dense cortical bone of the inner and outer tables and the velocity in the trabeculated medullary bone. Clement *et al.* [28] showed that the prediction of acoustic phase after traversal through an *ex vivo* skull could be improved by using a density dependent estimate of velocity. This was achieved using a CT scan to estimate skull density. Aubry *et al.* [29] and Marsac *et al.* [30] postulated a linear relationship between density and velocity and developed a model to estimate both parameters from a CT scan. They used this postulate to successfully achieve improved focusing in a beam propagated through an *ex-vivo* human skull. Pichardo *et al.* [31] and Connor *et al.* [32] also suggested relationships between density and acoustic velocity. Their models were obtained by comparing simulations and measurements of the deformation of an acoustic beam after transmission through several skulls. A genetic algorithm determined the relationship between density and velocity that minimized the difference between the measured and simulated beam. These studies found a non-linear relationship between density and velocity.

These previous studies disagree about how bone density and, in turn, velocity should be estimated from the CT Hounsfield units (HU). Different methods yield dramatically different results depending on the x-ray energy spectrum of the CT scan and the method of image reconstruction. The impact of these parameters needs to be characterized in order to obtain accurate estimates of velocity from CT.

An essential component that is missing from existing studies is an estimate of how accurately CT can predict the speed of sound in the skull. Prior work provides estimates of the optimal relationship between velocity and HU, but if the velocity and the HU are not strongly correlated, even an optimal prediction of velocity will result in a large amount of error. Direct measurements of the relationship between HU and velocity have been performed in various bones [33–37] but not in the skull. Because the composition of the skull is different from other bones [38], measuring velocity and HU at a variety of CT settings in the human skull will lead to a clearer understanding of the accuracy of CT derived estimates of acoustic velocity. Knowing the magnitude of the error in CT derived velocity estimates in the skull will enable investigators to determine its impact on phase corrections and on the efficiency of acoustic power transfer through the skull.

In this work, we measure the velocity in 91 human skull fragments from two *ex-vivo* human skulls and correlate the result to the average HU measured on two CT scanners at multiple energies and using several different imaging kernels and reconstruction techniques. We find

that both energy spectrum and reconstruction method can lead to significant differences in the measured relationship between HU and velocity. Our measurements also suggest that CT is able to describe a maximum of about 53% of the variation of acoustic velocity within the human skull.

II. Background

A. CT Parameters

Commercial CT scanners allow the user to make a tradeoff between dose and image contrast by altering the energy of the x-rays used to acquire the image. This tradeoff is possible because CT measures the linear attenuation of x-rays in tissue and low energy x-rays are more attenuated and produce higher contrast than high energy x-rays. The tradeoff is that dose must be increased as the energy decreases in order to maintain constant image noise [39].

CT reports the linear attenuation as HU. HU are a normalized representation of the linear attenuation coefficient designed to yield constant values for air and water regardless of the x-ray spectrum. They are defined by the equation [39]

$$HU = 1000 \frac{\mu - \mu_w}{\mu_w}, \quad (1)$$

where μ is the measured linear attenuation coefficient of the tissue and μ_w is the linear attenuation coefficient of water. μ is a function of the x-ray energy, and the change in μ with energy is different for different tissues. The relative changes between μ and μ_w are especially pronounced in bone, leading to a strong energy dependence in the measured HU. This is an important factor in velocity estimates because it implies that the relationship between speed of sound and HU must change with x-ray energy.

The method by which CT systems generate x-rays can further influence the measured HU. The easiest way to alter the energy spectrum of a CT scanner is to alter the peak voltage applied to the x-ray tube, but this method results in x-rays with a broad spectrum of energies [40] and vendors rarely report this spectrum to the user. A common assumption is that the mean energy (also called the effective energy) of a CT scan is 2/3 of the peak voltage applied to the x-ray tube. However, the real value can be as low as less than half of the peak value. This ambiguity makes it difficult to properly account for CT energy in velocity estimates.

This ambiguity can be greatly reduced through dual energy CT. Dual energy CT can remove uncertainty about the x-ray spectrum by using data acquired with two energy spectra to synthesize monochromatic images. These images are estimates of the images that would be acquired if the CT scan could be performed only with x-ray photons of a single energy [41]. Images generated in this way have a known x-ray energy, which is reported in units of keV.

CT systems also allow users to make a tradeoff between image noise and sharpness through the selection of different reconstruction kernels. Soft tissue kernels reduce noise through spatial averaging, but this also blurs the boundaries between tissues. Bone kernels do the opposite, enhancing edges at the cost of increased noise [39]. Except near edges, the mean HU measured in a given tissue should be the same regardless of kernel selection. However, edge blurring or enhancement can have a significant impact on acoustic simulations since the amount of acoustic energy that is reflected at tissue interfaces can decrease significantly as the boundary becomes less pronounced [42]. Though kernel selection should not change the measured HU, it can indirectly impact HU because vendors may change other parts of the reconstruction method in response to the chosen kernel. Beam hardening and scattering corrections are two examples of algorithms that could be implemented differently depending on the kernel selection. Vendors are not open about this type of detail in their reconstruction methods, making it difficult to predict the impact of kernel selection on the relationship between HU and acoustic velocity.

