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### Acoustically induced and controlled micro-cavitation bubbles as active sources for transcranial adaptive focusing

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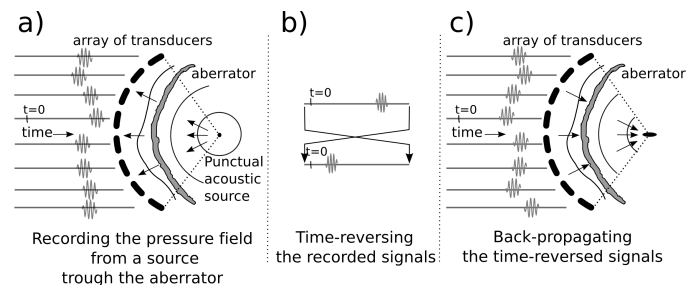
#### ABSTRACT

The skull bone is a strong aberrating medium for ultrasound in the low MHz range. Brain treatment with High Intensity Focused Ultrasound (HIFU) can however be achieved through the skull by multichannel arrays using an adaptive focusing technique. Time-reversal is a robust adaptive technique for correction of aberrations. It achieves moreover a matched filter and then allows the optimal energy concentration for thermal therapy. Nevertheless, this method requires a reference signal sent by a source embedded in brain tissues. Acoustically generated cavitation bubbles are active acoustic sources which can be remotely generated. Therefore, they are suited for this non-invasive time reversal aberration correction. We report here *in vitro* experiments where micro-cavitation was induced transcranially in agar gel at targeted positions using a coarse aberration correction either obtained from CT-scan based simulations or conventional steering. The bubbles' ultrasonic signature received by the array were then successfully used to optimally focus at the designated locations.

#### INTRODUCTION

Cavitation bubbles induced using intense ultrasound short pulses act as transient and punctual active acoustic sources, which can be remotely generated [1]. Such a remote source can be used advantageously as a reference target for adaptive focusing through complicated or aberrating media. Indeed, the impulse signal transmitted by the bubble can be recorded after propagation through the aberrating medium by a set of transducers located on the other side of the aberrator (Fig. 1.a) ). Then, if the signals received by the transducers are first digitized and stored in memories and next, time reversed (Fig. 1.b) ) and sent back, the acoustic wave generated from the

transducers propagates naturally in the medium towards the initial source, as if time was going backward (Fig 1.c) ). This effect is due to the time-reversal invariance of the wave equation. The whole time-reversal process presented here constitutes a robust adaptive focusing technique [2].



**Figure 1:** Principle of the time reversal process for an adaptive focusing application.

Cavitation bubbles have therefore a great potential for aberration correction in medical ultrasound, and, in particular, ultrasonic transcranial focusing. Indeed, a large discrepancy in acoustic velocities between the brain tissue and the skull bone (about 1500m/s and 3000m/s respectively) results in strong phase aberrations which severely degrade the beam shape, spreading the main lobe energy and increasing the side-lobes [3]. As the aberration is strong, a fine correction is difficult to achieve non-invasively without remotely generated sources. It is however highly desired for transcranial thermal ablation of brain tumors using High Intensity Focused Ultrasound (HIFU) [4] in order to carry out an efficient therapy and restrain its effects to the targeted zone. In this paper, ultrasonically induced cavitation bubbles are studied for this therapeutic application in

particular. Time-reversal focusing represents the optimal focusing strategy for this application: the time reversal process achieves a matched filter [5], which means that the pressure amplitude and the acoustic energy at a specified location (focus) and time (for pulse signals) is maximized for a given energy emitted by the set of transducers. As local energy deposition is crucial to efficiently induce thermal lesions in soft tissues, this property is essential for thermal therapy of tumorous tissue.

However, since the brain case is a closed aberrating shell, there is no easy way to remotely induce an acoustic source inside. A first coarse aberration correction is then required in order to both target accurately a specific location and to focus enough energy to induce micro-cavitation while avoiding any undesired secondary spots. Our team formerly proposed a time-reversal process based on prior CT (Computed Tomography) scan acquisitions [6]. The technique is non-invasive thanks to a numerical simulation based on a three-dimensional acoustic model of the skull, deduced from the CT images. Nevertheless, errors on modeling and repositioning lead to a suboptimal correction with this method, which is on the other hand a good pre-focusing technique.

