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Acoustic holograms for biomedical ultrasound applications

Sergio Jiménez-Gambín, Diana Andrés, Noé Jiménez, José M. Benlloch, Francisco Camarena

Instituto de Instrumentación para Imagen Molecular, Universitat Politècnica de València,
Consejo Superior de Invesigaciones Científicas, Camino de Vera S/N, 46085, València, Spain.
nojigon@upv.es

Abstract – **Optical holograms can modulate light wavefronts to generate visible images. In the same way, acoustic images can also be synthesized by holograms, shaping the areas where mechanical waves present a high amplitude, and areas where the media is at rest. We present acoustic holograms based on metasurfaces for emerging therapeutic applications of focused ultrasound for the non-invasive treatment of neurological disorders. When targeting acoustic beams into the brain, accurate focusing is mainly limited due to the strong phase aberrations produced by the refraction and attenuation of the skull. Acoustic holograms can overcome these limitations by synthesizing aberration-free ultrasonic fields of complex spatial distribution inside the skull. Our results show that, using low-cost 3D-printed holograms, ultrasonic beams can be focused not only at a single point, but overlapping at one or various target structures simultaneously, e.g., left and right hippocampi. Designs are validated by ex-vivo and in-vivo experiments to produce a bilateral blood-brain barrier opening in mice for drug delivery, and complex thermal patterns for localized hyperthermia. Other complex fields such as vortex beams for trapping small objects can also be synthesized inside the human skull. These results open new paths to spread emerging therapeutic ultrasound applications including blood-brain barrier opening, hyperthermia or neuromodulation using low-cost systems.**

I. Introduction

Focused ultrasound has become a key therapeutic modality for the non-invasive and non-ionizing treatment of neurological disorders, which currently affect one billion people worldwide. Through thermal ablation of thalamic and subthalamic areas [1], treatments have been developed for essential tremor, Parkinson's disease or chronic pain [2], while at moderate intensities it can be used for neuromodulation [3] or blood-brain barrier opening to deliver drugs in a safe and localized manner [4]. However, focusing therapeutic ultrasound into the central nervous system has been limited by two major drawbacks. First, the aberrant and attenuating effects of the skull and, second, the large mismatch between target to be treated and the pressure field distribution, which in most cases forces multiple sonications to cover the desired tissue. In addition, current phased-array technology does not allow the simultaneous sonication of two or more spatially separated volumes. In this work, we present 3D-printed acoustic holograms to correct the aberrations introduced by the skull and, simultaneously, generate ultrasound beams of arbitrary shape, using a simple and low-cost method. First, we design holograms to produce bilateral focused beams matching the shape of deep-brain nuclei [5] and, in addition, we design holograms to synthesize acoustic vortices inside the human skull [6].

Acoustic hologram are designed using time-reversal methods and CT images of an ex-vivo human skull [5, 6]. Holograms are 3D printed using stereolithographic techniques, and coupled to a 100-mm aperture, 140-mm focal and 500-kHz focused ultrasound transducer, as shown in Fig. 1(a). The field is measured with and without the skull bone in a water tank. To design the acoustic hologram we make use of the time-reversal invariance of the acoustic propagation. In this work, virtual sources were located around the target structure, following the shape and size of the deep-brain nuclei. Numerical simulations were performed with a k-space pseudo-spectral method for modelling the ultrasound propagation in heterogeneous media.

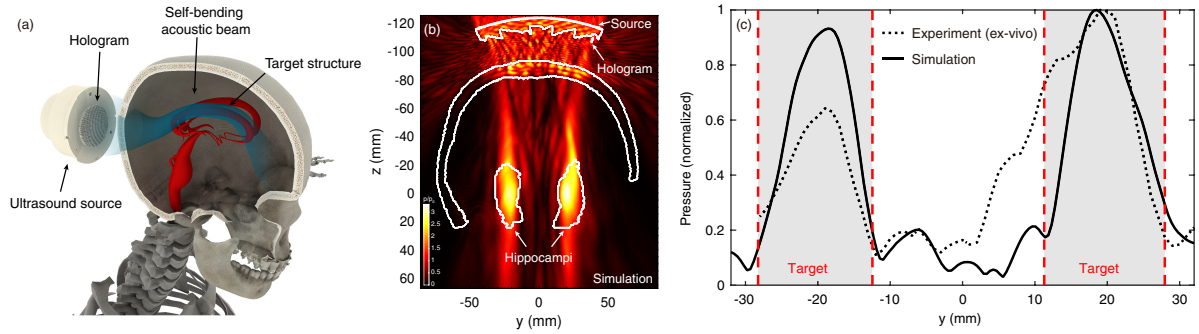


Fig. 1: (a) Scheme of the setup for bilateral focusing. (b) Simulated field targetting at the two areas of the hippocampus. (c) Experimental cross-section of the field obtained at $z = F$.