B. Hounsfield Units and Density

The relationship between HU and acoustic velocity is closely linked to the relationship between HU and density. Most prior studies report the acoustic velocity in terms of the CT-derived density; however, prior studies do not agree on the proper relationship between HU and density. Aubry *et al.* [29] and Marsac *et al.* [30], have suggested that bone density can be estimated by assuming that the attenuation, μ_s , measured by CT in a sample of bone is

$$\mu_s = \mu_b(1 - \Phi) + \mu_w\Phi. \quad (2)$$

Here, μ_b and μ_w are the linear attenuation coefficients of cortical bone and pure water and Φ is the porosity of the bone in the voxel. The bone porosity can be estimated directly using this equation, assuming that μ_b and μ_w are known. If values are also assumed for the density of cortical bone and water, porosity can be converted into an estimate of the density of the sample. The values of μ_b and μ_w depend on the x-ray energy and proper selection of these constants requires an accurate estimate of the effective CT energy. However, the effective x-ray energy is not well known, resulting in ambiguity in estimates of density.

Pichardo *et al.* [31] and Connor *et al.* [32] suggest that density can be calculated using only measurements of the average HUs in a region of pure water and pure air. Assuming values for the density of air and water, a linear relationship is defined by these two points. This relationship is given by

$$\rho = \kappa_1 \text{HU} + \kappa_0, \quad (3)$$

where

$$\kappa_1 = \frac{\rho_{\text{water}} - \rho_{\text{air}}}{H_{\text{water}} - H_{\text{air}}} \quad (4)$$

and

$$\kappa_0 = \frac{-\rho_{\text{water}} H_{\text{air}}}{H_{\text{water}} - H_{\text{air}}}. \quad (5)$$

Here, H_{water} and H_{air} are the average HU measured in the regions of water and air. It is important to note that, because HU are defined to have the same values for water and air regardless of the x-ray energy, this relationship does not account for x-ray energy. This suggests that the Pichardo and Connor methods will need to be generalized in order to account for photon energy.

III. Methods

Direct measurements of the HU and acoustic velocity were made in *ex-vivo* human skull bone fragments. The following sections detail the sample preparation, the CT measurements, the velocity measurements, and the mathematical methods used to fit the velocity measurements to the CT data.

A. Sample Preparation

Two *ex-vivo* dried human skulls (60 year old male, 62 year old female) were acquired from Skulls Unlimited [Oklahoma City, OK]. Samples were generated using a hole saw to remove bores with a 13 mm diameter. The inner and outer tables were separated from the diploë and the samples were then sanded in order to achieve flat and parallel interfaces. 91 fragments were generated with 48 from the outer table, 32 from the diploë, and 11 from the inner table. In order to better approximate *in-vivo* conditions, all fragments were degassed in water in a vacuum chamber for 48-72 hours before CT imaging and before performing acoustic measurements. This method of re-hydrating desiccated skull samples has been shown in pigs to have a statistically significant impact on the measured velocity [43] but the change was small, only 2.3%, and not likely to be a dominant source of error. Figure 1(a) shows a picture of several randomly selected fragments in their final form.

B. CT Imaging

In order to understand the impact of different CT parameters and methods, images of the fragments were acquired on two different systems with a variety of energies, kernels, and reconstruction methods. In all cases, the average HU was determined by computing the mean in a region of interest generated with an automatic segmentation algorithm. The algorithm uses Otsu's method [44] to select a threshold and then uses hole filling [45] to generate a region of interest. The center of the region is then selected as the center of a three-dimensional cylinder with a radius and height slightly smaller than the radius and

height of the fragment. In order to eliminate the impact of partial voluming, the intersection of the cylinder and the segmentation are used to compute the average HU.

The impact of x-ray spectrum was explored with dual energy scans and conventional scans at a variety of different peak voltages. Dual energy scans were performed on a Discovery CT750 [GE, Waukesha, WI] and monochromatic images were reconstructed at 60, 80, 100, 120, and 140 keV. The monochromatic images generated at 60 and 140 keV were also used to estimate the density of the fragments using a bone mineral density (BMD) reconstruction [46]. Conventional images were acquired at 80, 100, 120, and 140 kVp on the GE Discovery and 70, 80, 90, 100, 110, 120, 130, 140, and 150 kVp on a Siemens Somatom Force [Erlangen, Germany]. The Siemens system also allowed the use of a tin filter which increases the effective energy of the beam because lower energy x-rays are preferentially attenuated by the tin. Data was acquired using tin at 150 kVp.

In order to probe the impact of kernel selection, all of the above scans were repeated using both a soft tissue kernel and a bone kernel. The vendor specific names of the soft tissue kernels are STANDARD and Hr32 and the bone kernels are BONEPLUS and Hr64 for the GE and Siemens systems, respectively. The Stanford Essential Tremor protocol uses the BONEPLUS kernel for pretreatment scans. The Siemens system also allows the capacity to increase the sharpness of the kernel in steps, a feature that was only available when the comb filter was turned on, and scans were acquired in eight steps from a broad kernel to a sharp kernel at both 120 and 140 kVp. The significance of any changes in HU resulting from kernel selection was assessed by measuring the concordance correlation and Bland-Altman limits of agreement of the HU measured using a soft tissue kernel and those measured using a bone kernel.

Finally, the GE scanner offers an option for a model based iterative reconstruction (commercially known as Veo), a technique that decreases noise and improves edge sharpness. Veo images were acquired at 80, 120, and 140 kVp.

C. Measuring the Velocity

Figure 1(b) shows the experimental setup used to measure the longitudinal velocity in each fragment. An aluminum frame was constructed to hold the bone at the focal spot of a 500 kHz piston transducer (Olympus V301 [Tokyo, Japan], focused, 38 mm aperture, 25 mm focal length). The aluminum frame also held an optical hydrophone (Precision Acoustics, Dorchester, UK) just behind the bone fragment. The bone could be moved in and out of the focal spot by a lever without disturbing the transducer or the hydrophone, allowing for measurements of a transmitted pulse with and without the fragment present in the beam path. All experiments were performed in degassed water at room temperature.

