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Spherical array system for high precision transcranial ultrasound stimulation and optoacoustic imaging in rodents.

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Ultrasound can be delivered transcranially to ablate brain tissue, open the blood-brain barrier or affect neural activity. Transcranial focused ultrasound in small rodents is typically done with low-frequency single element transducers, which results in unspecific targeting and impedes the concurrent use of fast neuroimaging methods. Here we devised a wide-angle spherical array bidirectional interface for high-resolution parallelized optoacoustic imaging and transcranial ultrasound delivery (POTUS) in the same target regions. The system operates between 3 and 9 MHz, allowing to generate and steer focal spots with widths down to 130 μm across a field of view covering the entire mouse brain, while the same array is used to capture high resolution 3D optoacoustic data in real time. We showcase the system's versatile beam-forming capacities as well as volumetric optoacoustic imaging capabilities and discuss its potential to non-invasively monitor brain activity and various effects of ultrasound emission.

Index Terms—Spherical transducer array, Transcranial ultrasound, Optoacoustic imaging, Optoacoustic tomography, Focused ultrasound

I. INTRODUCTION

TRANSCRANIAL focused ultrasound (TUS) is emerging as an essential brain technology due to its potential in the non-invasive treatment of several neurological disorders, as well as a valuable tool for studying brain function. Beginning with applications in hyperthermic tissue destruction - now used in the clinic for the treatment of essential tremor [1], [2] - TUS has evolved into new applications including blood-brain-barrier (BBB) opening [3] and neuromodulation [4], [5]. It combines non-invasiveness with relatively high (mm-scale) spatial resolution and cm-scale penetration depth, not attainable with other therapeutic modalities such as surgical or radio-frequency ablation, deep brain stimulation [6] or transcranial magnetic stimulation [7]. Interestingly, several studies have demonstrated that TUS can remotely modulate neural activity in a range of models including cell cultures [8], rodents [9]–[11], non-human primates [12]–[14] and humans [15], [16], eliciting neuronal stimulation or suppression as well as motor responses. Though several ultrasonic parameters are known to influence neuro-stimulation [10], [11], [17]–[19], as of yet there is no emerging consensus on its underlying physical and physiological mechanisms [10], [20]–[22].

Low frequency ultrasound (<1MHz) is typically preferred for TUS as it ensures low attenuation when traversing the

skull at the detriment of larger focal spots in the range of several mm, which hinders specific targeting, especially in rodents (Fig. 1(b)). Together with the reverberations on the cranial vault at these frequencies [23], the large focus size makes the neural responses difficult to analyse. Moreover, single element transducers only allow one target point at a time further necessitating slow mechanical translation to target different brain areas. Frequencies in the 5 MHz range have been recently attempted for neuromodulation in mice [24], [25]. However, at higher frequencies murine skull is known to impose distortions and exhibit plate-like resonant transmission that further strongly depends on the skull thickness and ultrasound incidence angle [26].

Importantly, moving beyond the observation of secondary TUS responses, such as elicited movements or muscle electromyography [27], real time and non-invasive TUS treatment monitoring remains an open challenge, especially for subtle effects. Despite its excessive cost, bulkiness, and low temporal resolution, magnetic resonance imaging (MRI) [1], [3], [28], [29] is considered the gold standard for monitoring pre- and clinical high-intensity focused ultrasound treatments and BBB opening. MRI has also been used for neuromodulation applications [30], although alternative methods like fluorescence [20], optical intrinsic signal imaging [31], laser speckle [32], and electrical recordings generally provide a more direct and fine-grained readout of brain activity. These methods however involve surgical access through the skull while only attaining superficial imaging or local information around the electrode site. In contradistinction, volumetric optoacoustic tomography is typically implemented with high-frequency (5-10 MHz range) spherical transducer arrays that

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are ideally suited for high-resolution real-time 3D imaging of the entire mouse brain with optical contrast [33], [34]. In this way, hemodynamic changes in the mouse brain can be monitored using intrinsic contrast provided by hemoglobin's light absorption [33]. In addition, thermal changes have been successfully imaged with optoacoustic techniques [35]–[39] due to the temperature dependence of the Grüneisen parameter [40], which is involved in the thermoelastic generation of ultrasound upon light absorption.

