The application of sparse arrays in high frequency transcranial focused ultrasound therapy: A simulation study

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(Received 24 June 2013; revised 1 October 2013; accepted for publication 24 October 2013;
published 19 November 2013)

Purpose: Transcranial focused ultrasound is an emerging therapeutic modality that can be used to perform noninvasive neurosurgical procedures. The current clinical transcranial phased array operates at 650 kHz, however the development of a higher frequency array would enable more precision, while reducing the risk of standing waves. However, the smaller wavelength and the skull's increased distortion at this frequency are problematic. It would require an order of magnitude more elements to create such an array. Random sparse arrays enable steering of a therapeutic array with fewer elements. However, the tradeoffs inherent in the use of sparsity in a transcranial phased array have not been systematically investigated and so the objective of this simulation study is to investigate the effect of sparsity on transcranial arrays at a frequency of 1.5 MHz that provides small focal spots for precise exposure control.

Methods: Transcranial sonication simulations were conducted using a multilayer Rayleigh-Sommerfeld propagation model. Element size and element population were varied and the phased array's ability to steer was assessed.

Results: The focal pressures decreased proportionally as elements were removed. However, off-focus hotspots were generated if a high degree of steering was attempted with very sparse arrays. A phased array consisting of 1588 elements 3 mm in size, a 10% population, was appropriate for steering up to 4 cm in all directions. However, a higher element population would be required if near-skull sonication is desired.

Conclusions: This study demonstrated that the development of a sparse, hemispherical array at 1.5 MHz could enable more precision in therapies that utilize lower intensity sonications.
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Key words: ultrasound, sparse, phased array, sonothrombolysis, BBB

1. INTRODUCTION

Transcranial focused ultrasound is an emerging therapeutic modality that can be used to perform noninvasive neurosurgical procedures. It is currently being investigated through clinical trials for thermal ablation of tumors,¹ as well as functional neurosurgery to treat essential tremor^{2,3} and chronic pain.^{4,5} These three trials use a hemispherical dome composed of 1024 transducer elements (ExAblate 4000; InSightec, Haifa, Israel) to focus acoustic energy through an intact skull into the brain.

The use of lower intensity ultrasound as an adjunct therapy is being investigated through clinical trials for the treatment of acute ischemic stroke.⁶ The CLOTBUST study demonstrated that 2 MHz transcranial Doppler increased the efficacy of injected thrombolytics.⁷ A separate clinical trial (TRUMBI) was halted prematurely due to a high incidence of symptomatic intracerebral hemorrhaging,⁸ thought to be caused by the formation of standing waves,⁹ since an unfocused beam with a relatively low sonication frequency of 300 kHz was utilized. It has been shown that the use of higher frequencies [above 1 MHz (Ref. 10)] and low f-number transducer arrays¹¹ can significantly minimize standing waves and reduce the focal spot size. This motivates the

development of hemispherical arrays that operate at higher frequencies.

Preclinically, low intensity ultrasound combined with injected microbubbles is also being investigated for the treatment of ischemic stroke.^{12–14} Higher intensity ultrasound, which is capable of breaking up a blood clot without microbubbles or thrombolytics, is being investigated preclinically as well.^{15–17} Focused ultrasound in combination with circulating microbubbles is also capable of inducing localized blood brain barrier disruption (BBBD),^{18–21} which has been used to deliver a range of therapeutic agents, including anticancer drugs,^{22–25} stem cells,²⁶ and genetic material^{27,28} to the brain.

