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A numerical study on the oblique focus in MR-guided transcranial focused ultrasound

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Abstract

Recent clinical data showing thermal lesions from treatments of essential tremor using MR-guided transcranial focused ultrasound shows that in many cases the focus is oblique to the main axis of the phased array. The potential for this obliquity to extend the focus into lateral regions of the brain has led to speculation as to the cause of the oblique focus, and whether it is possible to realign the focus. Numerical simulations were performed on clinical export data to analyze the causes of the oblique focus and determine methods for its correction. It was found that the focal obliquity could be replicated with the numerical simulations to within $23.2 \pm 13.6^\circ$ of the clinical cases. It was then found that a major cause of the focal obliquity was the presence of sidelobes, caused by an unequal deposition of power from the different transducer elements in the array at the focus. In addition, it was found that a 65% reduction in focal obliquity was possible using phase and amplitude corrections. Potential drawbacks include the higher levels of skull heating required when modifying the distribution of power among the transducer elements, and the difficulty at present in obtaining ideal phase corrections from CT information alone. These techniques for the reduction of focal obliquity can be applied to other applications of transcranial focused ultrasound involving lower total energy deposition, such as blood-brain barrier opening, where the issue of skull heating is minimal.

1. Introduction

A series of recent clinical trials, including the treatments of essential tremor (Lipsman et al. 2013, Elias et al. 2013), obsessive compulsive disorder (Jung et al. 2015), Parkinson's Disease (Magara et al. 2014) and brain tumors (McDannold et al. 2010), have demonstrated the promise of MR-guided focused ultrasound as a non-ionizing, non-invasive neurosurgery tool. Early work in the field of transcranial focused ultrasound showed that by using a large-aperture hemispherical phased array of individually-driven transducer elements (Clement &

Hynynen 2002), it became possible to obtain a well-resolved focus without the need for a craniotomy by using amplitude and phasing corrections (Thomas & Fink 1996, Hynynen & Jolesz 1998) to correct for aberrations due to the skull. A range of potential future applications of transcranial focused ultrasound have also been described in the literature, including the treatments of trigeminal neuralgia (Monteith et al. 2013), epilepsy (Legon et al. 2014), third ventriculostomy (Alkins et al. 2013), and sonothrombolysis for the treatment of stroke (Burgess et al. 2012). As MR-guided transcranial high power focused ultrasound becomes a more prominent neurosurgery tool, it is imperative to investigate the role that various parameters have on the therapy, and determine if there are techniques that can be used to improve treatment outcomes.

In clinical applications of focused ultrasound where significant temperature elevations are involved, complete control of the deposition of heat in the brain is imperative to a safe and effective therapy. The close proximity of critical nerve structures and functional areas in the brain to any given target render this level of control even more important, to avoid peripheral thermal damage. Assuming that a hemispherical phased array were to sonicate to the geometric focus through a homogeneous medium, it is expected that the focus would be oriented along the main axis of the array, from symmetry. In this paper, it is shown that the heating at the focus during clinical treatments of essential tremor is often oblique to the main axis of the array when performing sonications through the skull, and the various causes of the oblique focus and their effects are investigated in this retrospective analysis.

Previous studies in transcranial focused ultrasound have investigated the targeting accuracy of brain therapy (Chauvet et al. 2013), by comparing the relative locations of the target focus and the actual focus in the three Cartesian directions. In addition, various studies from other brain therapy modalities, such as gamma knife radiosurgery, have been performed to determine the targeting accuracy (Walton et al. 1996, Bednarz et al. 1999, Massager et al. 2007, Castinetti et al. 2007), as well as discussion on the effects of errors in targeting (Castinetti et al. 2007). It is argued here that the obliquity of the focus observed in transcranial focused ultrasound treatments is another indicator of targeting accuracy. The spatial orientation of the deposition of heat in the brain could then be studied in a similar fashion to the effects of radiation dose contours in radiosurgery.

Using clinical data exported from a clinical trial of essential tremor using focused ultrasound (Lipsman et al. 2013), consisting of imaging data and treatment parameters, it will first be shown using numerical modeling that the presented real-time MR thermometry images and 1-day post-treatment MR images showing the oblique focus can be replicated, further validating a previously-introduced full-wave numerical model (Pulkkinen et al. 2014). It will then be shown that by using combinations of full-wave phase (White et al. 2005, Marquet et al. 2009) and amplitude corrections (White et al. 2005), it is possible to reduce the focal obliquity, as well as the more conventional metrics of the peak sidelobe ratio and the volume of heating.