The large angular tomographic coverage of spherical arrays was also shown to drastically improve the image quality as compared to imaging systems employing planar or linear arrays [41]. Since volumetric optoacoustic tomography typically uses large transducer elements densely arranged on the spherical array aperture, its geometry is ideally suited both for detecting weak optoacoustic responses from tissues as well as emitting ultrasound waves.

Here we developed an optoacoustically-guided transcranial ultrasound (POTUS) system optimally operating in the 3-9 MHz frequency range. In the emission mode, POTUS can generate and rapidly steer focal spots down to $130\ \mu\text{m}$ in the murine brain (Fig. 1(b)). In the imaging mode, POTUS can perform real time volumetric optoacoustic imaging to non-invasively monitor hemodynamic and, potentially, thermal effects of the ultrasound emission across the entire mouse brain.

II. METHODS

A. The experimental system

The custom-made POTUS array (Imasonic SaS, Voray, France) consists of 512 transducer elements with 2.5 mm diameter arranged on a spherical shell with 4 cm radius of curvature covering an angle of 140° (Fig. 1(a)). The individual elements are separated by 3.2 mm and 3.9 mm pitch in the elevational and azimuthal directions, respectively. The array is connected to a custom-designed multi-channel electronics DAQ, Falkenstein Mikrosysteme GmbH, Taufkirchen, Germany), which employ class D amplifiers (15 MHz bandwidth) that can drive all the array elements with digital waveforms of arbitrary duration. The driving voltage can be flexibly adjusted in the 3.5-20 Vp range, while transmission delays can be further adjusted on a channel-by-channel basis with 5.5 ns time resolution, which is much higher than the characteristic rise time at the emission frequency. In combination with the spherical distribution of the elements, this ensures that the grating lobes are minimized during emission thus attaining focusing capacity approaching the diffraction limit. When transmitting at 5 MHz frequency with 5 Vp magnitude, each transducer is effectively supplied with 0.1 Watts of electrical power, which is converted to acoustic power with an efficiency of approximately 30%. The same electronics are adapted to digitize the optoacoustic signals detected by the array elements at $40\ \text{MS}^{-1}$ and transmit the data via ethernet port to a personal computer for storage and post-processing. In the optoacoustic detection mode, 494 samples are recorded from each of the 512 channels following every laser pulse. This results in an effective data rate of $< 800\ \text{Mbps}$ flowing over

Fig. 1. (a) Schematic of the spherical array and the additional electronics used for the pressure field characterisation and optoacoustic volumetric imaging of murine brain. (b) Ultrasound focus size relative to the mouse brain. The focal spot of a low frequency single transducer (dark blue) [20] and linear array (red) [25] are compared against the proposed wide angle spherical array (pale blue).

the Ethernet when operating at laser pulse repetition rate of 100 Hz. The optoacoustic data acquisition is triggered by the light pulses from a nanosecond optical parametric oscillator laser (SpitLight; Innolas Laser GmbH, Krailling, Germany) whose wavelength can be tuned between 440 and 1300 nm on a per-pulse basis.

B. Imaging performance characterization

The imaging capabilities of the POTUS have been first characterized using a cloud of $90\ \mu\text{m}$ diameter black plastic microspheres embedded in optically clear phantom made of agar (1.3 g per 100 ml of water). The detected optoacoustic signals were bandpass-filtered between 0.1 to 6 MHz while image volumes were subsequently reconstructed using GPU-accelerated three-dimensional back-projection algorithm [34], [42]. For *in vivo* demonstration, an 8 week old Athymic Nude-Foxn1 nu mouse (Envigo RMS Division, Indianapolis, Indiana, USA) was anaesthetized using 1.5% isoflurane and imaged at 488 and 900 nm wavelengths. Light is delivered to the mouse brain through a central aperture in the spherical array of 8

mm in diameter (Fig. 1(a)). All procedures involving mice conformed to the national guidelines of the Swiss Federal Act on animal protection and were approved by the Cantonal Veterinary Office Zurich.