We study here experimentally the ability to induce, through the skull, micro-cavitation using the CT-scan-based pre-focusing technique and to use this induced source to reach the optimum focusing. We also study the ability to generate micro-cavitation in the vicinity of the first target using conventional steering as a pre-focusing technique.

## EXPERIMENTAL SET UP

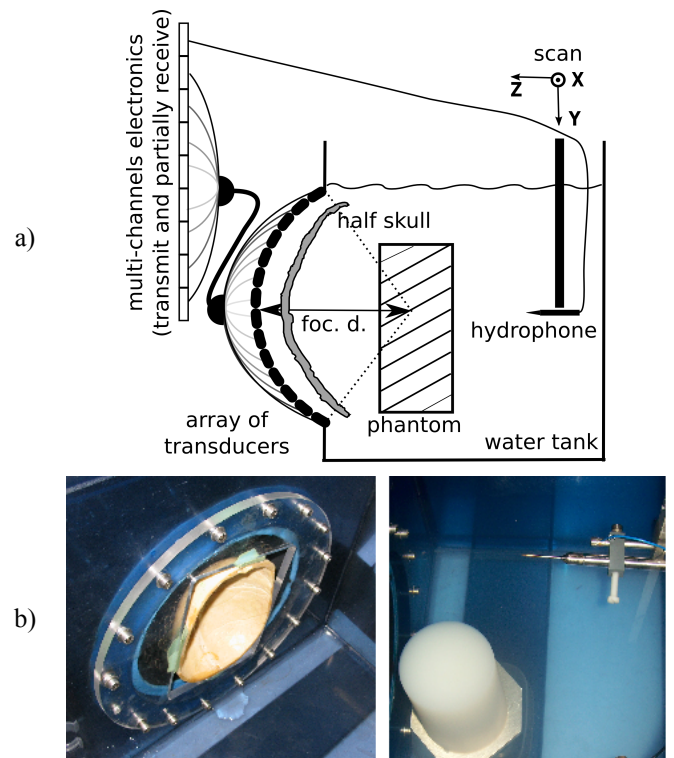
*Ex vivo* experiments were performed on a degassed human skull vault, mounted on a stereotactic positioning system and immersed in a degassed water tank maintained at 37°C (Fig. 2.). The skull, which was dry from storage in air, was immersed in water and degassed for a week in a vacuum chamber at 60 mm/Hg so that no air bubble stays trapped in porous zones. The purpose of this preparation is to reproduce *in vivo* conditions as closely as possible. In position, the skull is at an average distance of 19 mm (+/- 7mm) from the ultrasound probe.

The ultrasound array comprises 136 individual high power transducers (1MHz central frequency, bandwidth: 0.7 to 1.2 MHz, up to 20W.cm<sup>-2</sup> on their surface, diameter: 8mm), mounted on a spherical surface (aperture: 180 mm, focal distance: 140 mm) with a semi-random distribution. All are driven by a fully programmable emission channel, 54 of them also being able to receive.

Cavitation events occurred in a 1.75%w/v agar gel. Such gels have been reported to reproduce *in vivo* conditions of bubble formation under ultrasonic insonification in the low MHz range [7] The gel was prepared as follows. The agar powder (Fluka, BioChemika, for microbiology ref. 05040) was first added to stirred cold tap water. The resulting suspension was then covered and gradually heated to near 100°C, until the agar melted and a translucent solution was obtained. The hot solution was next degassed for 2 minutes to avoid the

introduction of bubbles in the final gel, and poured into a cylindrical mould (80 mm inner diameter, and 180 mm deep). The top end was first sealed off with a plastic film for one hour, allowing the solution to stand still at room temperature : bubbles potentially created while pouring could thus move up in order to be eliminated. It was then sealed off with a rubber seal lid. After around 24 hours at room temperature, the mold was opened and the gel removed and placed immediately into the water tank (Fig. 2). Testing began 10 min after immersion. In order to perform a statistical study twenty independent zones were sonicated per gel. Three different gels were prepared with a total of 60 different sonicated zones.