2. Materials and Methods

2.1. Patient Imaging Data

Sixteen MR and CT imaging datasets were obtained from a clinical trial of MR-guided focused ultrasound for the treatment of essential tremor (Lipsman et al. 2013). In the clinical trial, the VIM nucleus was targeted, and the patient was positioned such that the target focus was in close proximity to the geometric focus of the hemispherical phased array. The sonication powers and durations were such that a therapeutic level of heating could be obtained to cause a thermal lesion. The sonication powers and durations of the analyzed cases are listed in Table 1, along with the low levels of steering used to target the precise location of the VIM nucleus.

The resolution of the CT scans (Brilliance 40, Philips Healthcare, the Netherlands) used for the segmentation of the skull into simulation grid points was $1\text{ mm} \times 0.49\text{ mm} \times 0.49\text{ mm}$. Fast-spin echo T2-weighted MR images were used for image registration during the clinical trials, and obtained from a 3T scanner (General Electric, Milwaukee, WI, USA). An example of the exported MR data is shown in Figure 1 in the sagittal and coronal planes, showing the location of the skull inside a superimposed hemispherical transducer array.

1 day post-treatment 3D fast spoiled gradient echo MR images ($TR = 8.3\text{ms}$, $TE = 3.3\text{ ms}$) were obtained from each of the six treatment cases, labeled as Patients A–F. Coronal slices of these images through the lesion site are shown in Figure 2 and demonstrate the clinical oblique focus cases, where the white arrows highlight the location of the created lesions. The images are oriented such that the image y-axis corresponds to the inferior-superior direction of the treatment axes, and therefore shows the tilt of the focus off the main axis of the transducer array. For clarity, Figure 3 illustrates a 3D rendering of the oblique lesion volume for Patient C. This figure demonstrates the spatial orientation of the lesion in space using standard spherical coordinates.

2.2. Therapy Device

A phased array (ExAblate 4000, InSightec, Israel) consisting of 1024 independently-driven ultrasound transducers in a hemispherical configuration of 15 cm radius of curvature was modeled. The transducer locations in space were determined from the treatment export data and were assumed to operate as circular piston transducers, with maximum possible radius such that no two transducers would overlap. The resultant radius of each transducer was approximately 5 mm, where all transducers had the same size. The transducer elements operated at 650 kHz. The co-registration of the CT images and the therapy device were performed manually by the clinician during treatment, and the registration information was exported and used in the modeling.

2.3. Patient Treatment Modeling

In order to obtain the acoustic pressure field, a previously-introduced numerical model was used (Pulkkinen et al. 2014), which combines finite difference simulations (Croft 1977) with the grid method (Zhang 2004). This hybrid model calculates the pressure field in the brain

and the particle displacement field in the cranial bone. The governing equation of acoustic propagation in fluids is given by (Pierce 1989)

$$(\partial_{tt}^2 + 2\alpha_L c \partial_t)p = c^2 (\nabla^2 - \frac{1}{\rho} \nabla \rho \cdot \nabla)p, \quad (1)$$

where p denotes the acoustic pressure, α_L is the longitudinal attenuation coefficient, c is the speed of sound, and ρ is the density. In solid domains, the governing equation is given by (Auld 1973)

$$\rho \partial_{tt}^2 \mathbf{u} = (\mu + \eta \partial_t) \nabla^2 \mathbf{u} + (\lambda + \mu + \xi \partial_t + \frac{\eta}{3} \partial_t) \nabla (\nabla \cdot \mathbf{u}), \quad (2)$$

where $\mathbf{u}$ is the vector field of the particle displacements in the three Cartesian directions, λ and μ are the first and second Lamé coefficients, and η and ξ are the first and second viscosity parameters. Details of the numerical implementation of Equations 1 and 2 are given in the Appendix of Pulkkinen *et al* (2014). The longitudinal speed of sound, c_L , and attenuation, α_L , in skull, were found using a spline interpolation (Pichardo et al. 2011). Since the authors are unaware of any experimental shear speed and attenuation data as a

function of density, scaling factors were used, so that $c_s = \frac{1400}{2700} c_L(\rho)$ and $\alpha_s(\rho) = \frac{90}{85} \alpha_L(\rho)$ (White et al. 2006). A time step size of 10.5 ns combined with a spatial voxel size of dimensions 0.23 mm was used to obtain a maximum Courant-Friedrichs-Lewy (CFL) value (Courant et al. 1967) of 0.15, where the CFL is calculated as $CFL = c \Delta t \Delta h^{-1}$, for spatial discretization step size Δh and temporal step size Δt , where the CFL was calculated in each domain separately and for both longitudinal and shear sound speeds in bone. The spatial discretization was chosen in order to have seven points per wavelength in water.