II. Bilateral focusing at deep-brain nuclei

First, we selected the caudate, the putamen and the hipocampi nuclei as the therapeutical targets, which have a symmetrical three-dimensional complex shape. In Fig. 1(b) we show the simulated acoustic field produced by the hologram to focus on the hippocampus (marked in white lines). Figure 1(c) shows the acoustic field measured experimentally and obtained by simulation. The 3D printed lens generates a pair of diffraction-limited focal spots matching the location and shape of the target tissues. A good agreement is found between calculations and experiments. It is shown that the acoustic energy is mainly located at the targeting regions, allowing the steering of the beam and a bilateral focusing. For the caudate nuclei, the volume covered in one sonication was 3.9 mm^3, which represents 24% of the total target volume. The sonicated volume is defined as the tissue sonicated with an intensity higher than half the peak intensity. Similar values are obtained for the putamen, where 25% of its volume is covered, and the hippocampus, with 22%.

III. Focusing an acoustic vortex through the human skull

In addition, acoustic beams can contain phase dislocations, conforming acoustical vortices which are of great interest to biomedical applications because they allow manipulating and trapping small particles. Recently, it has been demonstrated that vortices can be used to trap and guide kidney stones fragments [7], or to selectively guide individual drug-delivery carriers based on microbubbles [8]. Acoustic holograms can be used to generate vortex beams with great accuracy by encoding the full-wavefront information into the manufactured lens [9]. However, focusing acoustic waves through highly aberrating layers such as the human skull at ultrasonic frequencies results in strong phase aberrations which prevent the sharp focusing of acoustic vortices.

We have designed an acoustic hologram to simultaneously correct the aberrations of the skull and introduce a phase dislocation to a focused acoustic beam. The setup is shown in Fig. 2 (a). Results, Fig. 2 (b-c), show that measurements agree with simulations even when the skull bones are in the propagation path. The engineered acoustic hologram generates a focused vortex at an arbitrary focal position inside the skull by encoding time-reversed fields containing phase dislocations with great accuracy using very simple and compact ultrasonic systems. On the one hand, acoustic holograms allow one to compensate the aberrations of the skull, and, on the other hand, they simultaneously tune the phase of the wavefront to generate a focused vortex by introducing a rotational phase profile. This results in a personalized single-element system that can focus a vortex inside the human skull.

IV. Conclusions

Acoustic holograms were designed to synthesize diffraction-limited arbitrary acoustic fields. We have validated the designs using experiments including human tissues. The results show that the full potential of 3D printed lenses can be unleashed using acoustic holograms, enabling its use for conforming acoustic beams of arbitrary shape through the skull in a simple and robust manner. The benefit is twofold, acoustic holograms can compensate the aberrations of the wavefront produced by the skull while, simultaneously, they allow bilateral sonications whose acoustic field fits the complex shape of deep brain nuclei such as hippocampi, putamen, or caudate nuclei. In this work, numerical and experimental results focusing through an ex-vivo human skull show that more than

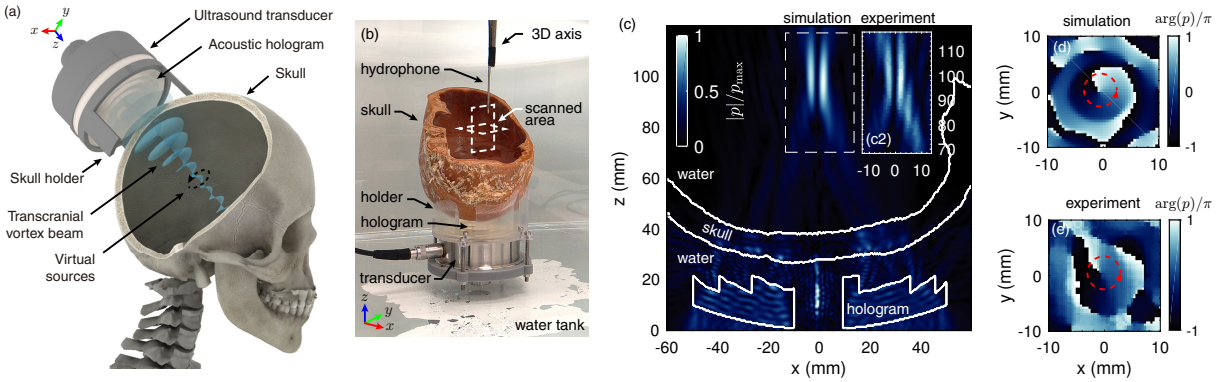


Fig. 2: (a) Scheme for transcranial vortex focusing. (b) Scheme of the experimental setup. (c) Simulated and (c2) experimental normalized sagittal field cross-section. (d, e) Numerical and experimental phase field.

20% of the volume of bilateral targets inside the brain can be covered with a single configuration. Furthermore, the steering capabilities of the acoustic holograms have been demonstrated by focusing at three different structures using one single transducer-skull position. In addition, vortices can also be focused inside the skull, enabling particle trapping applications for clot manipulation or localized drug delivery. In this way, acoustic holograms might be used to design low-cost and robust systems to focus at complex targets for ultrasound neuromodulation and blood-brain barrier opening applications. In addition, holograms enable the design of low-cost particle, drug or clot trapping and manipulation systems, or acoustic-radiation-force and torque exertion applications in the brain.

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