A needle hydrophone with a 3D positioning system was used to map the focal spots at 1MHz and low amplitude levels. Thanks to spacial reciprocity, the hydrophone was also used as a reference source to carry out the gold standard time-reversal process.

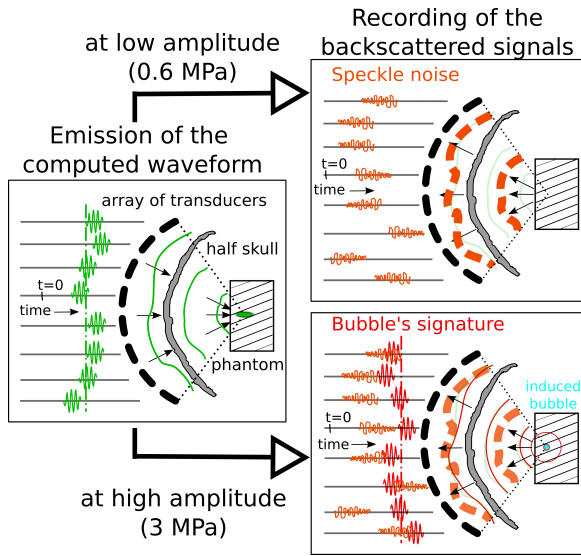


**Figure 2:** Experimental set-up: a) drawing and b) pictures of the half-skull mounted on the stereotactic positioning system (left), and an agar gel and the hydrophone (right) in front of the ultrasound array.

The first pre-focusing aberration correction was computed from the CT images so as to focus at the geometrical center of the array. The three-dimensional Hounsfield unit map issued from the CT-scan was converted to a density map and speed of sound map as described in [6]. The numerical simulation was then performed with a three-dimensional finite differences time domain (FDTD) code.

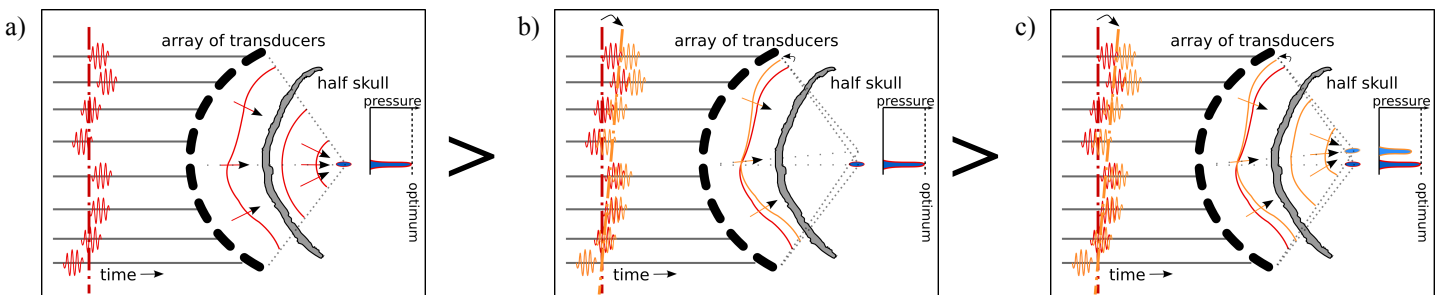
In order to record the acoustic emission of the cavitation bubbles, the computed pulsed waveform were emitted

experimentally twice by the (real) ultrasound array (Fig. 3.). Once at low power level (0.6 MPa peak pressure) and 10 seconds later, at high power level (3 MPa peak pressure, linear extrapolation). After renormalization the two recorded signals were subtracted in order to distinguish the bubble emission from the speckle noise. If it happened that more than one bubble signature appeared after subtractions, a time window was applied to select the strongest one.