Each sonicating transducer element was driven with a sinusoidal signal that increased linearly from zero amplitude to the prescribed sonication amplitude in five cycles. The Neumann boundary condition, defined as

$$\partial_n p = g, \quad (3)$$

was used on interfaces between transducer faces and water, where n is the normal to the transducer surface, p is the pressure, and g is a term describing the prescribed oscillation of the transducer surfaces. The absorbing boundary condition was used on other boundaries.

A Fast Fourier Transform of the final two cycles of the acoustic field was taken to obtain a stable average pressure field over the treatment domain. The total size of the treatment domain varied between $938 \times 954 \times 643$ and $938 \times 954 \times 693$ points, and each simulation was run over 20085 temporal steps, allowing enough time to simulate the propagation of ultrasound 30 cm in water.

From the pressure map, the absorbed power density was calculated, using the relation (Pierce 1989)

$$Q = \frac{\alpha}{\rho c} |p|^2 \quad (4)$$

in the brain tissue, and the relation (Hosten et al. 2008)

$$Q = \frac{\omega}{2} \Im(\sigma_i \bar{\varepsilon}_i) \quad (5)$$

in the skull bone, where ω is the angular frequency, σ denotes the stress tensor, ε denotes the strain tensor (Auld 1973), and $\Im$ denotes the imaginary component. The absorbed power density in the entire domain was then used as a time-independent heat source in the Pennes bioheat equation (Pennes 1948), defined as

$$\rho C_t \partial_t T = \kappa \nabla^2 T - \rho_b C_b W_b (T - T_b) + Q, \quad (6)$$

where ρ is the tissue density, C is the specific heat capacity of the tissue, κ is the tissue thermal conductivity, ρ_b is the blood density, C_b is the specific heat capacity of blood, W_b is the perfusion rate in the tissue, T_b is the blood temperature, and Q is a constant heat source, determined from the pressure field. (6) was solved using a finite difference time domain (FDTD) technique. Finally, the thermal dose, TD , was defined as (Sapareto & Dewey 1984)

$$TD = \int_0^t R(T(t'))^{T_{\text{ref}} - T(t')} dt', \quad (7)$$

for sonication duration t , where

$$R(T) = \begin{cases} 0.50, & T \geq T_{\text{ref}} \\ 0.25, & T < T_{\text{ref}} \end{cases} \quad (8)$$

and $T_{\text{ref}} = 43^\circ\text{C}$. Table 2 lists the values of the parameters used in the acoustic and thermal simulations.

2.3.1. Clinical Phase Corrections—The phase corrections used in the clinical trial follow previous work to correct the phase (Clement & Hynynen 2002). In this case, the direct line between the transducer face and the focus is drawn, and the phase delay calculated from the CT data is computed along this straight ray path. The focus is then steered to the target focus location.

2.3.2. Clinical Amplitude Controls to Reduce Skull Heating—Amplitude controls designed to reduce skull heating (Sun & Hynynen 1999) were used during the clinical trials. These amplitude controls distributed the deposition of energy evenly in the skull during the treatment in order to utilize the entire skull surface to minimize skull heating.

2.4. Investigation of Causes of the Oblique Focus

The effect of the distribution of transducer element powers used to distribute heating evenly on the surface of the skull, and the heterogeneity of the skull, which will be considered skull aberration effects, on the focus obliquity were studied. After determining the relative magnitude of each of these effects, it was then determined whether it was possible to compensate for these effects using the degrees of freedom afforded by the elements in the phased array system, namely phase and amplitude controls.

Three independent metrics were used to quantify the magnitude of these various effects on the focal obliquity: the peak relative sidelobe intensity of the acoustic pressure field with respect to the main lobe, the full-width half maximum of the temperature distribution, and the orientation of the focus in space, termed the *obliquity* of the focus.