C. Pressure field experimental measurement

To map the generated pressure fields in the ultrasound emission mode, the spherical transducer array was immersed in degassed water at room temperature (23 °C). The pressure field was characterized using a 75 μm -diameter PVDF hydrophone (Precision Acoustics Ltd., Dorchester, UK) scanned in three dimensions with automatic stages (Model: RCP2-RGD6C-I-56P-4, IAI Inc., Shizuoka Prefecture, Japan). The signal acquisition (50 MS/s, AlazarTech Inc., QC, Canada) is synchronized with the excitation by the same trigger (33220A, Agilent, Santa Clara, CA, USA). Stage control and data storage is performed on a PC using Matlab (MathWorks Inc., Natick, USA) interface. The signal recorded by the hydrophone was converted to pressure units using calibration curves provided by the manufacturer after removing the DC bias.

We first characterized a single transducer element by emitting a chirped frequency waveform increasing from 2 to 10 MHz within 5 μs . The hydrophone measurement was done using an additional 23 dB-gain amplifier (DCA-50-23, RF Bay Inc., Gaithersburg, MD, USA) and 300 averages for an improved signal to noise ratio. The whole transducer array was then characterized by simultaneously exciting all of its 512 elements with a bipolar square wave of 100 ns duration to mimic an impulse function. The signals were recorded without the additional amplifier and using 1000 signal averages per measured point. We subsequently changed relative delays between the transducer elements in order to steer the beam to different points in space separated by 1 and 2 mm from the spherical array's center.

Finally, we investigated effects of the mouse skull on the shape and intensity of the ultrasound focal spot. For this, we used an *ex vivo* skull from a 10-week-old female C57BL/6J mouse, which had an average thickness of 300 μm . The skull was stored in phosphate-buffered saline at 4 °C and placed between the hydrophone and the array for the measurement. After calibrating the position of the array's geometrical focus, a two-dimensional scan was performed with and without the skull.

D. Numerical modelling of the emitted ultrasound field

In order to generate an accurate numerical model matching the experimental results, we first modelled a single circular transducer (2.5 mm nominal diameter, 4 cm curvature radius) using Field II software [43], [44]. The transducer's surface is discretized using rectangular elements of 100 μm in size, and in steps of 6.6 ns in time. The impulse response of the transducer is approximated using a simple windowed cosine function and its parameters were empirically fit to the measured signals. In a second step, the impulse response is refined using a convolution optimization procedure (IRCOP) implemented within CVX (package for specifying and solving convex programs) in Matlab [45], [46].

To model the ultrasound field emitted by all the 512 transducers elements, their positions were represented using rotations and translations of a single transducer element. Within linear approximation, all array element contributions are then calculated independently and added together to obtain the total array pressure field.

The numerical model was validated by directly comparing the simulations to the system's experimental calibration results. The pressure field generated by the POTUS was calculated at the points in space corresponding to the hydrophone measurements. The simulated pressure field was then down-sampled to 50 MS s^{-1} , and interpolated to allow for a direct comparison and matching the measurements.

E. Beam steering

To leverage the high versatility of the POTUS hardware, three basic operating modes we implemented and simulated:

a) *Conventional beam steering*: a different emission delay is applied to each transducer element based on its expected time of flight to the desired focal spot location.

b) *Sparse focusing*: the emission is accomplished by a randomly selected subset of array elements.

c) *Focus blurring*: in order to increase the focal size for applications involving larger target regions, a slightly different emission delay, corresponding to a target point randomly located within a predefined volume of given size, is allocated to each transducer element. If the volume size is much bigger than the diffraction limited focal spot, a speckle pattern will be generated instead of a uniform focus broadening.

III. RESULTS

A. Optoacoustic imaging performance

The POTUS system was able to resolve a cluster of 90 μm point sources with resolutions ranging from 120 to 180 μm in the axial direction (Fig. 2(a)) and 180 to 280 μm laterally (Fig. 2(b)). Due to its large angular (tomographic) coverage, POTUS can produce volumetric optoacoustic images upon excitation with a single laser pulse (Fig. 2(c)–(f)). When applied to non-invasive imaging of the mouse brain, the system can provide a high-resolution image of the cortical vasculature at the 488 nm up to a depth of ~ 1.5 mm (Fig. 2(c), (d)). The same wavelength range was recently employed for imaging of fast neural dynamics by means of fluorescence calcium sensors [34]. On the other hand, hemodynamic changes in the entire mouse brain can be effectively imaged in the near-infrared spectral window [33], [47] (Fig. 2(e), (f)) owing to the diminished optical scattering and absorption of the brain tissue.

