Predicting variation in subject thermal response during transcranial magnetic resonance guided focused ultrasound surgery: Comparison in seventeen subject datasets

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Purpose: In transcranial magnetic resonance-guided focused ultrasound (tcMRgFUS) treatments, the acoustic and spatial heterogeneity of the skull cause reflection, absorption, and scattering of the acoustic beams. These effects depend on skull-specific parameters and can lead to patient-specific thermal responses to the same transducer power. In this work, the authors develop a simulation tool to help predict these different experimental responses using 3D heterogeneous tissue models based on the subject CT images. The authors then validate and compare the predicted skull efficiencies to an experimental metric based on the subject thermal responses during tcMRgFUS treatments in a dataset of seventeen human subjects.

Methods: Seventeen human head CT scans were used to create tissue acoustic models, simulating the effects of reflection, absorption, and scattering of the acoustic beam as it propagates through a heterogeneous skull. The hybrid angular spectrum technique was used to model the acoustic beam propagation of the InSightec ExAblate 4000 head transducer for each subject, yielding maps of the specific absorption rate (SAR). The simulation assumed the transducer was geometrically focused to the thalamus of each subject, and the focal SAR at the target was used as a measure of the simulated skull efficiency. Experimental skull efficiency for each subject was calculated using the thermal temperature maps from the tcMRgFUS treatments. Axial temperature images (with no artifacts) were reconstructed with a single baseline, corrected using a referenceless algorithm. The experimental skull efficiency was calculated by dividing the reconstructed temperature rise 8.8 s after sonication by the applied acoustic power.

Results: The simulated skull efficiency using individual-specific heterogeneous models predicts well ($R^2 = 0.84$) the experimental energy efficiency.

Conclusions: This paper presents a simulation model to predict the variation in thermal responses measured in clinical tcMRgFUS treatments while being computationally feasible. © 2016 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4955436>]

Key words: transcrania ultrasound, therapeutic ultrasound, acoustic simulation, tcMRgFUS, MRgFUS

1. INTRODUCTION

Transcranial magnetic resonance-guided focused ultrasound (tcMRgFUS) is a technique used to achieve targeted tissue necrosis deep in the brain through an intact skull.¹ Tissue denaturation is achieved through geometric and electronic focusing of ultrasound beams leading to a temperature rise at the focus. Magnetic resonance (MR) imaging is used for target visualization and monitoring target and surrounding tissue temperature. In addition to physician assessment of the patient's clinical response, MR temperature images of the focus are used as a measure of the effectiveness and completion of the treatment. TcMRgFUS is being investigated for the treatment of essential tremors,²⁻⁴ parkinsonian tremor,⁵ obsessive compulsive disorder,⁶ neuropathic pain,^{7,8} and brain

tumors.⁹ As the safety and efficacy of the technique are established, more targets in the brain are expected to be treated with tcMRgFUS.¹⁰

The presence of the skull causes aberrations in the propagation of acoustic waves into the brain. The speed of each ultrasound beam is altered differently depending on its path through the skull. This causes the ultrasound waves to not add constructively at the focus, changing the shape or location of the focus. These phase aberrations are currently corrected clinically using x-ray computer tomography (CT) images to calculate delays for individual elements of the transducer based on the imaged skull geometry and estimates of the speed of sound relationship with Hounsfield units (HU).^{11,12} The skull also reflects, refracts, and attenuates the ultrasound beam. The result is a loss of ultrasound pressure or intensity at the focus.

The complex propagation of the acoustic waves in the skull, which includes the effects of reflection, refraction, and attenuation, in addition to phase aberration, has been understood using simulations. The optimal design characteristics of tcMRgFUS transducers,^{13–15} the effect of reflections due to the skull and skull base,¹⁶ and the effect of absorption on the heat deposition in the skull¹⁷ have all been studied using simulations. These simulations using general human skull models, as opposed to patient-specific models, have informed the treatment planning protocols of clinical tcMRgFUS treatments.¹⁷ However, subject-specific simulations are essential in understanding the consequences of individual and population heterogeneity in skull acoustic properties. Different parts of any individual skull have dissimilar properties, and different subjects have skulls of variable thickness, density, and spatial arrangement. These differences manifest as a variance in observed clinical thermal responses in tcMRgFUS treatments.

The clinical protocol for tcMRgFUS treatments begins with a screening CT scan of the patient obtained before treatment. On the day of the treatment, the patient's head is shaved and the patient is placed in the tcMRgFUS system with water filling the space between the transducer and the skull. The screening CT is registered to the MR images obtained on the treatment day and used to derive the appropriate phase corrections to drive the transducer. The geometric focal location of the transducer is placed on the treatment target, and low power sonications are performed to ascertain the location of the acoustic focus. Any change in the location of the target is performed by mechanically or electronically moving the focal zone. Additional intermediate power sonications are performed to verify that the anatomic location targeted produces the desired clinical response. Once the clinical team is satisfied by the target location, sonications are performed with higher power with the aim of causing tissue necrosis.