2.4.1. Quantification of Obliquity—The *obliquity* of the focus was measured by fitting the normalized temperature distribution of the focus to a 3D Gaussian distribution, defined as

$$G = (2\pi)^{-3/2} |\Sigma|^{-1/2} e^{-1/2(x-\mu)^T \Sigma^{-1}(x-\mu)}, \quad (9)$$

where μ denotes the location of the peak temperature, and Σ is the weighted sample covariance matrix, defined as

$$\Sigma = \frac{\sum w_i}{(\sum w_i)^2 - \sum w_i^2} \sum w_i (x_i - \mu)^T (x_i - \mu), \quad (10)$$

where w_i corresponds to the temperature, and x_i the position, of the i^{th} voxel. The unit eigenvector corresponding to the maximum eigenvalue of the covariance matrix was taken as the major axis of the distribution, and the unit spherical representation of this eigenvector, defined by (θ, ϕ) , was used to quantify the oblique angles. In this case, θ is the polar angle and ϕ is the azimuthal angle. In the following, the *obliquity* will refer to θ , the tilt from the main axis. Figure 3 illustrates the obliquity metric on the 3D clinical lesion volume.

The real-time MR thermometry images are only available in certain planes for the clinical treatments, and as a result, the obliquity measured from the numerical simulations was compared to the 3D volumetric lesion data provided by the 1-day post-treatment MR images.

2.4.2. Transducer Power Effects—The transducer powers during clinical treatments are such that the deposition of acoustic power is equal across the surface of the skull (Sun &

Hynynen 1999). In order to determine the effect of this distribution of power on the focusing quality, the treatment was simulated assuming equal transducer powers on all elements, and the focusing quality was analyzed.

2.4.3. Skull Aberration Effects—The effect of the heterogeneity of the skull manifests in two ways during transcranial focused ultrasound therapy: through phase changes in the transmitted acoustic field, and through variable transmission to the focus from different elements in the array. We seek to investigate both these effects.

To determine the effect of the temporal shifts in the acoustic field over different regions of the skull, a full-wave phasing scheme was used. In this way, it was deemed possible to determine the optimal phasing solution, resulting in all element fields arriving in-phase at the target focus. To obtain the phases in this case, a source was placed at the focus and backwards propagated to the transducer faces, where the phase was read off. The inverted phase was then used as the optimal phase for transmission.

To determine the effect of the variable transmission to the focus, a similar inversion scheme was employed. Instead of the phase, the average acoustic power was determined at the transducer faces, and this value was reciprocated, such that the deposition of acoustic power at the focus is identical for all elements, as has been previously proposed (White et al. 2005). This was termed the “inverse amplitude correction” by White et al.

2.5. Simulated Cases

Five different cases were simulated to extract the independent effects of the skull aberration and distribution of transducer power, as listed in Table 3. *EIS* refers to the clinical replication, where the transducer powers distribute power evenly on the surface of the skull (Sun & Hynynen 1999). In this case, the clinical export phase and amplitude were used. *EIT* is the distribution of equal intensity on the transducers, where the clinical phase corrections are coupled with an even distribution of power on the surface of the transducer. The third case, *AC*, refers to the use of amplitude corrections coupled with the clinical phase corrections. The fourth case, *PC*, uses the clinical amplitude export with full-wave phase corrections, and *APC*, the fifth case, refers to the use of both amplitude corrections and full-wave phase corrections.

3. Results

3.1. Replication of Clinical Data

Figure 4 illustrates qualitatively the ability to replicate the focus morphologies observed during clinical treatments for Patient E. The simulated acoustic pressure field is shown in the bottom right of the figure (*Acoustic Pressure*), and the temperature map at the focus generated from this pressure field, using Equations 4 and 6, is shown in the bottom left (*Temperature*). The 1-day post-treatment MR image first presented in Figure 2 is magnified and shown in the upper righthand corner (*MR Imaging*), clearly illustrating the outline of the thermal lesion. The numerically-simulated thermal dose lesions are superimposed, with contours at 0.1, 1, 5, 10, and 60 minutes thermal dose, where the power was normalized to obtain the peak temperature obtained from the clinical export data in order to have a fair

comparison. In addition, the real-time thermometry image taken 24s after the start of the sonication, is shown in the upper lefthand corner (*MR Thermometry*). It is important to note the morphological similarities between the simulated temperature map and the real-time MR thermometry map; including the obliquity demonstrated in both cases. The thermal lesion, in particular, clearly demarcates the extent of the ablated tissue, manifesting as an oblique focus.