B. Emitted field

On the ultrasound emission side, the measured pressure field of a single element (Fig. 3(a)) has a focus 5 mm away from its surface with the near- and far-fields clearly distinguishable. A maximum pressure of 350 kPa is produced when driving the transducer with a voltage of 15 V. Cross-sections taken along the axial and lateral directions (Fig. 3(b))

Fig. 2. Optoacoustic imaging with POTUS. Spatial resolution characterization along the axial (a) and lateral (b) dimensions using a cloud of absorbing microspheres embedded in agar. Top-view (c) and side-view (d) maximum intensity projections of the volumetric images acquired non-invasively from a mouse brain at 488 nm illumination. (e) and (f) The corresponding images acquired at 900 nm laser excitation wavelength. The inset in (c) shows the orientation of the image with respect to the mouse head and the dotted curve depicts the mouse brains outline.

further demonstrate a good agreement between the numerical model and experimental results. Frequency bandwidth of 64 % (at -6 dB) is manifested in the focus (Fig. 3(c)) for both experimental measurements and numerical simulations.

When all the elements are driven in phase with 5 V amplitude, the emitted waves coincide coherently at the array's spherical center (4 cm away from its active surface), generating

a focal spot measuring 130 and 370 μm in the lateral and axial dimensions, respectively (Fig. 4(a)-(b)). The linear model predicts accurately the spot dimensions, yet the slightly asymmetric shape of the measured focus (Fig. 4(c), (e)) contrasts with the symmetric spot predicted by the simulations (Fig. 4(d), (f)). Lateral cross-sections (Fig. 4(g)) show an excellent agreement between measurements and simulations. On the other hand, the axial cross-sections (Fig. 4(h)) reveal an additional secondary peak 0.5 mm away from the center. As the peak pressure reaches 5 MPa at the focus for this particular measurement, the discrepancy can be attributed to the presence of non-linear effects in the focal zone. In fact, we observe an increase in the second harmonic components (Fig. 4(i)) when comparing the spectrum of the full array emission at the focus against the partial emission of 8 groups of 64 elements added linearly in post-processing.

C. Beam steering

We subsequently steered the focal spot by 2 mm in the lateral direction (Fig. 5(a)), again observing a good correspondence of its peak pressure to the numerical simulations (Fig. 5(b)). We calibrated the simulation to match the peak pressure at 2 mm steering (Fig. 5(c)). The predictive power of the linear model decreases together with the steering distance due to the appearance of non-linearities at higher pressure levels. Analysis of the focus quality reveals that grating lobes start to form additional spots with an intensity slightly above -10dB from the maximum (Fig. 5(a)). Therefore, the experimental results suggest a transition from A to B grade focus taking place at 2 mm steering distance [48]. The linear model (Fig. 5(b)) predicts a broadening of the focus, but not a separated spot at the plane studied. The beam width along the lateral x-direction should remain below 200 μm according to the modelling predictions, although the experimental values show a decrease below 200 μm (Fig. 5(d)). We also performed more elaborate simulations to render the expected focal intensity across the entire field of view (Fig. 5(e)-(f)). The simulation

Fig. 3. Characterization and fit of a single array element ultrasound field. (a) Schematic of the array with the transducers distribution and measured pressure field in the vicinity of the array's surface. (b) Axial (top) and lateral cross sections of (a) comparing measurements (black) and simulations (blue). (c) Frequency spectrum of the ultrasound field at the transducer's focus situated 5 mm away from its surface. Primed coordinates correspond to the single element coordinate system, where z' describes the distance to the transducer surface along the transducers radiation axis.