A commercially available transcranial phased array (ExAblate 4000; InSightec, Haifa, Israel) operating at a nominal frequency of 230 kHz (Refs. 11 and 29) is capable of producing a –6 dB lateral/axial focal spot size of 3.9 mm/7.8 mm (estimated through Rayleigh simulations in water). The clinically approved transcranial phased array described above operates at a nominal frequency of 650 kHz,⁵ resulting in an estimated focal spot size of 1.4 mm/2.8 mm. A smaller focus can be achieved with the use of higher frequencies, enabling more precise treatments. Making use of a quasi-random placement of elements, Pernot *et al.*³⁰ developed a

transcranial array that operates at 1 MHz. With a lateral/axial focal spot size of 0.8/4.2, the 1 MHz array has been used to create lesions *in vivo*^{31,32} and more recently focal temperature elevations in human cadavers.³³ At 1.5 MHz, the estimated focal spot size for a hemispherical array would be reduced to 0.6 mm/1.2 mm, small enough to allow the entire focus to fit within the 2–3 mm major blood vessels of the brain.³⁴ However, the attenuation and distortion of ultrasound through the skull increases with frequency, which means that a greater amount of energy would be lost in the skull and phase corrections would be necessary to resolve a focal spot.^{35,36} Furthermore, the quality of electronic beam steering depends on transducer element size and interelement spacing, relative to the wavelength, and it has been estimated that element counts an order of magnitude greater than what exist currently would be required for adequate off-axis focusing.³⁷

Sparse arrays enable steering of a therapeutic array with fewer elements while suppressing grating lobes.^{30,38–41} Sparse arrays have long been applied to the design of antenna arrays^{42,43} and have also been investigated for use in diagnostic ultrasound.^{44,45} However, the tradeoffs inherent in the use of sparsity in a transcranial phased array have not been systematically investigated. Before an array can be constructed, it is important to understand how focal pressure and focal distortion are affected as elements are removed, so that an array can be designed that minimizes the number of elements used, minimizes off-focus hotspots, and maximizes focal pressure. The objective of this simulation study is to investigate the effect of sparsity on transcranial arrays at a frequency of 1.5 MHz that provides small focal spots for precise exposure control.

2. METHODS

2.A. Simulation model

Ultrasound propagation in brain was computed using the Rayleigh-Sommerfeld integral

TABLE I. Water and brain parameters are based on those presented by Duck (Ref. 54).

	Water	Brain
Speed of sound (m/s)	1500	1562
Density (kg/m ³)	1000	1300
Attenuation (Np/m)	4.32×10^{-4}	4.35

$$p(x, y, z) = \sum_{m=1}^M \frac{jk^* \rho c}{2\pi} \frac{e^{-jk^* R_m}}{R_m} (u_m ds_m),$$

where ρ and c are the density and speed of sound of the medium, respectively, u_m and ds_m are the particle velocity and area of the m th source, respectively, R_m is the distance between the m th source and point (x, y, z) , and $k^* = k - j\alpha$ is the complex wavenumber of the propagation medium given an attenuation coefficient of α (see Table I). Pressure, $p(x, y, z)$, is calculated by decomposing the transducer surface into a set of point-like sources and summing the contributions from all acoustic sources at point (x, y, z) . A multilayer Rayleigh-Sommerfeld propagation model was used to simulate the propagation of ultrasound from a hemispherical dome through layers of water, skull, and brain. The phase corrections required to achieve transcranial focusing were determined by simulating a point source at the focus and propagating outwards to each transducer element. The phases of the average pressure over each element surface area were then calculated, inverted, and applied to the forward simulation. Details of the multilayer model have been described previously.³⁷ Shear waves were not incorporated into the model due to their high attenuation at the frequency being simulated.⁴⁶ The model does not account for nonlinear effects, a phenomenon which would be reduced given the relatively low f-numbers and low pressures investigated in these transcranial simulations.^{47,48}

FIG. 1. Simulated hemispherical arrays with 100%, 50%, 25%, 10%, 5%, and 1% populations of 3 mm elements.

TABLE II. Number of elements required to completely populate each hemispherical array.