Figure 5 summarizes the numerically-simulated heating maps for Patients A–F. It is useful to compare these heating maps to the focal lesions illustrated in Figure 2, demonstrating morphological similarities between the temperature maps at the end of heating and the resultant thermal lesions. Particular attention should be paid to Patients C and E, where the oblique focus is most notable in both the clinical and simulated images.

To add to these qualitative findings, Table 4 provides a quantitative comparison of the clinical oblique foci and the numerically-simulated cases (Case 1, as described in Table 3). The (θ, ϕ) spherical representation of the major axis of the oblique focus, first introduced in Section 2.4.1, is listed for all six cases. For the clinical cases, since the MR thermometry maps were only taken in one plane at a time, the 3D 1-day post-treatment MR images delineating the lesion were used to measure the clinical focal obliquity. It should be noted that in all six cases, there is agreement between the directionality of the oblique foci from the clinical export data and the numerical simulations. It was found that it was possible to correctly replicate the obliquity observed clinically to within $23.1 \pm 19.5^\circ$.

Using the qualitative similarities between the simulated temperature fields and the post-treatment MR images and real-time thermometry MR images, as demonstrated in Figures 4 and 5, as well as the quantitative comparison between the clinical and numerical results outlined in Table 4, it appears that the numerical simulations are able to replicate many of the morphological features demonstrated clinically, and allow for the further study of the causes of the oblique focus.

3.2. Investigation of Causes of the Oblique Focus

It was hypothesized that the oblique focus observed during clinical treatments was partially caused by the presence of sidelobes in the direction of the focal obliquity. The simulated acoustic pressure maps for Patients A–F are shown in Figure 6. It can be seen from these pressure maps that the sidelobes of the acoustic field are in the direction of the oblique foci illustrated in Figures 2 and 5.

This observation is further supported by Figure 7, where the temperature evolution over time is demonstrated for Patient E, where it appears that the manifestation of the oblique focus arises from the sidelobes, as highlighted by the white arrow in the leftmost panel at $t = 0.1$ s. These sidelobes become masked over time as the diffusion of heat generates a single focus, whereby the lesion forms, as can be seen after 5s of heating.

Interestingly, there also existed clinical data which suggested the existence of a main lobe, as opposed to side lobe, effect on the focal obliquity. As illustrated in Figure 8, using phase corrections has a minimal effect on the focal obliquity, while amplitude and phase

corrections appear to re-align the main axis of the focus in the inferior-superior direction. In addition, it is clear from the acoustic pressure field illustrated in (a) that the sidelobes in this case appear to have minimal effect on the observed focal obliquity, illustrated with the time-temperature evolution in Figure 9. This demonstrates that there are clinical cases in which either sidelobes or the main lobe can independently affect the observed focal obliquity.

Figure 10 illustrates the effect of each parameter on the focal obliquity, peak sidelobe ratio, and heating volume in the numerical simulations. The values used in the plots are summarized in Table 5. Figure 10 demonstrates that it is the aberration effects of the skull that lead to the oblique focus. From the figure, it appears that amplitude corrections, labeled as *AC* and *APC*, significantly reduce the focal obliquity by 52 and 72%, respectively, whereas full-wave phase corrections, as labeled *PC* and *APC*, contribute the most to the heating volume (29 and 38% reductions, respectively) and the peak sidelobe ratio (21 and 32% reductions, respectively).

On the other hand, the distribution of transducer power used to reduce heating on the surface of the skull appears to play little role in the observed focal obliquity, as can be seen when setting all element powers equally; that is, when moving from *EIS* to *EIT* in Figure 10. The distribution of power among the elements, however, does play a role in the correction of the oblique focus by compensating for the skull aberration effects which lead to variable deposition of power at the focus. This subtle distinction is important to note.

Figure 11 shows the simulated temperature maps, comparing the heating resulting from full-wave and clinical phase corrections. In this case, it is clear that there are improvements in the spatial resolution of the focus when using full-wave phasing corrections, since, intuitively, improved phase corrections lead to a higher concentration of deposited energy at the target focus. The obliquity of the focus, however, remains. In the righthand panel, when using amplitude corrections, the focus orients in the inferior-superior direction, thereby reducing the obliquity from this axis.

The combination of full-wave phase and amplitude corrections, therefore, leads to a focus resembling the focus obtained without the skull, as shown in Figure 12. It is emphasized in this figure that the distribution of power has minimal effect, while the full inversion of phase and amplitude leads to a focus with a similar morphology to the water-only case.