Because one cannot determine the efficiency of any particular skull from visual inspection of the CT images, the initial low power sonications are subject to a wide variety of thermal responses. For example, in the dataset studied in this article, we find a fourfold variation in skull efficiency to ultrasound. A power level that would achieve a 42 °C temperature rise in one subject would result in a 57 °C temperature rise in a different subject. The former temperature rise is suitable for the geometric verification of the focal spot, while the latter temperature rise is too high for an initial sonication, since it would achieve thermal necrosis, potentially at the wrong anatomic location. Clearly, a pretreatment prediction of the ultrasound transmission is critical for the treatment and protocol planning for tcMRgFUS.

A retrospective analysis of clinical tcMRgFUS treatments in recent work¹⁸ used patient-specific simulations to replicate the experimental protocol of tcMRgFUS treatments. The authors compared simulations to seven sonications in subjects treated with tcMRgFUS and found simulated temperatures overestimated measured experimental temperatures by 24%. The calculation time for each simulation in this study was long, between 40 and 65 h, and only five subject skulls were

considered. While the simulations modeled both acoustic and thermal effects, the thermal properties across different skulls were assumed to be identical and hence the simulated heterogeneity was solely based on the acoustic properties.

In this work, we validate an acoustic simulation technique that uses information from subject-specific CT scans to study the effect of the inherent acoustic properties of the skull on the thermal response observed in tcMRgFUS clinical treatments in an initial low power sonication. We study the difference in acoustic beam propagation due to the inherent acoustic properties of the skull, while keeping all other experimental-protocol dependent parameters constant. We model reflection, refraction, scattering, and absorption of the acoustic beam through the skull and compare the simulated skull responses to an experimentally derived measure of the ultrasound transmission through the skull in seventeen patients treated with tcMRgFUS. Additionally, we deconstruct the acoustic simulations to plot the effect of scattering, reflection, and absorption for each subject skull in order to understand the variation and impact of each component in this dataset.

This work does not attempt to recreate each individual patient's experimental protocol. We attempt to remove the effect of experimentally caused differences in this work, which would include patient positioning on the day of the treatment, the effect of phase correction, the thermal effects caused due to repeated sonications in the same location or near the same location, and many such experimentally determined factors. We attempt to probe the skull-based differences in this dataset. Further, due to a lack of subject-specific thermal property differentiation prior to the treatment, our analysis is based solely on acoustic properties.

2. METHODS

Seventeen datasets from two institutions (Stanford University, Stanford, CA, USA and University of Virginia, Charlottesville, VA, USA) were studied from patients treated with the InSightec ExAblate 4000 transcranial MR-guided focused ultrasound system coupled to a 3T GE Discovery MR750w. The same location, the ventral intermediate nucleus of the thalamus, was targeted in all patients, with the aim of treating essential tremor ($n = 11$) or parkinsonian tremor ($n = 6$). Each subject dataset included the screening CT images and the temperature images for every sonication of the tcMRgFUS treatment. The in-plane resolution of the CTs in the dataset ranged from 0.43 to 0.54 mm, while the slice thickness was constant at 0.62 mm. The CT scans were acquired at 100 kVp ($n = 1$), 120 kVp ($n = 13$), or 140 kVp ($n = 3$). The reconstruction kernel (head: $n = 10$, medium: $n = 6$, body: $n = 1$) and filter (bone plus: $n = 13$, standard: $n = 4$) used for different subject's CTs varied. The dataset also included information on the applied power, duration, and focal location used for each sonication. The acoustic power applied in the dataset ranged from 25 to 1300 W and the sonication duration ranged from 10 to 30 s.

Using these comprehensive data, we calculated two skull efficiency units for each subject: the experimental skull efficiency, which represents the thermal response observed in

the experimental treatment, and the simulated skull efficiency, which uses 3D heterogeneous acoustic simulations using subject-specific CT images to predict the skull acoustic response. We compared the experimental skull efficiency to the simulated skull efficiency in this dataset.

2.A. Experimental skull efficiency

In order to calculate the experimental skull efficiency and remove the effect of different MR parameters in each subject treatment monitoring, the temperature images for each subject were reconstructed with a single baseline subtraction. The thermal data for the treatments were reconstructed using a thermal coefficient of $-0.00909 \text{ ppm}/^{\circ}\text{C}$. The baseline subtraction was followed by a referenceless processing algorithm,¹⁹ with a frame region of interest as shown in Fig. 1(a). The inner and outer diameters of the frame were 32 and 64 mm, respectively, centered on the focal spot. The rectangular frame was chosen to be adequately far away from the focal zone to avoid the sonication-caused heating within the frame, while being sufficiently close to the focus to result in good background correction. The location and size of the frame were kept constant between sonications and constant and linear phase terms were corrected.