In each measurement, the hydrophone and oscilloscope recorded waveforms transmitted with and without the bone present at a sampling frequency of 800 MHz. A low pass filter was applied to each recorded waveform with a cutoff frequency of 750 kHz. The difference in arrival time, t , was measured by finding the location of the first zero crossing in each trace. The zero crossing was found by subtracting the mean of the signal in order to remove

DC bias and then detecting the first sign change after the front edge of the signal. The velocity in the fragment can then be estimated using

$$c_b = \frac{c_w}{1 + \frac{c_w \Delta t}{d}}, \quad (6)$$

where d is the thickness of the fragment (measured with a digital caliper) and c_w is the speed of sound in water at 20°C. This process was repeated three times for each fragment and the fragment was completely removed and replaced between each experiment in order to characterize variability in the measured velocity as a result of variations in the positioning of the fragment.

D. Fitting the Data

The measured speed of sound was fit to the HU of each image using a linear fit. This matches the assumptions made in prior studies [29, 30, 47]. The primary figure of merit for each fit is the R-squared value. The location of the y-intercept was also examined to determine if 1482 m/s [48], the speed of sound in water at 20°C, was included within the 95% confidence interval for a HU value of zero. This is expected because, from equation (1), the HU of water is always zero. Thus, an accurate model of velocity as a function of HU should predict the speed of sound in water at the y-intercept. When computing the 95% confidence intervals, an adjustment was made for clustering in order to account for the repeated measurement of velocity and HU on the same fragment.

IV. Results

A. Measurement of Velocity

Figure 2 shows sample traces measured by the hydrophone with and without the bone present and marks the location of the first zero crossing. The standard deviation of the three velocity measurements averaged 2% across all fragments and the maximum standard deviation was 11%. The measured velocity ranged from 1,996 m/s to 3,114 m/s. One fragment from the diploë was excluded because the transmitted signal was too attenuated to find the zero crossing with sufficient accuracy. The results from the other 90 fragments are included in all of the following analyses.

B. Impact of CT Energy

Figure 3(a) shows sample images from the dual energy scan on the GE system and several of the conventional scans on the Siemens System. Fragments from the inner and outer table and the diploë are shown. The units used to define the energy of the scans in Figure 3(a) reflect the type of scan performed. The selected energy for the monochromatic images is known and presented in keV. For the conventional CT, only the peak tube voltage is known and is presented in kVp. The conventional images appear brighter than the monochromatic images of the same numerical value because the effective energy of the x-rays in a standard CT scan is less than the peak energy.

The brightness of the image decreases with increasing x-ray energy. This agrees with literature values for the attenuation of bone as shown in Figure 4(a). This figure shows the average HU measured in monochromatic images of a fragment of cortical bone and compares it to the HU estimated using equation (1) for pure cortical bone with linear attenuation values for cortical bone, water, and air taken from the National Institute of Standards (NIST).

Figure 4(b) shows the impact of this energy dependence on the measured relationship between HU and velocity. Increasing the energy alters the slope and the magnitude of the change increases as the energy decreases. For a given HU, the figure shows a change in the predicted velocity on the order of hundreds of meters per second as the energy used to acquire the CT images changes.

Comparison of the measured velocity to the HU measured with conventional CT scans also yielded similar insights, showing that the relationship between HU and velocity is highly dependent on the peak energy. The tin filter impacted the relationship in the same way, resulting in a shift in the data consistent with an increase in the effective energy of the scan. Slopes, y-intercepts, and R-squared values for all of these images are provided in Tables I and II.

C. Impact of Reconstruction Method

Figure 3(b) shows sample images acquired using a soft tissue kernel and a bone kernel at 120 kVp on both the GE and Siemens systems. Dual energy scans reconstructed with soft tissue and bone kernels at an energy of 80 keV are also shown. More structure is visible in the images acquired with the bone kernel. There is also a change in the average HU measured in each image as shown in Figure 5(a) which shows the difference between the average HU measured with a bone kernel and the average HU measured with a soft tissue kernel. The difference is plotted as a function of bone fragment thickness. For sufficiently large fragments in the conventional scans the difference is small but increases exponentially as the thickness decreases. The difference between the dual energy scans, however, is much smaller, even for smaller fragments.

The concordance correlation for the relationship between the HU measured with a soft tissue kernel and the HU measured with a bone kernel are only 0.58 and 0.47 for the standard scans on the GE and Siemens systems respectively. In contrast, the dual energy scans on the GE system yield a concordance correlation of 0.99. The Bland-Altman 95% limits of agreement for the dual energy scan are between -42 and 54 HU, a range of 10% relative to the average HU measured across all energies for the two kernels. The limits of agreement for the standard reconstruction on the GE and Siemens systems were -32 to 673 and -222 to 864. These ranges span 45% and 72% respectively of the mean HU measured across energies and kernels for the standard reconstruction.

The impact of the reconstruction kernel on the relationship between HU and velocity is shown in Figures 5(b), 5(c), and 5(d). The figures show that for conventional scans, velocity estimates made using the bone kernel will be lower than estimates made using a soft tissue kernel if a consistent relationship between HU and velocity is assumed. The dual energy

scans (Figure 5(b)) result in a more consistent relationship regardless of the type of kernel used.

