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Non-invasive transcranial ultrasound therapy guided by CT-scans

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Abstract - **Brain therapy using focused ultrasound remains very limited due to the strong aberrations induced by the skull. A technique using time-reversal was validated recently in-vivo on 20 sheeps [1]. The principal handicap of this technique is the need of an hydrophone at the focal point for the first step of the time-reversal procedure, which is minimally invasive but lightly traumatizing. A completely noninvasive therapy requires a reliable model of the acoustical properties of the skull in order to simulate this first step. 3-D simulations based on high-resolution CT images of a skull have been successfully performed with a finite differences code developed in our Laboratory. Thanks to the skull porosity, directly extracted from the CT images, we reconstructed acoustic speed, density and absorption maps and performed the computation. Computed wavefronts are in good agreement with experimental wavefronts acquired through the same part of the skull and this technic was validated in-vitro in the laboratory[2]. A stereotactic frame has been designed and built in order to perform non invasive transcranial focusing. Here we will describe all the steps of our new protocol, from the CT-scans to the therapy treatment and the first in vivo results on monkeys will be presented. This protocol is based on protocols already existing in radiotherapy [3].**

I. Introduction

The feasibility of the practical clinical realization of non invasive surgery using High Intensity Focused Ultrasound in order to burn tumors have been demonstrated [4,5]. However ultrasonic brain tumor hyperthermia remains very limited due to the strong aberrations induced by the skull. A large discrepancy between the skull's high acoustic velocity (about 3000m.s^{-1}) and the brain tissues low velocity (about 1540m.s^{-1}) combined with a severe attenuation of ultrasound in the bone strongly degrade the beam shape.

Recent studies showed it was possible to correct the aberrations by using adaptive techniques [6,7]. But those techniques require ultrasonic sources inside the brain. In the case of brain hyperthermia, a hydrophone could be introduced close to the tumor while performing the biopsy, in order to record the signals coming from this hydrophone on the therapeutic array. Once the diagnostic is confirmed and the hydrophone removed, one has to emit the time reversed signals with amplitude compensation in order to correct both phase and amplitude aberration induce by the skull. Then steering the signals enables to precisely heat the whole tumor spot by spot [7].

Recently, the possibility to deduce the acoustical properties of the skull from MRI and CT images raised new hopes for non invasive brain therapy. Hynynen *et al* [8] proposed to use MRI images for extracting the skull profile, without information on the internal heterogeneity. Then, using a three layer model they numerically highlighted the necessity to perform phase correction to focus through the skull. However, such a simple model is not sufficient to model accurately the phase aberrations induced by the skull. Moreover the skull's absorption is not modeled although it plays a important role in the defocusing effect of the skull, as show by White et al [7].

The method proposed here consists in simulating the first step of time-reversal. From CT-scans, acoustical properties are extracted; then the propagation through skull is simulated with a 3D finite differences code. Figure 1 shows a brief overview of all the protocol's steps.

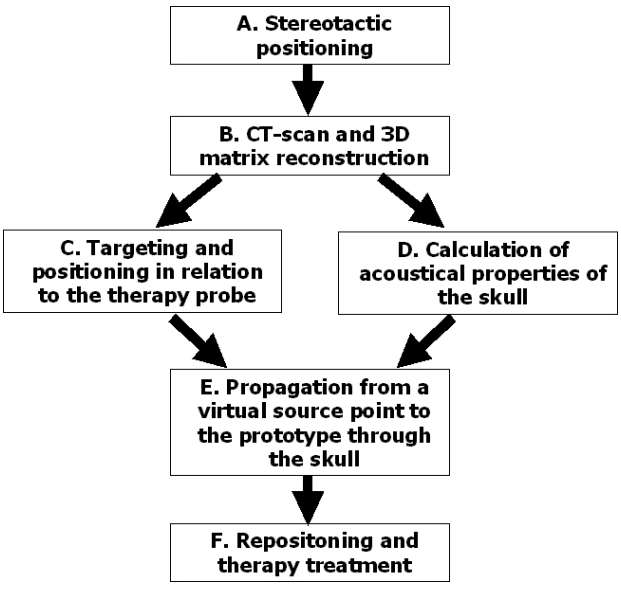

Fig.1 Step summary of the protocol. The link between the CT scan and the therapy treatment is done by computer processing.