Previous studies²⁰ have shown that the specific absorption rate (SAR) can be estimated by measuring the rate of temperature increase immediately after the ultrasound power is turned on, when the conduction and perfusion losses are small compared to the absorbed power losses. The rate of temperature increase at the first sonication of each subject was used to calculate the experimental skull efficiency. This sonication fulfilled the criterion of having enough temperature rise to be above the noise floor while also remaining unaffected by treatment related factors (e.g., tissue changes due to previous sonication at the location or perfusion changes during the duration of the treatment). This removed the thermal effects of repeated sonications at the same spot (the temperature increase at a site of retreated sonications would

depend on the temperature effects from the last sonication). We also applied a noise threshold for choosing the first sonication; the first sonication was only chosen where the temperature was greater than 2.5 times the standard deviation calculated in the frame region of interest. This was true for 10 of the 17 patients. For 6 patients the second sonication was used to calculate the experimental skull efficiency, since the “initial” sonication did not result in adequate temperature rise to exceed 2.5 times the standard deviation of the noise. In one subject, the third sonication was used, since the first and second sonication had artifacts that obscured the low temperature rise.

The maximum temperature at the focus 8.8 s after the start of the ultrasound was reconstructed for all included initial sonications; this is the time that the center of k -space was acquired for the 3rd temperature image. The reconstructed maximum temperature for the first included sonication for a representative subject is shown in Fig. 1(b). As shown in Fig. 1(b), this time interval was within the 10 s interval shown in previous studies to permit a good approximation of the SAR.²¹ The maximum temperature reconstructed at 8.8 s was divided by the power of the sonication to calculate the experimental skull efficiency. The reconstruction of the maximum temperature at the same time point for each individual subject allows for consistency in the calculation of the experimental skull efficiency, in the presence of different MR parameters used in each clinical treatment. Since each subject’s first sonication was at a different power, the division of the reconstructed temperature rise 8.8 s after sonication by the applied acoustic power allows for normalized comparison of the experimental skull efficiency. Further, since the aim of this work was to predict using simulations the power required for the initial sonication for tcMRgFUS treatment in different subjects, the estimated experimental efficiency for the first sonication was used.

The standard deviation of the experimental skull efficiency was calculated using the standard deviation of the temperature measured in the referenceless processing frame divided by the sonication power.

FIG. 1. (a) An axial temperature image depicts one sonication with the referenceless frame used for processing. The frame is centered on the hotspot and has inner and outer dimensions of 32 and 64 mm, respectively. (b) The reconstructed temperatures of the first sonication (meeting the inclusion criteria) for a representative subject are shown, with the first point at 37 °C at time 0 added as an assumption. The time and power of the ultrasound are shown as an inset in the bottom. The maximum temperature reconstructed at 8.8 s was divided by the power of the sonication to calculate the experimental efficiency (eff) = 0.0233 °C/W.

2.B. Simulated skull efficiency

The simulated skull efficiency for each subject was the maximum focal SAR calculated using the hybrid angular spectrum (HAS) technique.²² The HAS technique models the linear propagation of acoustic waves in heterogeneous media. The 3D pressure pattern in a heterogeneous tissue model is calculated by alternating wave propagation between the space domain and the spatial-frequency (angular spectrum) domain. In this work, the skull was modeled as a heterogeneous tissue with each voxel modeled as a different tissue-type with properties established using the CT-based HU of the voxel. The resolution of the simulations equaled the resolution of the subject's screening CT. The acoustic properties of the skull were generated using the equations presented in Table I.

The speed of sound values for the skull voxels was generated based on the previous work²³ that reports the speed of sound values in the skull at a frequency close to the operating frequency of the transducer modeled in the simulation,

$$c = 1460 + 0.7096 \times HU, \quad (1)$$

where c is the speed of sound and HU is the value of Hounsfield unit for the voxel in the skull. Any voxel with a HU value less than 400 was assigned the speed of sound of soft tissue,²⁴ 1500 m/s, since the brain was considered as a homogeneous media for the purpose of beam propagation.

The density of each voxel was estimated using the fraction of bone and fraction of water in the voxel, using

$$\rho = f \times \rho_{\text{bone}} + (1 - f) \rho_{\text{water}}, \quad (2)$$

where f is the fraction of bone in the voxel, ρ_{bone} is the density of bone, and ρ_{water} is the density of water. For this dataset, the density of bone was considered 3000 kg/m³ and that of water 1000 kg/m³ based on previous skull simulation studies.^{12,23,25} The fraction of bone was calculated from the HU of the voxel using the equation

$$f = \frac{\frac{HU}{1000} \times \frac{\mu}{\rho_{\text{water_eff}}}}{\rho_{\text{bone}} \times \frac{\mu}{\rho_{\text{bone_eff}}} - \frac{\mu}{\rho_{\text{water_eff}}}}. \quad (3)$$

The effective μ/ρ_{eff} for bone and water was calculated using the beam spectrum as a function of energy $[S(E)]$ from a head model with 15 cm water and 1 cm of calcium, for example,

$$\frac{\mu}{\rho_{\text{water_eff}}} = \frac{\sum S(E) \times \frac{\mu}{\rho}(E)_{\text{water}}}{\sum S(E)}, \quad (4)$$

where μ stands for linear attenuation coefficient and ρ stands for density.