In addition to the standard soft tissue and bone kernels, the Siemens system allows the user to increase the sharpness of the kernel in steps. The result of fitting the velocity data to these scans can be seen in Table II. The scans are identified as Ub and Ur (the commercial names given on the system) where Ub represents the regime generally used to image soft tissue and Ur represents the regime generally used to image bone. The number following the identifier corresponds to the kernel's sharpness, with higher numbers indicating a sharper kernel.

D. Model Based Iterative Reconstruction

Veio is a technique that uses a model of photon propagation through tissue and an edge preserving technique to reconstruct the image. It results in the best fit as measured by the R-squared value (an average of 0.52 for the three energies measured, see Table I). Figure 6 shows the fit resulting from the Veio data at 80, 120, and 140 kVp and compares it to the fit resulting from a conventional reconstruction performed with a soft tissue kernel on the same system.

E. Impact of Vendor

Figure 7 compares the linear models generated with the two vendors at 120 kVp for both a soft tissue and a bone kernel. The two systems agree well for the bone kernels but there are substantial differences when using the soft tissue kernel. In general, the speed of sound data did not fit as well to average HU measured with a soft tissue kernel on the Siemens system. The average R-squared values for the Siemens soft tissue data was 0.28 compared to 0.46 for the measurements acquired with a soft tissue kernel on the GE system.

F. Relationship Between HU and Velocity

A linear fit of velocity to HU was performed for each of the CT images acquired. Figure 8(a) shows examples of the 95% confidence intervals for scans reconstructed with bone and soft tissue kernels on both systems as well as a dual energy scan reconstructed with a bone kernel and the scans performed with the Veio technique. Figure 8(b) shows the confidence intervals for select scans at the y-intercept. The 95% confidence interval at $HU = 0$ were large, averaging ± 198 m/s, however, several of them did not include 1482 m/s. 1482 m/s was included for all energies with the bone kernels on both systems and all the dual energy scans on the GE system. The linear fits are summarized by their slopes, y-intercepts, and R-squared values in Table I for the GE system and Table II for the Siemens system. The scans are sorted by energy and reconstruction kernel and other important parameters are specified in the third column. The tables can be used to find the relationship between HU and velocity that best matches the configuration used to obtain a CT scan.

V. Discussion

These results provide estimates of the relationship between HU and velocity for a variety of different CT parameters. CT parameters can have a significant impact on the measured HU and therefore need to be accounted for when determining the proper relationship between

HU and velocity. Models that fail to account for these variations will provide inaccurate velocity estimates and erroneous phase corrections, leading to a blurring of the acoustic beam and a less efficient transmission of ultrasound energy through the skull. The results also provide insight into how well CT is able to predict acoustic velocity in the skull, with R-squared values that suggest that CT can accurately describe about 53% of the variation in velocity.

A. Accounting for Energy

Comparing the results of this work to prior studies elucidates the error that can result from failing to correctly account for the CT energy. Prior studies report velocity in terms of CT derived density. Comparing the results from these studies is hindered by the lack of agreement about how to compute density from HU. However, using their proposed transformations between HU and density, it is possible to convert their results from density to HU. Once these earlier results are obtained in terms of HU they can be compared to the results presented in this paper.

Figure 9 shows the comparison between this study and the models suggested by Aubry *et al.* [29], Connor *et al.* [32], and Pichardo *et al.* [31]. Each prior model was transformed from a model relating velocity to density to one relating velocity to HU using the methods proposed by the respective authors. The Aubry model accounts for x-ray energy and therefore produces a distinct estimate of the relationship between HU and velocity for each CT energy and the agreement is good for the monochromatic images obtained with the dual energy data. However, the Connor and Pichardo methods, which do not account for CT energy, only achieve agreement at 80 keV.

Aubry accounts for energy using literature values for the x-ray attenuation of cortical bone. Because the attenuation of bone is energy dependent, this method requires obtaining an estimate of the effective energy of the CT scan. This works well when the energy is known but when the energy is not known (as in Figure 9(b)) ambiguity about the correct value for the attenuation of bone results in poor agreement at 140 kVp. This is likely because it is not clear what energy to assume. This figure assumes that the effective energy is 2/3 of the peak voltage, an assumption that appears to be accurate at 80 kVp but not at 140 kVp.

This lack of agreement for the conventional scan illustrates the difficulty of obtaining consistent results across vendors, energies, and other scan parameters. It is especially noteworthy that the same assumption about the relationship between effective energy and peak energy does not work well across multiple energies even on the same scanner with the same reconstruction kernel. More accurate knowledge of the x-ray energy is required in order to obtain consistent results.

There are several ways this difficulty can be addressed. The simplest is to use dual energy CT to acquire treatment planning images. This would eliminate the ambiguity around the selection of an effective CT energy for the scan. Another alternative would be to construct a phantom with a known relationship between HU and speed of sound that could be scanned at the same time as the patient in order to provide calibration. Investigators could also work

with vendors to obtain more accurate estimates of the x-ray spectrum of a conventional single energy scan.

A final option is to standardize the way density is estimated from HU. Two common methods of doing this are the method employed by Aubry [29] and BMD reconstructions [46]. The Aubry method, briefly reviewed in Section II-B, can be done with a conventional scan but, as shown in Figure 9(b), there is enough uncertainty in the effective x-ray energy to make Aubry's method difficult to employ with sufficient accuracy. BMD reconstructions rely on dual energy scans. Using dual energy data to estimate the density eliminates the uncertainty about the effective x-ray energy and provides a second measurement of the linear attenuation of the sample. This extra measurement can be used with Equation (2) to estimate density without assuming a value for the density of cortical bone, relaxing one of the assumptions of the Aubry method. BMD reconstructions were performed and the resulting R-squared values are similar to those obtained with raw HU.