3.3. Skull Heating Considerations

It is important to note that manipulation of the power distribution among the elements can lead to uneven skull heating levels, since the clinical power distribution (*EIS*) is designed to distribute heat evenly on the surface of the skull. Figure 13 demonstrates the increased skull heating when using amplitude corrections on Patient C. It is shown that there are multiple regions on the inner surface of the skull, adjacent to brain tissue, where the temperature elevation exceeds the temperature elevation at the focus. As a result, full inversion of power may be infeasible, particularly with patients that require significantly more total power to achieve therapeutic temperature elevations.

4. Discussion

It was first shown that a hybrid numerical model was able to replicate some of the trends of the focal obliquity observed in clinical treatments of essential tremor. It was then shown that the occurrence oblique focus in MR-guided transcranial focused ultrasound can be attributed to the intensity of sidelobes in the acoustic pressure field. It was found that a reasonable configuration to reduce focal obliquity is by using amplitude corrections to deposit acoustic power evenly at the focus from all elements in the array. Combined with full-wave phase corrections that take into account the refraction due to the skull along the ray path, it is possible to also reduce the peak sidelobe ratio and the heating volume of the focus.

The analysis in this paper was performed for a relatively central target within the brain, namely the VIM nucleus in the thalamus. It was assumed that the focus was well within the steering range of the phased array. Future studies may look at the effect of phased array controls on focusing at targets at the extreme regions of the steering range.

By using amplitude corrections, the total deposition of power at the focus is lower for a constant total array power, since the powers of the transducer elements that contribute more to the temperature rise at the focus are being reduced, and the powers of the transducer elements with low transmission efficiency are being increased (White et al. 2005). As a result, it may be infeasible to use amplitude corrections with the powers required for thermal ablation. Further retrospective analysis of skull heating in clinical trials and prior (Hynynen et al. 2006, McDannold et al. 2004) and future experimental studies may indicate general trends of maximum acoustic power deposition on the surface of the skull. Using these safety guidelines as an upper bound to the acoustic power assigned to a single element, the amplitude corrections could then be used safely.

Reinforcing previous studies (Smith et al. 1986, O'Donnell & Flax 1988, Thomas & Fink 1996, Sun & Hynynen 1999), it was also shown that phasing corrections are critically important to focusing quality in transcranial focused ultrasound. The clinical phase corrections (Clement & Hynynen 2002) use average CT-derived corrections in a ray model, and only compensate along the direct ray path from the transducer element to the focus. It was found that by using full-wave phase corrections (Marquet et al. 2009), it is possible to reduce the presence of sidelobes and the heating volume significantly. Combining the phase and amplitude corrections, it is possible to correct the focus close to the case with no skull present. It has been generally assumed that amplitude corrections should play minimal role at this frequency (Aubry et al. 2003) to achieve high focusing quality, but it is shown here that the manifestation of the oblique focus in clinical results as a result of imperfect phase corrections can be somewhat rectified by the use of amplitude corrections.

With increasing computer processor speed and memory capabilities, it is becoming more feasible to implement complex acoustic models for transcranial treatment planning. As a result, it may be possible to integrate more accurate models to minimize side-lobes and optimize the deposition of energy at the target focus. In addition, a random sparse array (Goss et al. 1996) or array with elements optimally-positioned (Hutchinson et al. 1996)

could potentially reduce the side lobe effect with similar efficacy to these more complicated models.

The implementation of amplitude controls is, of course, a very delicate matter. Since the EIS algorithm is used to minimize skull heating during treatment, any deviation from this power distribution will necessarily increase temperature at some point in the skull. Therefore, a balance may be found based on retrospective analysis of patient skull heating, as well as treatment efficacy studies, to determine the optimal phased array controls to use in each case.

In some patients, the treatment involved the sonication of slightly shifted points, in addition to the target point. The shift, if at all, was typically on the order of a millimeter, and hence it is believed that there should be minimal impact on the obliquity observed. It is possible, however, that as a result of these additional sonications, some of the 1-day post-treatment MR images could be mischaracterized as oblique foci. As mentioned previously, however, there have been studies on treatment targeting accuracy in transcranial focused ultrasound at the higher frequency of 1 MHz (Chauvet et al. 2013), and as a result, there is still some targeting inaccuracy ranging from 0.4 – 0.7 mm in the Cartesian directions. This may also play a role in some error associated with the analysis.