Element width (mm)	Elements
6	3996
3	15 878
1.5	63 158
1	141 824
0.5	566 294

The model incorporated human CT skull data (LightSpeed VCT; GE Healthcare, Chalfont St. Giles, UK) taken from five cadaver skulls (The Bone Room, Berkeley, CA). The CT volumes consisted of $512 \times 512 \times 328$ voxels, where voxels were $0.625 \times 0.625 \times 0.625$ mm³ in size. The CT data were used to construct surface meshes of the skull geometry (using the isosurface algorithm developed by Treece *et al.*⁴⁹) and the image intensities were used to estimate skull density values (as was done previously by Connor *et al.*⁵⁰). Meshes were created such that surface element areas were all less than $(\lambda/2)^2$, a spatial sampling rate capable of representing the pressure field since propagation distances are long relative to the wavelength and evanescent waves are ignored.^{51,52} Hemispherical arrays with 30 cm diameters, composed of trapezoidally shaped elements, were simulated in this study (Fig. 1). Trapezoids, with the midline width equal to the height, were used to reduce the spaces between elements, and so they range from squares near the base of the array to trapezoids near the apex. Sparsely populated arrays were generated by removing elements at random from fully populated arrays. Finally, speed of sound and attenuation values were calculated using previously determined frequency dependent relationships⁵³ and were integrated over each beam path.

2.B. Simulation specifications

Transcranial simulations were conducted using 1588 element arrays, each composed exclusively of elements with

widths of either 0.5, 1, 1.5, 3, or 6 mm. Arrays with element populations of 1%, 5%, 10%, 25%, 50%, and 100% of the full array were simulated as well for the 0.5 and 3 mm element cases (see Table II). Lateral sonication targets at ± 4 cm along the posterior and medial-lateral axis were investigated. In the axial direction, sonication targets at ± 2 and ± 4 cm were investigated. Targets 2 mm away from the inner skull surface in each axis were also sonicated to assess the feasibility of full cavity sonications (Fig. 2).

2.C. Metrics and analysis

Each simulation target and array combination was compared based on a series of metrics. All simulations were initially conducted with a transducer element surface pressure of 1 Pa. For cases where element size was varied, results were also presented assuming a constant power applied to each element, which would decrease the relative element surface pressure of larger elements. This represents a more practical comparison, as multichannel drivers may limit the available power per transducer, so long as they are operating within their maximal intensity. Individual element powers within a single array were kept constant, since it represents the best use of a phased array where per-element power is the limiting factor.

Grating lobe values were calculated by finding the largest pressure value along the steered axis, beginning and ending at a point 2 mm from the inner skull surface. When calculating the grating lobe amplitude, points within 5λ of the focus were not included to ensure the main lobe was excluded. A maximum side lobe value was calculated as the amplitude of the largest side lobe within a $(3\lambda)^3$ volume surrounding the focus, sampled in a 0.1λ grid. A side lobe ratio value was then calculated by dividing the maximum side lobe amplitude by the focal pressure. Finally, the -6 dB pressure depth of field and lateral width were calculated for each case. The values and vertical error bars in the plots from the transcranial

FIG. 2. Fourteen sonication targets are shown. The X axis specifies the anterior to posterior direction (after the head has been tilted forward), the Y axis specifies the lateral left to right direction, and the Z axis specifies the inferior to superior direction. Coordinate values shown are in centimeters. The $X_{\max}$, $Y_{\max}$, and $Z_{\max}$ locations are 2 mm away from the inner skull surface. The darker region in the middle represents the brain tissue and the outer lighter region represents the skull.

FIG. 3. Transcranial sonication targeting the geometric focus with a fully populated 1.5 MHz array composed of 3 mm elements without phase correction (left), with phase correction (center), and with a 10% sparsely populated array with phase correction (right). The normalized pressure plots show a lateral focal cross section, where Y is the medial-lateral direction and X is the anterior-posterior direction. (Lines denote 10% pressure contours.)

sonications represent the mean and standard deviation, respectively, over the five skulls simulated.