The advantages of BMD and its reliance on dual energy data provide further evidence of the advantage of using dual energy CT to estimate acoustic velocity. Dual energy scans can eliminate the ambiguity in the effective energy of the x-rays, provide more reliable estimates of the density of the bone, and be implemented immediately. Future studies and treatments should consider dual energy CT as the method of choice for treatment planning scans in tcMRgFUS.

B. Kernel Selection

The concordance correlation coefficients and Bland-Altman limits of agreement for the standard reconstructions on the GE and Siemens scanner show that different reconstruction kernels cannot be treated as giving the same results. The lack of agreement between the two measurements shows that kernel also needs to be accounted for in order to obtain accurate velocity measurements. The exception to this was the dual energy data which showed strong agreement between the HU measured with a soft tissue kernel and a bone kernel. In one sense this provides further evidence that dual energy scans should be used for treatment planning in the future. However, without more knowledge about how kernel selection impacts the reconstruction algorithm on each CT system it is impossible to say whether or not the results would be the same with a dual energy scan on a different system.

The change in HU resulting from different reconstruction kernels is difficult to predict because large variations are probably due to other changes in the reconstruction method made by the vendor in response to the change in reconstruction kernel. InSightec [Tel Aviv, Israel], a manufacturer of FUS systems that uses CT to estimate phase corrections, addresses this uncertainty by specifying the reconstruction kernel that must be used in pretreatment CT scans (the BONEPLUS kernel used in this study is specified by them for the GE system). More clarity from vendors about how the reconstruction method is altered based on kernel selection would also help to alleviate this problem. Another option may be to calibrate the CT scan using a phantom with a known density. Scans of the phantom could be performed with both kernels in order to estimate how much difference to expect.

Such a method would give insight into how much variation to expect but wouldn't allow for a complete correction because the difference between the bone and soft tissue kernels depends on the thickness of the fragment (Figure 5(a)). It is possible that this effect would be less pronounced *in-vivo* because these fragments have sharper edges and corners than intact skull bone. Still, the difference between the measured HU for the two reconstruction kernels is large enough to merit further investigation of this question.

C. The y-intercept

Several of the models did not predict a y-intercept of 1482 m/s. One potential explanation for this is that the relationship between HU and velocity might not be fully linear. Connor *et al.* [32], and Pichardo *et al.* [31] proposed nonlinear models that decrease in slope as they approach the y-axis (see Figure 9). Because most of the CT parameters result in a model with a y-intercept that is less than 1482 m/s, allowing the slope to decrease with decreasing HU could bring 1482 m/s into the 95% confidence intervals of the y-intercept.

Systematic errors in the velocity measurement could also lead to errors in the predicted y-intercept. Wear *et al.* [49] showed that pulse spreading in materials with a frequency dependent attenuation leads to some error in speed of sound measurements that use zero crossings. This pulse spreading is the result of the selective attenuation of higher frequency components in the signal. Assuming an attenuation of 1.8 Np/cm, Wear predicts that the speed of sound measurement in a 2 mm fragment with a velocity of 1965 m/s will overestimate the actual velocity by about 7%. Wear also suggested a method to correct for these errors but it requires knowledge of the attenuation of the material. Because the fragments are small relative to a wavelength, multiple reflections within the fragment make it difficult to estimate attenuation in order to apply Wear's technique. If attenuation increases with HU these errors would increase in magnitude with increasing HU and would lead to an overestimation of the slope and an underestimation of the y-intercept. The agreement between 1482 m/s and the y-intercept could improve if the attenuation was known and the Wear corrections could be properly applied.

Another possible explanation is related to the changes in HU with different reconstruction kernels. It is possible that these changes lead to unexpected behavior in the HU at lower values. This might also explain the few cases where the predicted y-intercept is greater than 1482 m/s, though it is worth noting that the CT parameters that result in a y-intercept greater than 1482 m/s also result in the lowest R-squared values (see Table II). Testing these hypotheses is difficult because there are not enough fragments with sufficiently low HU to determine the behavior of the function near the y-axis. Because bone always has a value that is significantly higher than zero HU, it may not be essential to determine the function's behavior in this regime.

D. Limitations of the Velocity Measurements

A limitation of the current study is that it does not account for the propagation of shear waves in the skull. It has been shown that when the incident acoustic wave is not normal to the bone surface, some of the energy in the longitudinal wave will be converted into a shear wave in the bone [50]. These shear waves can impact the quality of the acoustic focus

because they propagate at a slower velocity and have a distinct propagation path relative to a purely longitudinal wave. Because the shear wave is converted back to a longitudinal wave as it exits the bone, the measurements performed in this study do not distinguish between the two pathways. Rather, these experiments measure longitudinal velocity in the skull and minimize shear wave conversion by orienting the transducer to achieve normal incidence of the acoustic beam on the sample. As a result, the shear wave propagation path is unlikely to contribute significantly to the acoustic energy transmitted through the fragment and measured by the hydrophone. The low standard deviation across velocity measurements suggests further evidence that the shear wave propagation path is not contributing significantly to these results.

Measurements of the longitudinal velocity in the skull are likely sufficient for many FUS applications. While shear waves will be present during *in vivo* treatments, prior studies have suggested that they can be reasonably neglected for a hemispherical array [42]. The quality of the focus will be more significantly impacted by shear waves in transducer geometries that generate more oblique angles of incidence and further work is required to characterize the shear wave velocity in the skull in order to enable accurate modeling in these cases.