4.1. Limitations of the Obliquity Metric

The focus was assumed to be non-spherical, in the characteristic cigar shape in focused ultrasound. In this study, this was found to be a rather good approximation due to the use of a hemispherical phased array. In the case where the focus approaches a spherical volume, the concept of obliquity as defined here becomes increasingly poorly defined. One potential solution is the use of the ratio of minimum and maximum eigenvalues as a secondary metric to determine the extent to which the focus is oblique. If the ratio is close to 1, then the focus is almost spherical, and hence not oblique. In the case where the ratio is small, then the focus is oblique, and the proposed metric defines the obliquity.

4.2. Discrepancies between Numerical Modeling and Clinical Data

The existence of some discrepancy in Table 4 will be discussed. The correspondence between the numerical simulations and the clinical data ranges from between 5.2 to 47.8°. There are numerous potential sources of discrepancy. First, the simulated thermometry maps were compared to the 3D 1-day post-treatment MR images, since real-time thermometry is done in a single plane. As a result, biological effects and variable brain tissue response to different heating levels could explain some discrepancy in the lesion obtained after completion of the treatment. Second, there was no direct registration between the post-treatment images and the images obtained during treatment, aside from anatomical landmarks. These discrepancies could account for some translation and rotation errors. Given these potential sources of error, it is quite clear from the resultant mean angle discrepancy of 23.2 ± 13.6 that there is good correspondence between the simulated and clinical data.

5. Conclusions

This paper demonstrated that a previously-introduced full-wave numerical simulation model was able to replicate the focal obliquity observed during clinical trials. In addition, it was shown that by using full-wave phase and amplitude corrections, it was possible to significantly reduce the manifestation of the oblique focus. Future work will look at the effects of the transducer power distribution for off-center targets. It is imperative that other phasing techniques are studied, and their effect on focusing quality analyzed.

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Figure 1.
The sagittal and coronal MR images obtained during a treatment, demonstrating the location of the head inside the transducer array.

Figure 2.
1 day post-treatment coronal MR images showing the site of the lesion and the obliquity of the focus in Patients A–F.

Figure 3.
A 3D rendering of the segmented clinical lesion illustrated in Figure 2, for Patient E.

Figure 4.

A comparison of the clinical and numerical simulation results for Patient E, illustrating the clinical and numerical results. The numerically-simulated thermal dose contours are superimposed on the 1-day post-treatment MR image for comparison.

Figure 5.
The simulated temperature fields at the focus for Patients A–F, after 20s of heating, in the coronal plane.

Figure 6.
The simulated pressure fields at the focus for patients A–F. The contours are at 10% intervals.

Figure 7.
The simulated temperature maps in the sagittal plane after 0.1, 5, 10, and 20 s of heating, showing obliquity resulting from the sidelobes in Patient E.

Figure 8.

A demonstration of the effect of (b) phase and (c) phase and amplitude corrections on obliquity caused by the main lobe in Patient K (a) with numerical simulations. The images illustrate normalized pressure fields.

Figure 9.

The simulated temperature maps in the coronal plane after 0.1, 5, 10, and 20 s of heating, showing obliquity resulting from the main lobe in Patient K.

Figure 10.

The composite effects of the power amplitude distribution and the skull aberration on peak sidelobe intensity, full-width half maximum, and obliquity. 1: clinical replication (EIS), 2: distribution of equal intensity on the transducers (EIT), 3: amplitude corrections, 4: full-wave phase corrections with EIS amplitude distribution, and 5: inverse amplitude and phase corrections. The solid line is the respective value when sonicating through a homogeneous medium with no skull. The heating volume is the region heated above 50% of the peak temperature at the focus. The error bars are one standard deviation.

Figure 11.

A demonstration of the effects of amplitude and phase corrections, showing the simulation results for Case 1 (left), Case 4, (center), and Case 5 (right).

Figure 12.

A comparison of the acoustic pressure fields at the focus when using full-wave and clinical phase corrections.

Figure 13. Heating maximum-image projection maps normalized to the peak focus temperature. The arrows indicate locations of heating in excess of the focus temperatures.

A summary of the acoustic powers and durations for each of the simulated patients A–F, taken from the clinical treatment data. In addition, the steering of the focus from the geometric center of the array in the left-right (LR), anterior-posterior (AP), and inferior-superior (IS) directions is listed.