Fig. 4. Full array emission characterization. Array's focal region scanned at two intersecting planes (a) and the corresponding simulation (b). The planes are shown in detail for measurements (c), (e), and simulations (d), (f). Comparison between measurements and simulations for (g) lateral and axial (h) beam width obtained from cross-sections indicated by dashed lines in (c)-(f). The FWHM is indicated by the labels. (i) Frequency spectrum at the focus (logarithmic vertical scale) for the full array and partial emission by 8 groups of 64 elements, added *in silico*.

Fig. 5. Beam steering capabilities of POTUS. Comparison between the measured (a) and simulated (b) peak pressure at $x = 2$ mm from the array's focus. Contours represent the relative intensity in dB, as indicated by the labels. Comparison of the measured and predicted peak pressure (c) and lateral beam width (d) for different steering distances in x . Predicted relative pressure (e) and lateral beam width (f) over a 4 mm by 4 mm steering area in the xz plane. (g)-(i) Steered pressure field calculated at three representative positions in (f) with the FWHM indicated by the labels.

predicts a smooth decay of the peak pressure (Fig. 5(e)) as the focus is steered away from the array's center, reaching a minimum of 36% at 4 mm. The lateral beam width (Fig. 5(f)) is expected to stay below 290 μm within the calculated steering range. Unexpectedly, the model predicts a smaller spot when the beam is steered further away from the arrays geometrical center (Fig. 5(f)). By examining the pressure field at three different foci locations, i.e. $(x, z) = (0, 0)$; $(4, -2)$; $(4, 0.6)$, we found that the FWHM measurement is accurate (Fig. 5(g)-

Fig. 6. Simulations of sparse focusing and focal spot blurring. (a) Normalized peak pressure decay along the radial direction when reducing the number of active elements (color labels). Normalized peak pressure at $y = 0$ is shown in the inset for each array subset. (b) The peak pressure distribution when introducing random channel delays inside a volume. Color labels indicate the size of the blurred volume. Normalized peak pressure at $y = 0$ is displayed in the inset for each blurred volume size.

(ii) yet does not fully entails the increase in the side lobes occurring when the beam is steered.

The number of active transducers was then progressively reduced from 512 down to 16 (Fig. 6(a)) with the target set at the geometrical center of the array. The selection of active channels was randomized in order to avoid aliasing effects. Note that the focus size remains constant even after dramatically decreasing the number of active transducers. However, the contrast decreases with the number of transducer elements used (Fig. 6(a)) as the peak pressure at the focuses decreases linearly with the number of active elements. The focal region can be readily smeared by distributing random delays inside a volume of 83, 166, and 250 μm (Fig. 6(b)). As expected, the focal area grows up to the limit where a speckle pattern appears (250 μm) according to the ultrasound wavelength and curvature of the spherical array.

D. Transcranial pressure field

When the mouse skull appears in the ultrasound path, acoustic aberrations are generated in the focal spot (Fig. 7(a)) while the peak pressure decreases (Fig. 7(b)). Despite the presence of a side-lobe at 6 MHz (Fig. 7(a)), the FWHM of the focal spot (estimated via pressure distribution) always remains below 500 μm (Fig. 7(c)). The pressure declines non-monotonically reaching a maximum at 5 MHz, in agreement

Fig. 7. Transcranial pressure field at the geometrical focus measurements at different frequencies. (a) Normalized peak pressure at $z = 0$ and 3, 6, and 9 MHz as indicated by labels. Upper row shows the measured free-field (without the skull) whereas the lower row shows the transcranial field (with the skull). (b) Peak pressure ratio between transcranial and free-field measurements as a function of frequency. (c) Lateral FWHM of the peak pressure for transcranial and free-field data as a function of frequency.

with previously reported resonant insertion loss behaviour of murine skull primarily associated to plate transmission modes [26].