3. RESULTS

3.A. Through-skull phase correction

Using a fully populated array with 3 mm elements, sonicating the geometric focus through the skull without phase correction resulted in significant distortion (Fig. 3) and shifting of the focus by 2.0 ± 0.9 mm, where the error denotes standard deviation over all five skulls. In the fully populated case, phase correction was able to resolve a strong focus at the intended target and resulted in a focal pressure 4.6 ± 0.2 times the uncorrected case. A strong focus was achieved in the 10% populated array as well, resulting in a focal pressure of approximately 10% of the fully populated case.

3.B. Focal dimensions

The axial pressure profiles obtained from steering along the acoustic axis are shown in Fig. 4 for three different element populations. The lateral pressure fields through the focus at two sonication locations using four different element populations are shown in Fig. 5. Figure 6 and Table III illustrate how the axial and lateral focal dimensions vary given changes in target location and sparsity. The axial focal length varied from approximately 0.5 to 4.1 mm and the lateral focal width varied from approximately 0.4 to 2.1 mm as the target was steered. The axial length generally increased as the focus was steered laterally and inferiorly away from the geometric focus. Neither the lateral nor axial focal sizes changed substantially as element populations were decreased, varying by 7% on average and 20% at maximum for a given location.

FIG. 4. Axial focal profiles are shown steered 40, 20, and 0 mm inferiorly (plotted over the ranges $[-55, -30]$, $[-30, -10]$, and $[-10, 15]$, respectively). The 100% (left), 10% (middle), and 1% (right) cases were simulated. Each plot shows three distinct pressure profiles, divided at the -30 and -10 mm points.

FIG. 5. Pressure field plots from transcranial simulations steered (a)–(d) 40 and (e)–(h) 65 mm laterally. Simulated arrays had (a) and (e) 160, (b) and (f) 1588, (c) and (g) 7940, and (d) and (h) 15 879 3 mm elements. (Lines denote 10% pressure contours.)

3.C. Variation of element width

Simulations were first conducted using phased arrays with a fixed number of elements ($n = 1588$). Figure 7 shows the relationship between peak focal pressure and element size

assuming constant acoustic powers, grouping the plots by degree of distance steered. Grating lobe pressures began to dominate focal pressures at the posterior inner skull surface as element sizes increased to 3 mm. As the element size was further increased to 6 mm, the grating lobe amplitudes surpassed

FIG. 6. Half pressure focal lengths steered superiorly for three different levels of sparsity.

focal amplitudes for all near-skull targets, except in the lateral Y direction, where the human skull is narrower. Increasing the element size past 3 mm also did not result any consistent increase to the focal pressure. Given a sonication power of 0.5 W, the transducer surface intensities for the 0.5, 1, 1.5, 3, and 6 mm elements would be approximately 200, 50, 22, 5.6, and 1.4 W/cm².

3.D. Focal pressure and gain

Each focal target was simulated with 3 mm elements with varying degrees of sparsity, assuming a transducer surface pressure of 1 Pa. Figure 8 describes the changing focal pressures with element population size as the beam was steered in the posterior, lateral, and superior directions. For a given focal target, the focal pressure is roughly proportional to the number of elements. This is best illustrated by the normalized pressure plots (dotted lines), which would help identify systematic efficiency changes caused by the removal of elements. The effect of steering on focal pressure was also evaluated—Fig. 9 shows these trends for the 1%, 5%, and 10% element population cases.

3.E. Sidelobe magnitude

The sidelobe-to-focus ratio was calculated for a range of sparsities using 3 mm elements (Fig. 10). Steering laterally

produced the largest sidelobes, with a highest mean sidelobe pressure ratio of approximately 0.8. Relative sidelobe size generally increased as the beam was steered laterally and as it was steered superiorly. Sidelobes generally increased as element populations were reduced. On average, the 25%, 10%, and 1% populations resulted in sidelobes 2.9%, 4.2%, and 20.8% larger, respectively, than the 100% population. The increase in sidelobe amplitude as element populations were reduced can be seen in the lateral pressure contours (Fig. 5).