Table 1

Patient	Power (W)	Duration (s)	Focus Shift (mm)		
			LR	AP	IS
A	750	13	-2.9	1.3	-2.0
B	1100	20	-2.1	2.3	-4.9
C	850	20	1.3	1.0	-7.3
D	950	30	0.6	-0.9	-1.3
E	600	24	4.2	0.8	-4.0
F	350	27	0.2	1.3	-4.0
G	754	27	-1.0	2.0	-0.3
H	754	24	1.0	0.3	-1.6
I	656	24	0.0	0.0	0.0
J	549	24	-0.7	-1.3	0.3
K	593	24	-0.7	0.0	0.3
L	803	24	0.3	2.3	-1.3
M	750	24	-1.0	0.3	0.0
N	754	24	-2.6	-1.6	0.7
P	500	27	-0.3	0.3	-0.7
Q	996	40	0.3	0.0	-0.3

Table 2

Simulation parameters used in the simulation of the acoustic and thermal fields (Duck 1990, Cooper & Tezek 1972, Connor & Hynynen 2002, Connor & Hynynen 2004).

Material	ρ (kg m ⁻³)	c_L (m s ⁻¹)	α_L (Np m ⁻¹)
Water	1000	1500	0
Brain	1037	1400	4.28
	κ (W °C ⁻¹ m ⁻¹)	C (J kg ⁻¹ °C ⁻¹)	W (s ⁻¹)
Water	0.62	4180	0
Brain	0.53	3640	8.33×10^{-3}
Skull	0.43	1440	3.33×10^{-4}
	ρ_b (kg m ⁻³)	C_b (J kg ⁻¹ °C ⁻¹)	T_b (°C)
Blood	1030	3620	37

Table 3

The five cases simulated to extract the causes of the oblique focus.

Simulated Case		Description	Phase	Amplitude
1	EIS	Equal Intensity on the Skull Surface	Clinical	Clinical
2	EIT	Equal Intensity on the Transducer Surface	Clinical	Equal
3	AC	Amplitude Corrections	Clinical	Inverse
4	PC	Phase Corrections	Full-Wave	Clinical
5	APC	Amplitude and Phase Corrections	Full-Wave	Inverse

Table 4

A quantitative comparison of the obliquity measured from 1-day post-treatment MR lesion information and the numerically-simulated results, listing the clinical and numerically-simulated obliquity, as well as the angle between these unit spherical vectors.

Patient	Clinical Data (θ, ϕ)	Numerical Simulation (θ, ϕ)	Angle ($^{\circ}$)
A	(64.2, 102.2)	(49.1, 107.1)	15.3
B	(69.6, 20.4)	(54.3, -46.9)	32.9
C	(32.3, 78.2)	(79.4, 97.5)	47.8
D	(77.4, 80.6)	(79.4, 97.5)	6.0
E	(42.3, 122.5)	(40.6, 111.9)	8.1
F	(48.1, 122.6)	(63.7, 129.4)	16.0
G	(62.4, 130.7)	(62.4, 142.0)	5.2
H	(38.4, 74.0)	(62.6, 113.0)	33.7
I	(40.9, 60.3)	(70.3, 96.3)	34.7
J	(38.3, -89.0)	(57.0, -106.0)	21.8
K	(55.3, 78.8)	(44.2, 90.4)	13.4
L	(54.8, -164.5)	(60.9, 102.3)	45.7
M	(62.8, 139.1)	(76.6, 148.4)	14.1
N	(49.4, -96.2)	(27.6, -100.7)	22.1
P	(65.9, -165.2)	(72.4, 144.7)	18.3
Q	(61.3, 47.7)	(82.1, -148.7)	36.3
Mean			23.2 $\pm$ 13.6

Summary of values presented in Figure 10. 1: clinical replication (EIS), 2: distribution of equal intensity on the transducers (EIT), 3: amplitude corrections, 4: full-wave phase corrections with EIS amplitude distribution, and 5: inverse amplitude and phase corrections.

Table 5

	EIS	EIT	AC	PC	APC
Peak Sidelobe Ratio (a.u.)	0.47±0.07	0.52±0.07	0.45±0.06	0.37±0.03	0.32±0.03
Heating Volume (mm ³)	15.8±3.4	17.6±4.7	14.8±2.4	11.2±1.2	9.8±1.1
Oblliquity (degrees)	32.7±12.4	39.3±15.0	15.6±6.2	34.4±10.3	9.1±5.3