**Figure 3:** Experimental process to record a cavitation bubble signature

The CT scan-based simulation allows to perform a first coarse aberration correction when no reference position is available in the brain, but it is a time-consuming process. Once the optimal aberration correction has been evaluated for one position (Fig. 4.a)) - considered as the reference position -, to target positions in its vicinity, conventional electronic steering was advantageously used. It consists in adding an extra phase-delay law to the wavefront of the reference emission law (Fig. 4.b)). These additional phase delays were directly deduced from geometrical acoustical path differences, assuming a constant speed of sound in the medium. The focusing to neighbour positions is not optimal since the aberrations encountered by the beams differ. However the technique is valid in a limited

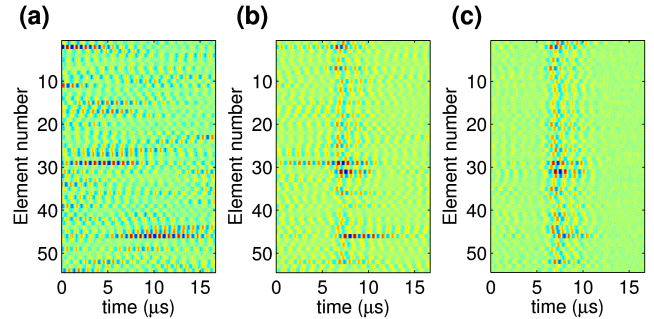


**Figure 4:** Concept of conventional steering, illustrated here for targets located in the focal plane of the array and reached using beam-steering from a set of pulse signals which optimally focus on the geometrical center of the array.

isoplanatic area around the reference position [8] (isoplanatic area : area over which the wavefronts are closely correlated).

## RESULTS

The computed pulsed waveform were emitted experimentally twice by the (real) ultrasound array. At low power level (Fig 5.a), the recorded pressure field consisted only of backscattered echoes from the gel itself (i.e speckle noise) while at high power level (Fig 5.b), a bubble appeared and generated a short pulse. After subtraction, the bubble signature is better selected. (Fig. 5.c).

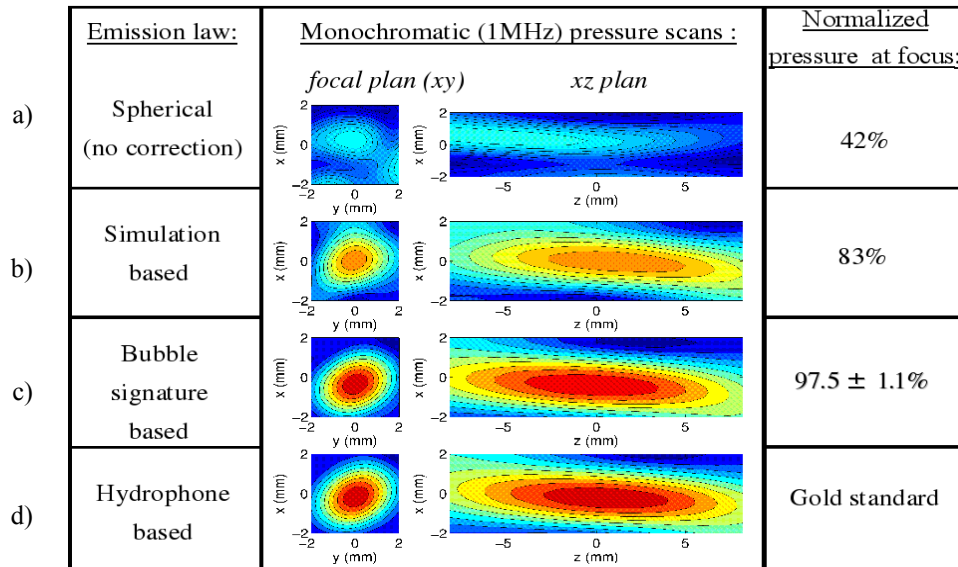


**Figure 5:** Backscattered signals recorded by the transducers at a) low power level and b) high power level, and the difference c) between b) and a), with amplitude compensation.