The average grating lobe ratios increased as the element population size was decreased (Fig. 10), resulting in a 46%, 125%, and 566% increase from the 100% population to the 25%, 10%, and 1% populations, respectively. Relative grating lobe amplitudes also generally increased as the beam was steered away from the geometric focus. The effect of sparsity on each phased array's ability to steer without generating off-focus pressure concentrations can be seen in Fig. 5. For the case where the focus was steered to within 2 mm of the skull wall using the 1% populated array, the pressure amplitudes off-focus surpassed the focal amplitude [Fig. 5(e)].

4. DISCUSSION

This study demonstrated that sparse arrays provide sharp focusing through the skull with a reduced number of elements, with both the choice of element size, and the degree of sparsity, being tightly linked to the achievable steering range. The through-skull focal spot dimensions of 0.6×1.4 mm could be achieved even at the lowest, 1% sparsity. However, the reduced number of elements increased the magnitude of the grating lobes. For practical purposes, the 10% populated array was capable of steering 4 cm laterally, however significant grating lobes were identified when it was steered to the inner skull surface. This would be most relevant to the design of clinical arrays that are dedicated to specific, central targets, such as neurosurgical procedures or acute ischemic stroke. It was also observed that the use of 3 mm (3λ) elements produced the largest focal amplitudes overall, of those simulated through the skull, if per-element power was kept constant. They also enabled steering within the entire skull cavity without substantial grating lobe generation, if a large enough element population was used. This indicates that elements of this size would be well-suited to the construction of a sparse, transcranial array.

The simulations have generally shown that focal pressure decreases proportionally as elements are removed, which indicates that the sparse arrays are about equally capable of depositing their transducer elements' energy through the skull as the fully populated arrays. Practically, this means that removing half of the elements would require a doubling of transducer surface pressure to achieve equivalent focal pressures—requiring approximately twice as much power to the entire array. This is consistent with the relationships observed by Ellens *et al.*³⁸ for flat, therapeutic arrays. The additional power required is a result of the energy

TABLE III. Axial focal lengths at different levels of sparsity. The laterally steered values are averages of both X and Y directions.

Direction steered	Distance (cm)	Axial length of focus (mm)		
		100%	10%	1%
Laterally	0	1.40 (± 0.01)	1.41 (± 0.02)	1.39 (± 0.04)
	± 4	1.6 (± 0.3)	1.7 (± 0.3)	1.7 (± 0.3)
	Inner skull	1.8 (± 0.4)	1.9 (± 0.4)	2.0 (± 0.5)
Axially	-4	2.8 (± 0.4)	2.7 (± 0.3)	2.9 (± 0.6)
	+4	0.9 (± 0.1)	0.9 (± 0.1)	0.9 (± 0.1)
	Inner skull	0.8 (± 0.4)	0.8 (± 0.4)	1.0 (± 0.3)

FIG. 7. Peak focal pressure vs element width, given 0.5 W acoustic power per transducer element. Plots show targets near to the geometric focus (top), 4 cm away (middle left, right), and at 2 mm from the inner skull surface (bottom left, right). The axial steering and lateral steering datasets are separated for clarity. Maximum grating lobe pressures are shown, marked GL in the legend. All arrays were simulated with 1588 elements.

FIG. 8. The plots show peak focal pressure at a range of element population sizes, grouped by axis steered, given 1 Pa transducer surface pressures and 3 mm elements. Dotted lines represent pressure divided by the number of elements, normalized to the fully populated array.

FIG. 9. Peak focal pressure at different steered distances, grouped by axis, given 1 Pa transducer surface pressures. Data are plotted for the 1%, 5%, and 10% cases. Error bars on the horizontal axis represent the differing inner skull locations between each of the five skulls. Solid lines indicate the case where 3 mm elements are used (requiring 1588, 795, and 160 elements to populate the 10%, 5%, and 1% arrays). Dotted lines indicated the case where 0.5 mm elements are used (requiring 56 629, 28 314, and 5662 elements to populate the 10%, 5%, and 1% arrays).

deposition into the grating lobes. This means that sparse arrays may not be the optimal method for transcranial therapies that require large energy deposition in the focus, such as thermal ablations, where skull heating would limit the energy delivered.