E. The Limits of CT as a Model of Velocity

The measured R-squared values and 95% confidence intervals show a large amount of uncertainty in estimates of velocity based on HU. The best R-squared value, obtained using the Veo reconstruction on the GE system, is 0.53 and the standard deviation of the difference between the modeled and measured velocity for this dataset is 160 m/s.

The impact of this uncertainty on actual treatments depends on how much the uncertainty in velocity propagates into errors in phase corrections which then lead to a loss of pressure at the focal spot. Quantifying this loss of pressure is difficult because the amount of pressure lost depends on the properties of the skull and is patient specific. A full characterization of the impact of the uncertainty in the relationship between HU and acoustic velocity would require hydrophone measurements or simulations of the propagation of an acoustic beam through skulls from across a patient population.

While this full analysis is outside of the scope of this study, a rough estimate of the loss in intensity at the focal spot can give some insight into how much treatments can be improved if better estimates of velocity become available. The lost intensity can be approximated by assigning a phase error for each element in a 1024 channel system (e.g. Exablate, InSightec) and estimating the resulting intensity as [51]

$$I / I_0 = \left| \frac{1}{1024} \sum_{n=1}^{1024} e^{i\Phi_n} \right|^2, \quad (7)$$

where $||$ denotes the absolute value. The phase error, Φ_n , can be assigned using the statistics of the velocity error as

$$\Phi_n = 2\pi f \left(\frac{1}{c_b + \epsilon_{v,n}} - \frac{1}{c_b} \right) d, \quad (8)$$

where f is the frequency of the ultrasound signal, c_b is the speed of sound in the bone, $\epsilon_{v,n} = \mathcal{N}(0, \sigma^2)$ is a velocity error with $\sigma = 160$ to match the statistics of the Veo results, and d is the thickness of the skull fragment. The actual speed of sound, c_b , depends on the composition of the skull and is patient specific. For this analysis an approximation is made and c_b is set to 2500 m/s.

The result of this analysis is highly dependent on the thickness of the skull. For a skull that is 1 cm thick the intensity at the focal spot is about 48% lower than the intensity that would be obtained with perfect corrections. For a skull that is 0.5 cm thick, the resulting intensity is only decreased by 15%. These results are in the same range as a prior study that found the intensity obtained with CT derived phase corrections was about 50% lower than the intensity obtained using phase corrections derived from hydrophone measurements [52]. These numbers suggest that there is an opportunity to significantly improve the efficiency of acoustic transmission through the skull by improving the method of estimating acoustic velocity during treatment planning of tMRgFUS.

Examining the sources of uncertainty in the data may provide insight into how an improvement in the accuracy of velocity estimates can be achieved. Several factors contribute to the uncertainty in the relationship between velocity and HU. One source of uncertainty is error in the measurement of velocity. As discussed in a previous section, Wear *et al.* [49] predicts that frequency dependent attenuation in the fragments leads to error in measurements of velocity that use zero crossings. Some of the variation in speed of sound as a function of HU could be reduced if Wear's corrections could be properly applied.

While every attempt has been made to generate homogeneous samples, assigning average HU labels to describe heterogeneous bone fragments is another potential source of error. If the relationship between HU and velocity is highly nonlinear then a simple average of the HU in a fragment is an inaccurate way of labeling the sample. The amount of error resulting from this labeling would depend on the extent to which the relationship between HU and velocity is nonlinear. Previous studies of the relationship between bone and acoustic velocity have resulted in linear models [33–37]. Other studies have shown linearity between acoustic velocity and the porosity of a material [35, 53, 54]. Porosity, in turn, is linear with HU under the assumption of a two material model (see Equation (2)). Combined with the linear results of this study, this evidence strongly suggests an approximately linear relationship between HU and velocity, implying that errors due to assigning an average HU value will be small.

It is unlikely that measurement error can completely account for the uncertainty in velocity estimates. Another potential source of error is differences in the chemical makeup of the two skulls. If the skulls have different chemical compositions, for example, through increased mineralization of the bone, the relationship between HU and velocity could change. This would result in a patient specific relationship between HU and velocity.

To test this hypothesis, the relationship between HU and velocity can be recalculated considering the data from each skull independently. Figure 10 shows that when the skulls are considered individually there is a clear difference in both the slope and y-intercept of the fit between HU and velocity. The uncertainty in the models changes significantly as well, with R-squared values of 0.57 and 0.78 for skulls 1 (female) and 2 (male) respectively.

The difference between the R-squared values and the shift in the fit between the two skulls provides strong evidence that the relationship between HU and velocity is patient specific. The differences between skull 1 and skull 2 also emphasize that the results presented in this study should not be taken as definitive models of velocity as a function of HU. Further work needs to be done to characterize either an average relationship across a patient population or a method for adapting velocity estimates to specific patient skulls. Such a study will require a large number of skulls and is outside the scope of the present work. One patient specific method that could be studied is to follow Vyas *et al.* [47] who suggested adapting estimates of acoustic scattering to a specific patient by adjusting the slope of the relationship between HU and scattering based on the highest measured HU in the image. A similar technique may be applicable to velocity.