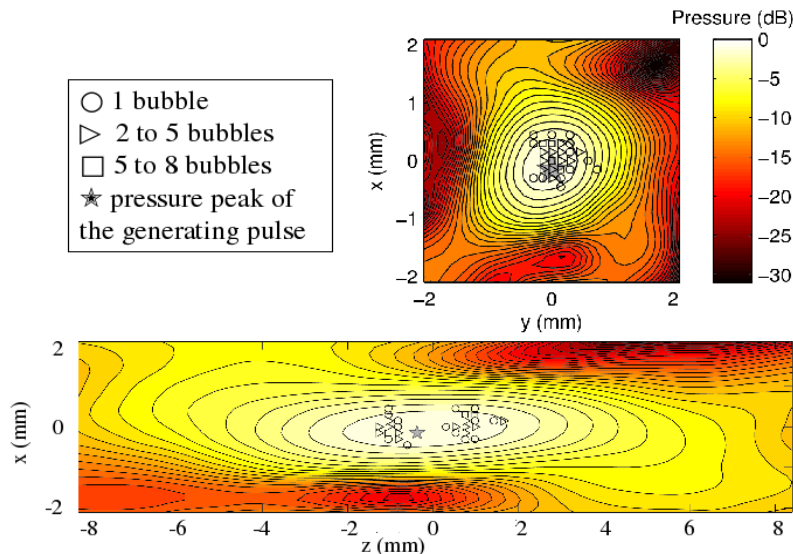
The aberration correction is then directly deduced by time-reversing this signature. For HIFU applications the monochromatic component at 1MHz was extracted, and the focal spots obtained with the different monochromatic emission laws are compared (Fig. 6.). As expected, because of the strong aberration, the focal spot obtained without any correction (Fig 6a) is away from the geometrical focus of the array (~6 mm), and is widely spread in comparison to what can be obtained with a hydrophone-based correction (Fig. 6d). The amplitude of the acoustic pressure at focus is moreover low compare to the one reached using the optimal phase emission law. The simulation-based set of emission correctly locate the focus at the geometrical center of the array, but the focal spot is still asymmetrical and the pressure at focus suboptimal. With the bubble-signature-based law, the symmetry of the focal spot is restored and the optimal pressure is reached.

The focus location with this law however depends on the cavitation event. By repeating 60 times the process to induce a bubble, and get the aberration correction from its signature, 82% of the cavitation events have been shown to be actually distributed in the -1dB focal area of the generating beam (Fig. 7.). The cavitation location is thus precisely controlled. Moreover, only one high power impulse insonification was needed each time to record a bubble signature on a new gel location.

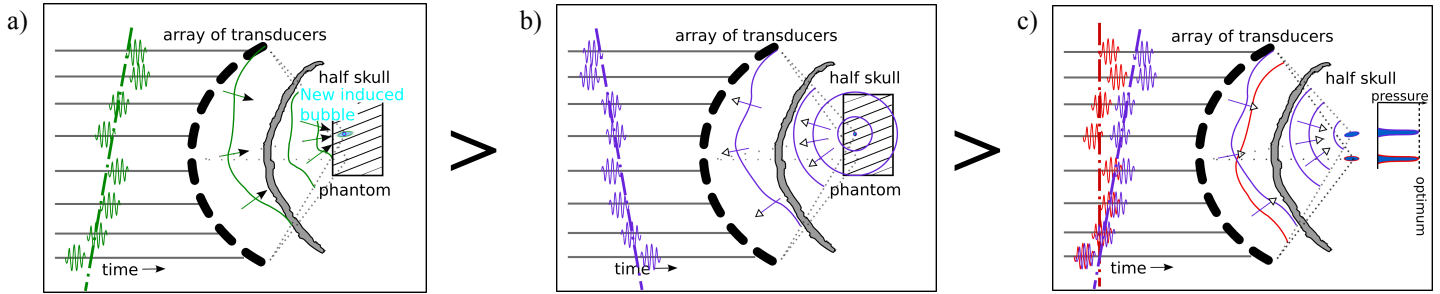
To optimally correct new positions in the vicinity of this first one (i.e. the geometrical centre of the array) conventional steering was used as a pre-focusing technique (Fig. 8.) in order to induce new cavitation bubbles . Six different positions at a distance of 6 mm away from the geometrical centre in the focal plane were targeted. For each position, micro-cavitation was induced, and monochromatic back-propagation of the bubble's signature were performed. Peak pressure was compare to the optimal pressure at each location. (Fig. 9.) For each of this six



**Figure 6:** Monochromatic pressure fields measured in the vicinity of the geometrical center of the array (position  $(x,y,z)=(0,0,0)$  on the plots)



**Figure 7:** Estimated bubble locations within the initial impulse simulation-based focal spot, and their occurrence while the experiment is repeated 60 times on independent gel positions. The experiment consists in sending the impulse version of the simulation, recording a bubble signature, processing this signature, and back-propagating the extracted monochromatic aberration correction. The estimated locations are the locations of the pressure peak obtained in the final back-propagation. The projection of the positions on the focal plane  $(xy)$ , and the  $xz$  plane are shown.