Absorption values of each voxel were calculated using the bone fraction of the voxel,

$$\alpha = f \alpha_{\text{bone}} + (1 - f) \alpha_{\text{soft tissue}}. \quad (5)$$

The absorption of bone²⁶ (α_{bone}) was set at 1.1 Np/cm/MHz as derived in the Appendix. This is close to the values reported in the other table value estimates.^{27,28} The absorption of soft tissue ($\alpha_{\text{soft tissue}}$) was set at 0.04 Np/cm/MHz.²⁸

The porosity of each voxel in the skull was calculated using the maximum HU value in the skull (excluding the inner ears, since this region has very dense bone). Figure 2(a) plots the histogram of the CT Hounsfield unit values of the skull and brain for three different subjects. Each subject had a different maximum HU value. To calculate the subject porosity distribution, the maximum HU voxel in each skull was considered to have a porosity of 5%. The choice of 5% porosity for the highest HU voxel is based on previous data reporting the range of porosity value for compact bone.^{29–32} For the three skull histograms shown in Fig. 2, the maximum HU values were 2100, 2250, and 2600. The porosity (ϕ) of the rest of the voxels in the subject was calculated from this value,

$$\phi = \frac{f_{\text{maxsubject}} - f}{f_{\text{maxsubject}}} + 0.05, \quad (6)$$

where f is the bone fraction of a voxel calculated using Eq. (1) and $f_{\text{maxsubject}}$ is the bone fraction of the voxel with the maximum HU value in the subject skull. Thus, while the bone fraction (and hence density) of a particular voxel in the skull is based on the range of HU values in the entire dataset, the porosity value of each voxel is based on the individual distribution of the HU values in the skull. The scattering component of the attenuation was based on the porosity of the skull voxel using the equations for calculating the porosity as

TABLE I. Tissue acoustic properties.

Simulation-type	Scattering (α_s) (Np/cm/MHz) porosity (ϕ)	Absorption (α_a) (Np/cm/MHz)	Speed of sound (c) (m/s) (Ref. 1)	Density (ρ) (g/cm ³)
A. Simulated skull efficiency	Scattering based on voxel porosity, Eq. (3) for porosity ($5\% < \phi < 25\%$) $\alpha_s = 0.0243 * \phi - 0.1908$ for porosity ($25\% < \phi < 40\%$), $\alpha_s = 0.171 * \phi - 3.74$ for porosity ($40\% < \phi < 60\%$), $\alpha_s = 3.2$ for porosity ($60\% < \phi$) $\alpha_s = -0.16 * \phi + 12.87$	$\alpha = f + (1 - f) \times 0.04$ where f = bone fraction	$c = 1460 + 0.7096 * HU$	$\rho = f \times 3 + (1 - f)$
B. Scattering-only	α_s	0.04	1550	1000
C. Reflection-only	0	0.04	1550	$\rho' = (\rho \times c) / 1550$
D. Absorption-only	0	$\alpha = f + (1 - f) \times 0.04$	1550	1000
E. Homogenous model	0	0.04	1550	1000

FIG. 2. (a) A histogram of the distribution of the voxel Hounsfield unit in three subjects is shown (the individual subjects are each depicted by different line plots). For each subject the maximum Hounsfield value is different and the highest Hounsfield value for each subject is fixed with a porosity of 5%. (b) The variation of acoustic scattering values with porosity values used for all subjects is shown; the highest voxel for each subject from (a) are denoted by a porosity value of 5% as shown by arrows from (a) to (b). (c) The variation of the acoustic scattering values in (Np/cm) with Hounsfield units is shown for the three subjects, with the line-plots representing the respective subjects from (a).

detailed in the simulation type A in Table I. These equations are derived using data from Tavakoli and Evans²⁶ which report the change in scattering with the porosity of a skull sample and are derived in the Appendix. Once the trabecular bone threshold was found for each subject, at 40% porosity that was patient-specific in Hounsfield units as shown in Fig. 2, we allowed the scattering values to stay constant within the region of trabecular bone. This range of trabecular bone was within the range reported in previous studies.^{29,30,32} The relationship of scattering as a function of porosity used for all subjects is shown in Fig. 2(b) with a decrease in scattering assumed after the range reported in Tavakoli and Evans²⁶ as the porosity increases towards soft tissue values. The relationship between scattering and HU for different skulls is shown in Fig. 2(c).