IV. DISCUSSION

We have demonstrated the design and characterization of a hybrid optoacoustic system for high-resolution generation and monitoring of transcranial focused ultrasound. POTUS delivers a 3D-steerable ultrasound focus through an adult murine skull with typical widths $\leq 400 \mu\text{m}$ when operating in the frequency range of 3-5 MHz. In addition, volumetric optoacoustic images of the whole mouse brain are retrieved by the system with a spatial resolution in the $\simeq 200 \mu\text{m}$ range (Fig. 2(a),(b)), opening bidirectional mouse brain interfacing possibilities similar to MRI-guided FUS in humans [1], [2]. Previously reported therapeutic ultrasound systems have employed low-frequency spherical arrays designs for applications in humans [29], thus allowing no targeting specificity when applied to the mouse brain. In comparison with other approaches employing single-element [17], [20] and linear-array [25] probes (Fig. 1(b)), our work explores the design, simulation and measurement of completely new regimes for TUS in small rodents. Moreover, one of the main challenges for efficient monitoring of the TUS effects arises from the limited space available for

introducing additional imaging system components [20], [28], [31]. POTUS circumvents this problem by using the same array to deliver ultrasound and record volumetric optoacoustic images in real-time.

Overall, the small dimensions of the focal spot and accurate electronic beam-forming and steering capabilities of the newly developed POTUS system hold great promise to enable precise targeting of very small functional brain regions, thus providing highly selective access to entirety of the mouse brain without employing slow and cumbersome mechanical scanning approaches. Moreover, the possibility to operate at different frequencies with the same device is particularly appealing for studies looking at the mechanisms underlying targeted BBB opening and US neuromodulation [49], [50]. Yet, accurate knowledge of the pressure field is crucial when it comes to designing in vivo TUS experiments and performing experimental data analysis.

In general, numerical simulations of the emitted ultrasound field were found to be in good agreement with experimental measurements. The minor deviations can be ascribed to a combination of one or more factors, such as (a) existence of non-linear effects in the focal region, (b) temperature drifts affecting the speed of sound, and (c) variations in transducer's impulse response. We note that non-linear effects produced at the focus of the array are challenging to assess due to the large volume, high frequency, and wide solid angle covered by our spherical matrix array system [51]. Further efforts on improving the modelling accuracy may include the combination of a linear model outside the focus with more sophisticated non-linear methods in the focal area [52]–[55]. In addition, approaches for accurately accounting for ultrasound propagation through the mouse skull should be considered [19], [56]. It should also be noted that the large number of individual transducer elements in our simulations could have masked any potential differences between the elements. However, the IRCOP method is not expected to produce more accurate results, even if optimized on the actual experimental measurements, because the transducer elements are in fact not identical.

Interestingly, in our measurements the extent of the generated focal spot was larger along the axial dimension (Fig. 4, Fig. 5(a),(b)), whilst the reconstructed microsphere appeared smaller in the axial direction (Fig. 2(a), (b)). This apparent discrepancy originates in the very different nature of the sources used for excitation and detection, and therefore does not imply a violation of the reciprocity principle. Note that the optoacoustic signal emitted by the microsphere has a dominant high frequency content chiefly determining the reconstructed size in the axial dimension whereas the achievable lateral resolution is mainly governed by the limited angular coverage. On the other hand, the transmission electronics produces much more low frequency content as compared to the microsphere, thus resulting in focal spots elongated in the axial direction.

POTUS operates at relatively high frequencies, hence particular care should be taken to control any temperature increase in the brain and the skull. Based on previous reports [57], [58], a simple calculation yields the limit of $<1^\circ\text{C}$ local temperature increase in the brain tissue if the pressure is

kept below 1 MPa when operating in the 3–7 MHz range. The temperature increase in the murine skull is more difficult to assess - most of the evidence exist for human skulls [59], [60], whose behaviour differs significantly from mouse skulls [26], [61], [62]. The assessment of thermal confound in ultrasound neuromodulation is an important aspect, usually addressed using rule-of-thumb calculations or more detailed simulations performed retrospectively [63]. POTUS has the potential to provide experimental evidence on both ultrasound and thermally induced neuromodulation, although transcranial thermal monitoring using optoacoustic imaging has still to be developed and validated.

V. CONCLUSION

We propose a new hybrid approach employing wide-angle spherical transducer array for transcranial delivery of focused ultrasound and 3D optoacoustic tomography of the rodent brain (POTUS) with high spatial resolution in the 200 μm range. Experiments and simulations demonstrate an excellent focusing accuracy and high versatility of the system. The spherical geometry of the array therefore provides a promising platform for 3D image-guided TUS in small rodents with potential applications ranging from neuromodulation and targeted BBB opening to therapeutic ultrasound interventions.

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