Another potential solution is to examine other imaging modalities to see if they are better able to estimate the velocity across patients. Given that other investigators are already exploring the possibility of obtaining phase corrections using ultrashort echo time (UTE) MRI [55, 56], studies should be performed to determine if UTE-MRI can capture more of the variation in the speed of sound than CT. Since MRI is often used to monitor treatments, it may also be worth considering combining data from the two modalities in order to recover more of the power lost as a result of phase corrections estimated with inaccurate velocities. Future studies should examine these options because significant improvements in velocity estimates and phase corrections will lead to the more efficient transfer of acoustic energy through the skull, resulting in a decrease in the energy required to achieve ablation at the focal spot. Reducing the required energy improves treatment safety by decreasing the dose delivered to intervening tissue. It may also lead to the capacity to treat patients who cannot currently be treated because the power required to achieve ablative temperatures at the focal spot exceeds the limits of the transducer [57].

VI. Conclusion

Measurements of the relationship between acoustic velocity and HUs in human skull bone are presented for a variety of CT scans. The results show that CT energy must be accounted for in order to accurately estimate the acoustic velocity from HUs. This can be achieved with dual energy CT, by obtaining calibration measurements, or by working with the vendor to obtain accurate estimates of the x-ray spectrum of a given scan. Other CT parameters also play a role in the measured relationship between HU and velocity.

The measurements also show that CT is able to capture only about one half of the variation in acoustic velocity within the skull. Some of the remaining variation is likely due to errors in the measured velocity but it is also likely an indication that some of the variations in velocity are not well modeled by HUs. This could be because the variation in velocity results

from changes in the chemical makeup of the skull, a variation not necessarily captured by the measured HU.

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(a)

(b)

Fig. 1.

a) Photo of randomly selected fragments. b) Experimental setup for measuring velocity. An aluminum frame holds the fragment at the focal point of the transducer and holds a hydrophone just beyond the fragment. The hydrophone captures the transmitted ultrasound pulse with and without a bone fragment present.

Fig. 2.

Traces measured by the hydrophone with the bone fragment present (red trace) and without it present (blue trace). The fragment shifts the pulse forward in time and attenuates the amplitude. The velocity in the fragment is measured using the difference in arrival time as estimated by the location of the first zero crossing.

(a) Effect of energy

(b) Effect of reconstruction method

Fig. 3. Example CT images of a fragment from the inner table, the diploe, and the outer table. a) Samples of CT scans for characterization of the impact of x-ray energy on the relationship between HU and velocity. The images acquired on the GE scanner are monochromatic images acquired using dual energy CT. The images from the Siemens system were acquired with a variety of peak voltages in a conventional method that doesn't report energy spectrum. Both scans are performed with a bone reconstruction kernel. In addition to the dual energy scans, conventional CT scans were performed on the GE system at 80, 100, 120, and 140 kVp (not shown). b) Samples of CT scans for characterization of the impact of CT kernel and reconstruction technique. On both systems, images were acquired with both soft tissue (ST) and bone (B) kernels. On the GE system, dual energy (DE) scans were acquired with both soft tissue and bone kernels and images were acquired using a model based iterative reconstruction (Veo) technique. Conventional images were acquired with an x-ray energy of 120 kVp and dual energy scans were reconstructed at 80 keV. The scale bars are HU.

Fig. 4.

The impact of CT energy as measured by the dual energy scan on the GE system with a bone kernel. a) The dotted line shows the HU calculated using Equation (1) and linear attenuation values from NIST. The circles show the average HU measured in the densest sample of cortical bone as measured by the average HU (red), the average HU value of all the fragments from the inner and outer tables (yellow), and the average HU value of all the fragments from the medullary bone (purple). Error bars show the standard deviation. b) Speed of sound as a function of HU for five different energies.

(a) Average difference across all fragments.

(b) Dual energy on the GE Discovery.

(c) Conventional on the GE Discovery.

(d) Conventional on the Siemens Somatom.

Fig. 5.

The impact of kernel selection on HU as measured with a CT energy of 120 kVp in the conventional scans and 80 keV in the dual energy scans. a) Average HU measured with the bone kernel minus the average measured with the soft tissue kernel plotted as a function of bone fragment thickness. b), c), and d) speed of sound as a function of HU as measured using dual energy scans (b) and standard scans on the GE system (c) and standard scans on the Siemens system (d).

Fig. 6.

The linear fit resulting from data generated using the Veo technique compared to the fit from conventional CT on the GE system with a soft tissue kernel.

Fig. 7.

The linear fit resulting from data collected on the GE system (solid lines) and the Siemens system (dashed lines) using both a soft tissue (blue) and a bone (red) kernel at 120 kVp.

Fig. 8. 95% confidence intervals for select scans a) across all HU and b) at the y-intercept. For comparison with the y-intercept, the speed of sound in water is shown by the black dashed line.

(a) Monochromatic data.

(b) Conventional data.

Fig. 9.

Comparison of the measurements presented in this paper to prior models. a) Comparison to prior models using data from the monochromatic images acquired with the dual energy scan on the GE system. b) Comparison to prior models using standard CT scans with unknown effective energies. In order to estimate Aubry's model at each energy, an effective energy of $2/3$ of the peak tube voltage was assumed.

Fig. 10.

The measured relationship between acoustic velocity and HU when only data from one skull at a time is considered. The data in this figure is from the Veo scan performed on the GE system at 120 kVp.

TABLE I

Table of slope, y-intercept and R-squared values for each GE fit.

Legend: BW: beam wobble, Veo: model based iterative reconstruction, DE: dual energy, BMD: bone mineral density reconstruction.