Figure 3 plots the distribution of Hounsfield units, speed of sound, density, attenuation, absorption, and scattering for one sagittal slice of a representative subject. The acoustic property

distribution for speed of sound and density in Figs. 3(b) and 3(c) follows the distribution of the HU in the slice, since the density and speed of sound values are based on a linear function of HU. The attenuation distribution in the slice, on the other hand, has high values in the low HU (and hence high porosity) region of the skull as observed in the top left and the bottom right in Fig. 3(d). Similarly, in regions near the top of the head, a difference in the distribution of absorption and scattering can be noticed.

The ExAblate 4000 (InSightec, Israel) brain system with a frequency of 680 kHz, an aperture of 30 cm, and a geometric focus of 15 cm was modeled with 1011 elements arranged in a hemispherical configuration. The manufacturer provided the approximate element locations; the exact dimensions of each element varied and were assumed to be circular for this simulation. Further, only one transducer was modeled even though the transducers used at the two different sites were of different frequencies (Stanford University, 680 kHz

FIG. 3. (a) A sagittal slice showing the distribution of Hounsfield unit values in a subject. The distribution of (b) speed of sound (m/s), (c) density (kg/m³), (d) attenuation (Np/cm), (e) absorption (Np/cm), and (f) scattering (Np/cm) values derived from (a) are shown. The figures are oriented as they were used in the simulation, with the transducer placed on the left of the picture, superior to the skull, and focusing into the brain.

and University of Virginia, 710 kHz). The space between the transducer and the skull was modeled as water (speed of sound 1500 m/s, attenuation 0 Np/cm, density 1000 kg/m³), and the brain was modeled as homogeneous soft tissue (speed of sound 1500 m/s, absorption 0.04 Np/cm, scattering 0 Np/cm, density 1000 kg/m³). For each subject skull, the geometric focus of the transducer was centered on a consistent position in the brain in the thalamus, centered on the side of the brain targeted during the treatment, as shown in Fig. 4(a). The pineal gland was used for target localization in the simulations since it was easily visible on the CT.

The simulations assumed perfect phase aberration correction by applying the time-reversal phases³³ calculated for each subject. The phase of each element at the geometric focus was calculated for a water-only model and a model that included the skull. The difference in phase at the focus between these two models was then applied to each element when running the phase corrected simulations. The acoustic intensity converted into heat due to the absorption was calculated using

$$\text{SAR} = \frac{\alpha \times |P|^2}{\rho c}, \quad (7)$$

where P is the 3D pressure pattern calculated using the HAS technique. Figure 4(b) shows the SAR pattern at the focus superimposed on a sagittal CT image of a subject. The calculated simulated SAR was spatially averaged to MR temperature resolution (1.02 mm isotropic) to replicate the voxel averaging in the experimental skull efficiency. The spatially averaged SAR at the target location (maximum voxel in the focus) in the simulation was considered the simulated skull efficiency of the subject skull.

The simulations were calculated on an Intel® Core™ i7 laptop (Lenovo Thinkpad X220) with a 2.70 GHz processor

and a 4 GB RAM. The calculation time for each subject simulation on average was 20 min.

2.C. Decomposing the loss in propagation

We decomposed each component of the acoustic loss in the propagation of the acoustic waves in the simulation—reflection, absorption, and scattering—for each individual skull using equations listed in the simulation types B–E in Table 1. Each simulation modeled only one kind of acoustic loss while keeping all others equal to the losses in a homogeneous model. The focal pressure values calculated using each individual component simulation were compared to the values for a homogeneous-only model, where the skull and brain were replaced with homogeneous brain tissue. The focal pressure from the component simulation was compared to the focal pressure from the homogeneous model simulation to calculate the loss attributed to reflection, scattering, or absorption.

3. RESULTS

A histogram and the cumulative frequency plot of the experimental efficiency in the dataset are shown in Fig. 5. The experimentally seen variation in a subject's thermal response varies significantly in our dataset, with the minimum experimental efficiency of 0.0206 [°C/W] and the maximum experimental efficiency almost fourfold larger at 0.0791 [°C/W].

Figure 6(a) shows a comparison of the simulated efficiency to the experimental efficiency for all the seventeen subjects, with the error bars for the experimental skull efficiency plotting the standard deviation of the calculated slopes. The simulated efficiency is predictive of the experimental efficiency seen in the treatments ($R^2 = 0.84$), with the standard

FIG. 4. (a) An axial slice of the x-ray CT image of a subject showing the method used to localize the target for a patient treated in the left side of the brain using the pineal gland (at the midline of the brain). The geometric focus of the transducer is located 12 mm anterior and laterally from this location. (b) Figure showing a simulated specific absorption rate (SAR) pattern (with zoomed-in inset) of an example subject, the SAR pattern is shown in (W/m³).