It was anticipated that the use of less directed smaller elements would produce the best results for larger degrees of steering. In preliminary free-field simulations where the focus was steered 7.5 cm laterally, it was observed that elements 1–1.5 mm in size produced the largest focal pressures (data not presented). However, this was not observed in the transcranial case, for targets placed near to the skull wall. This likely results from the fact that ultrasound transmits most efficiently through the skull when the incident beam is normal to its surface. For the cases where the sonication target was close to the skull, elements producing beam paths normal to the skull that are near the target would contribute most to the focus and elements far from the target or with oblique insonation angles would contribute far less. This would lessen the real-

izable steering benefit obtained from using less directed elements. Still, the results suggest that peak focal pressures plateau when elements between 3 and 6 mm are used in the near-skull steering cases (Fig. 7).

With the addition of the skull layer, the organized off-focus superposition of pressures that normally leads to strong grating lobes was not observed [Fig. 5(h)]. However, energy was still deposited away from the focus, taking the form of off-focus hotspots that were concentrated near the array's geometric center. As element populations were reduced, the amount of energy deposited near the geometric focus was increased, which is consistent with the observed grating lobes described by Goss *et al.*³⁹ and the formation of off-focus intensities described by Gavrilov and Hand.⁴¹ Focal sizes did not vary substantially with sparsity, which illustrates that the focal precision desired from a higher frequency phased array would be preserved with sparse element populations.

The relatively low focal pressures produced by sparse arrays make them best suited to applications where ultrasound

FIG. 10. Sidelobe (top) and grating lobe (bottom) ratios at each sparsity for steering in the posterior (left), lateral (middle), and superior (right) directions. (Note: Only lower error bars are drawn for higher values.)

is used in conjunction with injected substances, such as microbubbles for BBBD,¹⁸ for targeted drug delivery,^{22,55} or low intensity sonothrombolysis,^{7,13} and neuro-stimulation,^{56,57} which all require relatively low pressures. At 1.5 MHz, BBBD requires pressures of approximately 560 kPa (Ref. 58) and low intensity sonothrombolysis at 1 MHz requires pressures of approximately 160 kPa.¹³

These simulations indicate that a 1.5 MHz array constructed with 3 mm-wide transducer elements and a 10% element population—1588 elements—could sonicate all midrange (± 4 cm) targets, while keeping grating lobes under -10 dB of the main lobe. Focal pressures of 600 kPa could be achieved at all midrange targets with a per-element acoustic power of 0.5 W, requiring 794 W in total. This would be sufficient to achieve BBBD and more than sufficient for low intensity sonothrombolysis. Grating lobes begin to become more of an issue as the focus is steered to the inner surface skull. However, a 3 mm-element array with a 50% population—7940 elements—could steer to the inner skull surface along the X, Y, and Z axes, while keeping the grating lobes under -6 , -10 , and -8 dB, respectively. Focal pressures of 600 kPa could be achieved at all inner skull targets with a per-element acoustic power of 0.2 W, requiring 1588 W in total. Larger focal pressures could of course be achieved with higher power multichannel driving systems, however care would still need to be taken to ensure that the array is sufficiently populated to avoid the occurrence of off-focus bioeffects.

5. CONCLUSION

This study investigated the effect of employing sparsity in a hemispherical phased array at 1.5 MHz. Results show that focal pressure decreased proportionately as elements were removed, however, focal quality was not substantially affected, providing highly concentrated energy delivery. Choice of element size represents a trade-off between the benefits of increased surface area and the reduced ability to steer. Finally, this study has demonstrated that the development of a sparse, hemispherical array at this frequency could enable more precision in therapies that utilize lower intensity sonications.

ACKNOWLEDGMENTS

This work was supported by grants from the National Institutes of Health (NIH) (Nos. R01EB00903 and EB00326) and the Canada Research Chair program (CRC).

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