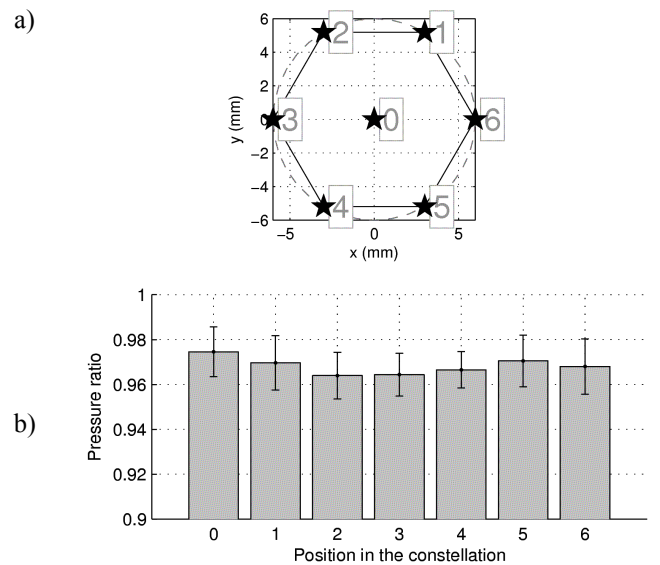


**Figure 8:** Principle of aberration correction using conventional steering as a pre-focusing technique. a) the steered impulse signal is focused in the agar gel and induces micro-cavitation. b) the bubble signature is recorded through the skull. c) the bubble signature is time-reversed and sent back in the medium.

positions the optimal aberration correction was reached.

## DISCUSSION

Our experimental set-up allowed recording a bubble signature for all targeted positions. The phase aberration caused by the skull could then be optimally corrected using this signature. We observed that for a single emission event, one to four bubble signatures could be identified on the received signals, depending on the gel position. The strongest signature was selected for further treatment. Moreover, when repeating the bubble induction on the exact same gel position, we found out that after several iterations (between two and five depending on the gel position) a bubble signature could no longer be identified, and only background signals from the gel itself remained. These two observations support the idea that cavitation in agar gel is linked to the presence of nuclei [9] randomly distributed in the gel. Indeed, it is very likely that one (or more) of these nuclei is close enough to the acoustic pressure peak and has a radius large enough to become destabilized and generate its own signature. It would also explain the variation in the estimated bubble location (Fig. 7.). In addition, as the medium is static, the depletion of cavitation nuclei large enough to be excited in theinsonified zone could explain the loss of bubble signatures after a few emissions at the same location. The notion of gas nuclei is more difficult to model *in vivo* [10] than in gel, and therefore their dynamic and location in brain tissue are even more difficult to predict. However, it should be feasible to destabilize some nuclei using a high enough pressure level. This pressure level would anyway be of the order of the one used for HIFU therapy. Considering that the time of irradiation is six order of magnitude smaller for cavitation bubble induction, the energy deposition is far lower.



**Figure 9:** Constellation of 6 bubbles generated in the focal plane of the array using electronic beam steering. The position 0, the geometrical centre of the array, is reached using the impulse version of the simulation. The positions of the targets are shown on a). b) shows the pressure reached using the bubble's signature obtained for each of these points with respect to the reference pressure obtained using the hydrophone-based time reversal performed at the exact same location.

## CONCLUSION

Ultrasonically-induced cavitation bubbles were efficiently induced remotely and non-invasively through the skull. Each bubble acts as a punctual acoustic source suited for a time reversal aberration correction. The bubble's signature was successfully used to optimally correct the strong aberrations induced by the bone.

This method should greatly benefit transcranial brain therapy. Its *in vivo* implementation raises the interesting questions of cavitation nuclei in biological tissues, cavitation threshold, and the dynamic of such bubbles.

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