FIG. 5. A histogram and a cumulative percentage graph plot the distribution of the experimental skull efficiency in the dataset into equally spaced bins. The values of the experimental skull efficiency on the x -axis is shown in $^{\circ}\text{C}/\text{W}$, the primary y -axis plots the frequency of subjects in each bin, and the dotted line and the secondary y -axis plot the cumulative percentage of the data.

deviation plotting the variation in the inherent temperature data. Figure 6(b) separates out the subjects treated at each site (Stanford and University of Virginia) and plots the correlation of the simulated and experimental skull efficiency independently; the R^2 value for each are higher at 0.96 (Stanford) and 0.90 (University of Virginia) and the adjusted R^2 (taking into account the difference in sample size for the two sites) are 0.90 (Stanford) and 0.79 (University of Virginia). Considering the two site data either separately or together, the simulations predict the variation in the power required for the initial sonication well.

Figure 7(a) shows the decomposition of the individual loss components, absorption, reflection, and scattering for each subject in the dataset. A sagittal slice cut 5 cm from the top of the skull of each respective subject in Fig. 7(a) is shown in Fig. 7(b). The component analysis for all three effects shows a decreasing trend from left-to-right in Fig. 7. In other words, losses due to each component decrease as the simulated skull efficiency increases. Further, the losses

due to scattering are 2–3 times higher than the losses due to absorption in each individual skull in the simulations, consistent with prior studies that experimentally measured losses in small fragments of human calvarium.³⁴

While these trends hold on average, there are variations in the contributions of each of the three sources of loss. This can be observed in the twelfth and the thirteenth subjects' skulls in Fig. 7; while scattering is higher as you go from left-to-right in this pair, the reflection losses are lower, compensating for the higher scattering. Another interesting comparison is that of the eighth skull with the seventh and ninth. The eighth skull is mostly cortical bone, with the contribution to the loss from absorption higher than the skulls on either side. In this case, some of the absorption loss is compensated by the decrease in scattering loss compared to the seventh and ninth.

Figure 8 compares three subjects to illustrate the difficulty in predicting observed treatment efficiencies with CT appearance or scattering alone. Subjects 2 and 7 have a similar appearance on the sagittal CT slices [Fig. 8(a)], with both skulls showing a similar demarcation in the three layers of the calvarium. The two subjects had different experimental skull efficiency (22% difference) and simulated skull efficiency (48% difference). Alternatively, subjects 7 and 8 present a very different appearance in the sagittal CT slices. Subject 7 has more cortical bone than subject 8 [Fig. 8(b)], but the two subjects had very similar experimental skull efficiency (10% difference) and simulated skull efficiency (13% difference).

4. DISCUSSION

The results of this study demonstrate that simulation can predict the variation in skull thermal responses using only information available before treatment, in a clinically appropriate calculation time of 20 min. The large variation

FIG. 6. (a) The correlation of the simulated skull efficiency with the experimental skull efficiency for all sixteen subjects in the dataset is shown. A linear fit of the simulated skull efficiency with the experimental skull efficiency is shown with a dashed-line plot. The R^2 of the linear fit is 0.8358. The error bars denote the standard deviation of the calculated experimental skull efficiency by dividing the standard deviation of the noise of the temperature image (in the frame) with the applied ultrasound power of the sonication. (b) The correlation of the simulated skull efficiency with the experimental skull efficiency for the sixteen subjects in the dataset, with each individual site correlated separately. The R^2 of the linear fit is 0.96 for Stanford University (Stanford) subjects and 0.90 for University of Virginia (UVA) subjects.

FIG. 7. (a) The decomposition of individual loss components absorption (black), reflection (red), and scattering (blue) are shown in the *y*-axis for each individual skull in the dataset. The *x*-axis shows the normalized simulated skull efficiency, with the subjects going from low simulated skull efficiency on the left to high simulated skull efficiency on the right. (b) Sagittal slices of the individual subject skulls are shown with each subject skull plotted below the decomposition in (a). All the images are scaled similarly (scale shown in the figure right) and show the area 5 cm from the top of the skull. (See color online version.)

in the observed temperature rise in different subjects after the same applied energy underscores the importance of estimating skull efficiency before treatment. In our dataset, there was a large variation in the power required to achieve this sonication. Had the same power been used to begin the treatment protocol in these subjects, significantly different temperature rises would have been observed at the focus. Predicting this variation would allow the correct power to be used during initial low powered sonications delivered to the subject, adding an important safety feature to tcMRgFUS treatment.