Energy (kVp)	Kernel	Other Identifier	Resolution in mm (axial, slice)	slope (m/s/HU)	y-intercept (km/s)	R-Squared
60	ST	DE	0.5, 0.6	0.78	1.41	0.43
60	B	DE	0.5, 0.6	0.79	1.38	0.43
80	ST		0.5, 0.6	0.67	1.33	0.44
80	ST	Veo	0.2, 0.6	0.77	1.09	0.52
80	ST	BW	0.5, 0.6	0.71	1.26	0.49
80	ST	DE	0.5, 0.6	1.2	1.37	0.44
80	B		0.5, 0.6	0.57	1.28	0.47
80	B	BW	0.5, 0.6	0.55	1.28	0.46
80	B	DE	0.5, 0.6	1.2	1.35	0.44
100	ST		0.5, 0.6	0.82	1.3	0.45
100	ST	BW	0.5, 0.6	0.88	1.21	0.51
100	ST	DE	0.5, 0.6	1.4	1.36	0.44
100	B		0.5, 0.6	0.65	1.33	0.44
100	B	BW	0.5, 0.6	0.7	1.2	0.49
100	B	DE	0.5, 0.6	1.5	1.34	0.44
120	ST		0.5, 0.6	0.98	1.24	0.47
120	ST	Veo	0.2, 0.6	1.1	1.08	0.52
120	ST	BW	0.5, 0.6	1	1.22	0.5
120	ST	DE	0.5, 0.6	1.7	1.34	0.45
120	B		0.5, 0.6	0.75	1.32	0.46
120	B	BW	0.5, 0.6	0.79	1.22	0.49
120	B	DE	0.5, 0.6	1.7	1.33	0.45
140	ST		0.5, 0.6	1.1	1.27	0.46
140	ST	Veo	0.2, 0.6	1.2	1.08	0.53
140	ST	BW	0.5, 0.6	1.1	1.21	0.51
140	ST	DE	0.5, 0.6	1.8	1.33	0.45
140	B		0.5, 0.6	0.81	1.32	0.44
140	B	BW	0.5, 0.6	0.82	1.3	0.46
140	B	DE	0.5, 0.6	1.8	1.33	0.46
	B	BMD	0.5, 0.6	1.9	-0.532	0.49
	ST	BMD	0.5, 0.6	1.9	-0.528	0.48

TABLE II

Table of slope, y-intercepts, and R-squared values for each Siemens fit.

Legend: Ub: Soft Tissue Stepped , Ur: Bone Stepped, Tin: using a tin filter, LR: low resolution (1 mm slices).

Energy (kVp)	Kernel	Other Identifier	Resolution in mm (axial, slice)	slope (m/s/HU)	y-intercept (km/s)	R-Squared
70	ST		0.4, 0.5	0.37	1.83	0.23
70	B		0.4, 0.5	0.57	1.25	0.43
70	B	LR	0.4, 1	0.59	1.24	0.44
80	ST		0.4, 0.5	0.42	1.82	0.24
80	B		0.4, 0.5	0.63	1.27	0.43
90	ST		0.4, 0.5	0.48	1.8	0.25
90	B		0.4, 0.5	0.68	1.28	0.42
90	B	LR	0.4, 1	0.7	1.27	0.44
100	ST		0.4, 0.5	0.53	1.79	0.26
100	B		0.4, 0.5	0.73	1.28	0.43
100	B	LR	0.4, 1	0.74	1.28	0.44
110	ST		0.4, 0.5	0.57	1.78	0.27
110	B		0.4, 0.5	0.77	1.28	0.42
110	B	LR	0.4, 1	0.8	1.27	0.43
120	ST		0.4, 0.5	0.58	1.81	0.25
120	ST	Ub36	0.5, 0.4	0.76	1.55	0.34
120	ST	Ub44	0.5, 0.4	0.86	1.32	0.47
120	ST	Ub49	0.5, 0.4	0.86	1.22	0.45
120	ST	Ub59	0.5, 0.4	0.56	1.58	0.34
120	B		0.4, 0.5	0.81	1.27	0.43
120	B	Ur77	0.5, 0.4	0.86	1.27	0.47
120	B	Ur81	0.5, 0.4	0.87	1.26	0.47
120	B	Ur85	0.5, 0.4	0.88	1.27	0.47
120	B	Ur89	0.5, 0.4	0.89	1.27	0.47
120	B	LR	0.4, 1	0.83	1.28	0.44
130	B		0.4, 0.5	0.84	1.28	0.43
130	B	LR	0.4, 1	0.85	1.3	0.43
140	ST		0.4, 0.5	0.65	1.78	0.26
140	ST	Ub36	0.5, 0.4	0.8	1.58	0.33
140	ST	Ub44	0.5, 0.4	0.95	1.3	0.47
140	ST	Ub49	0.5, 0.4	0.89	1.28	0.43
140	ST	Ub59	0.5, 0.4	0.6	1.59	0.34
140	B		0.4, 0.5	0.87	1.3	0.43
140	B	Ur77	0.5, 0.4	0.94	1.26	0.47
140	B	Ur81	0.5, 0.4	0.95	1.26	0.47
140	B	Ur85	0.5, 0.4	0.96	1.26	0.47

Energy (kVp)	Kernel	Other Identifier	Resolution in mm (axial, slice)	slope (m/s/HU)	y-intercept (km/s)	R-Squared
140	B	Ur89	0.5, 0.4	0.97	1.27	0.47
140	B	LR	0.4, 1	0.88	1.3	0.43
150	ST		0.4, 0.5	0.66	1.79	0.25
150	ST	Tin	0.4, 0.5	0.87	1.76	0.28
150	B		0.4, 0.5	0.88	1.32	0.42
150	B	Tin	0.4, 0.5	1	1.41	0.42
150	B	Tin,LR	0.4, 1	1	1.42	0.42
150	B	LR	0.4, 1	0.9	1.32	0.43