These variable temperature elevation responses between patients to the same input power imply differences between patients in the treatment envelope, which is the region for each subject that can be treated using electronic steering. For example, in a patient with low experimental skull efficiency, the loss of power with electronic steering may be too large to allow for treatment far from the geometric focus of the transducer near the center of the brain, whereas in a patient

with a high experimental skull efficiency, the focus may be electronically steered³⁵ to treat regions further away from the center of the brain. This may be important in selecting patients with Parkinson disease in whom the target may be the globus pallidus interna.³⁶ High skull efficiency also allows for flexibility in the choice of transducer elements to be used. A simulation technique that can predict this patient-specific treatment envelope would be an extension of the simulation tool proposed here and an important tool to plan tcMRgFUS treatments, especially as regions outside the center of the brain are targeted.¹⁰ Another extension of this work would be phase aberration correction. For example, recently proposed techniques for phase correction have been shown to result in higher intensity at the focus at the expense of longer time for correction compared to the current clinically used techniques.^{37–39}

For the acoustic parameters used as inputs to the simulation, we build on equations used previously for simulating acoustic beam propagation in the skull^{12,25,34} and extend

FIG. 8. (a) The sagittal slices showing the distribution of Hounsfield units for three subject skulls are shown, with the same image scaling for the images. The subject numbers (2, 7, and 8) are derived from their location from the left on Fig. 7(b). Subjects 2 and 7 have a similar CT appearance, with the inner and outer skull layer clearly visible, while subjects 7 and 8 have a very different CT appearance. The high Hounsfield units in the jaw and those in the inner ear (not seen in this image) were not included in the calculation of the histogram. (b) A histogram of the distribution of the voxel Hounsfield unit values in three subjects in (a) are shown (the individual subjects are each depicted by different line plots). (c) The experimental and simulated skull efficiencies of the three subjects are listed in the table.

these equations for use in a large dataset. We model each voxel in the skull as a mixture of bone and water and calculate the bone fraction of each voxel of the skull. The density and absorption of each voxel is then dependent on the fraction of bone in the voxel, resulting in a linear relationship between the acoustic property and Hounsfield unit. The limits for these properties are based on measurements²⁶ and simulation models presented previously.^{25,28,34} The loss in acoustic beam intensity as it travels through a medium is dependent on reflection and attenuation. Attenuation losses include both tissue absorption and scattering losses. Particularly in the skull, previous work has demonstrated that the trabecular bone accounts for ~85% of loss due to scattering compared to the cortical bone.^{25,34} Using the highest density voxel in each skull (with an assumed porosity of 5%) to set the porosity of all voxels in the skull allows us to find a subject-specific threshold for trabecular bone rapidly and automatically and set the scattering values for those voxels, whereas previous work has used time consuming operator-driven segmentation to find this delineation.²⁹ Previous studies^{29–32} have reported porosity values ranging from 5% to 30% and we used the lowest (and most dense cortical bone) in this work at 5%. One of the differences of our model compared to the previous models^{12,25} is that this work does not model a global relationship between attenuation (or scattering) and bone density (or Hounsfield units) as seen from Fig. 2(c). Our model based on measurements allows for a scattering component that depends on the organization of the bone (hence the porosity) that is subject specific. So, while the bone component of the skull bone will have a certain Hounsfield unit value, how the pores are arranged will change the porosity. Further, our assumption of a scattering plateau is based on a hypothesis that the differences in scattering between compact bone and trabecular bone are larger than the differences between scattering in the trabecular bone voxels within the porosity range of 40%–60%, based on reported porosity values range in trabecular bone;^{29,30,32} this assumption likely results in some underestimation of scattering, but still takes into account the larger difference in cortical and trabecular bone scattering. This work does not model the differences in scattering within the voxels in trabecular bone. For the range of porosity from 60% to 80%, we assume a decreasing trend of attenuation with porosity, to allow for a continuous decrease in scattering component of each tissue voxel as its porosity travels closer and closer to the soft tissue, similar to the negative slope of scattering with porosity for this range reported.⁴⁰ While this work was done on bone phantoms, data related to human skull bone and porosity are limited and a simulation model that also models scattering differences in trabecular bone based on human bone samples would be more accurate.

The simulated skull efficiency only considers the innate skull-caused heterogeneity in the subject's CT to account for the diversity of the thermal responses seen in the experimental results. The experimental skull efficiency on the other hand includes the effect of the skull-based variation as well as other parameters that are determined on the day of the treatment: the accuracy of the phase correction,

the exact transducer placement, and the exact location of the target. Including these experimental factors could likely result in a better correlation of the simulated efficiency with the experimental efficiency, but those calculations can only be done retrospectively (once the treatment is completed and phase correction and transducer location values are available).

In general, these component analyses demonstrate the complex interplay of the effect of shape, size, spatial distribution, density, and porosity of subject skulls on simulated and experimental efficiencies. One thing to note about the component analysis is that the loss mechanism was only quantified as the pressure change at the focus. The changes due to a change in focal area for different loss mechanism simulations are not quantified in this focal pressure-based comparison. On average, the skulls with the clearer demarcation between the three layers of the cranium (and hence higher scattering in this model) have lower efficiency. On the other hand, just considering scattering as a variable to estimate transmission efficiency is not enough as it can be seen by subjects five, six, and seven, where the interaction between scattering and absorption results in different simulated skull efficiencies. Metrics that take into account only one of the parameters that affect ultrasound transmission will only partially differentiate between skull efficiency.⁴ Figure 8 shows three subject skulls, two with very similar and two with different appearance in the sagittal CT images. The appearance on the CT does not predict the experimental and simulated skull efficiency difference observed in these subjects.

The HAS technique used for calculating the SAR pattern at the focus is a linear wave propagation technique and hence does not include the effect of nonlinear wave propagation. The simulation technique also does not account for the effects of mode conversion as the wave propagates through the skull. The attenuation of shear waves in the skull is larger than that of longitudinal waves, so their effect on the focal SAR is likely small. But when considering skull temperature rise and focal locations closer to the skull, these effects will be more important.

Other potential reasons for the difference in simulated skull efficiency with experimental skull efficiency include effects of differences in experimental protocol at the two sites. The frequency and transducer element locations were different in the two sites; the elements in the path of calcifications that were turned off in the treatments were not considered in the simulations since all calcifications were segmented as normal brain tissue. The reflections from the skull base were ignored in these simulations as were the differences in CT filters used for different subjects and at the two different sites (the CT filters used were on average consistent within site but different between sites). While this work focused on the innate skull-caused effects on the focal energy in the brain, perhaps the better correlation between the simulated skull efficiency with the experimental skull efficiency when considering individual sites separately is explained by these experimental protocol differences.

5. CONCLUSION

We present a simulation to predict the variation in thermal responses measured in clinical tcMRgFUS treatments. We compare the predictions from this tool, the simulated skull efficiency, to an experimentally derived measure of skull thermal response, the experimental skull efficiency. We show that the experimental skull efficiency correlates with simulated skull efficiency ($R^2 = 0.84$). Further, we decompose each individual loss term, namely reflection, scattering, and absorption, in the acoustic propagation through the skull and report on the effect sizes of each component for each subject skull in the dataset.

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CONFLICT OF INTEREST DISCLOSURE

The authors have no COI to report.

APPENDIX: CALCULATION OF SCATTERING EQUATION

In this section the derivation of the scattering equations in Table I are explained briefly. The scattering equations from a porosity of 5%–40% are derived from the data reported in Table II of the cited article by Tavakoli.²⁶ The values from Table II are given below in both dB/MHz and Np/MHz/cm. The dB/MHz values from the article are converted to Np/cm and then the effect of the attenuation change with frequency is calculated using equation

$$\text{Atten}_{\text{bone}} = \text{Atten}_{1\text{MHz}} \times \text{Freq}^{1.7}. \quad (\text{A1})$$

Figure 9 plots the same data (for all frequencies) as reported in Table II using the relationship between attenuation and frequency.

The absorption of the sample, which should not change with frequency [since the frequency effect has been separated using Eq. (A1)], stays the same over the different frequencies.

TABLE II. Data from Ref. 26, reproduced.

Porosity	Attenuation (0.6 MHz)		Np/MHz/cm
	dB/MHz	Sample thickness cm	
40.6	18.9	1.2	3.022 104 536
38	16.7	1.2	2.670 325 172
35.2	15.2	1.2	2.430 475 606
32.1	12.4	1.2	1.982 756 415
28.7	9.8	1.2	1.567 017 167
25	7.3	1.2	1.167 267 89
20.1	6.5	1.2	1.039 348 121
16.1	5.9	1.2	0.943 408 294
11	5.2	1.2	0.831 478 497
5	4.9	1.2	0.783 508 583

FIG. 9. The figure plots the change in attenuation with porosity for a sample containing bone material in three frequencies. The value of attenuation at 5% porosity, 1.1 Np/cm/MHz, is considered the absorption of the sample in this work.

The relationship of scattering with frequency is different, allowing the separation of absorption and scattering in the sample. Since the sample used to calculate the attenuation change with frequency at different porosity levels was the same sample, the amount of material in the sample did not change; hence we hypothesized that the absorption in the sample did not change. As seen in Fig. 9 this was indeed the case, at 5% porosity (which would mean, the sample has the lowest porosity and all attenuation observed would be absorption).

Finally, once the scattering component from the absorption component was separated as explained above, we fitted two lines to the scattering component at 0.6 MHz. To be noted, only the absorption component as affected by frequency was removed, the scattering component was still in the equation and does change with frequency. So in order to find out the effect of porosity on scattering for this work, we looked at the scattering as it is affected by porosity at the frequency of 0.6 MHz, which is the closest for our modeled transducer at 0.68 MHz. Two lines shown below are fitted to the trends seen in the graph to derive equations shown in Table I of this work (Fig. 10).

FIG. 10. The figure plots the relationship attenuation change with porosity for a sample for a frequency of 0.6 MHz. Two line fits are used to estimate the relationship, one for the porosity value till 25% and the next for porosity value till 40%. The strength of the line fits are reported in the figure, the equations are reported in Table I.

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