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Different steps of our protocol will be explained and first in-vivo experiments performed on monkeys (*macaca fascicularis*) will be presented.

II. MATERIALS

The therapeutic prototype is a high power 300 elements phased array. The 300 high power piezocomposite transducers (8 mm diameter, 0.5 cm^2 active area, 900 kHz central frequency, Imasonic, Besançon, France) are mounted in a spherically curved holder with a 14 cm radius of curvature. The transducers are connected to a 300-channels electronic driving system. Each electronic channel is individually programmable (phase and amplitude) and possesses its own emission/reception electronic board.

On the front part of the prototype, a water cooling balloon is placed. This balloon has two aims: first of all the water inside will assure a good transmission rate of the ultrasonic wave, secondly thanks to a cold water circulation (12°C) inside the balloon skin burns are significatively decreased.

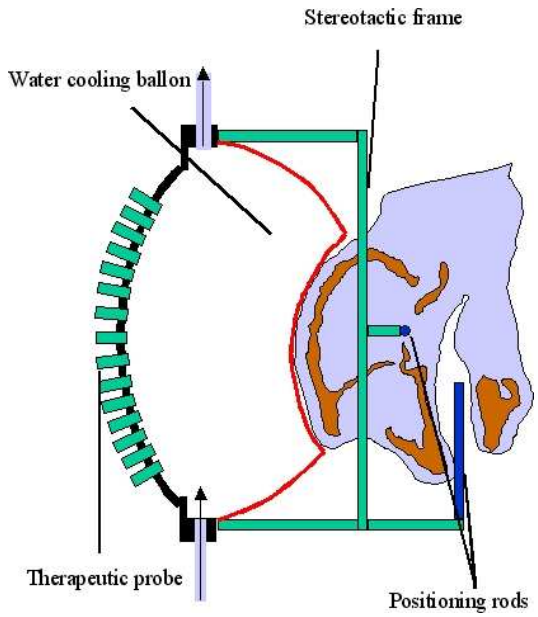

Fig 2. Scheme of the positioning during the therapeutic treatment. The stereotactic frame is set on the front part of the probe. The water cooling ballon provides a good ultrasound transmission.

III. PROTOCOL

A. Stereotactic positioning

A major problematic of this protocol is to have a good precision in all the positionings. In that purpose a stereotactic frame has been built in house inspired by those used in cranial surgery for large animals (cat, dog and monkeys). The monkey's position in relation to the frame is locked by two rods in the mouth and two rods in the ears of the animal

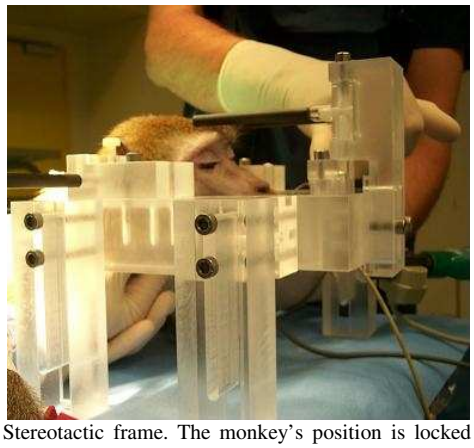

Fig. 3 Stereotactic frame. The monkey's position is locked by four rods. Two in the mouth and two others in the ears.

So a reproductible position of the monkey is provided with a precision of a few millimeters thanks to marks made on these rods. Commercial stereotactic frames can be more precise as they are screwed-down in the skull bone and the precision can be submillimetric.

The positions of the frame and the therapy probe in the CT-scans have to be located. In a first time the front part of the probe was fixed on the stereotactic frame, so the position of each transducer can be found when the different slices were read. Figure 4 shows a monkey in the CT scan with its stereotactic frame.

Fig. 4 Monkey in the CT scan with its stereotactic frame. The front part of the therapy probe has been put on the frame in order to locate the position of each transducer.

B. CT-scan and 3D matrix reconstruction

Data given by the CT scan are in the DICOM format. A Matlab program has been developped in order to be able to read and treat directly these data. All the CT-scans are read and the whole volume of the skull is reconstructed.

C. Targeting and positioning in relation to the therapy probe

The next step of the therapeutic protocol will be the choice of the target point. This target point must be closer than 3 centimeters from the geometrical focal point in order to have enough energy.

We calculate the relative position of the target point to the ultrasonic transducers.

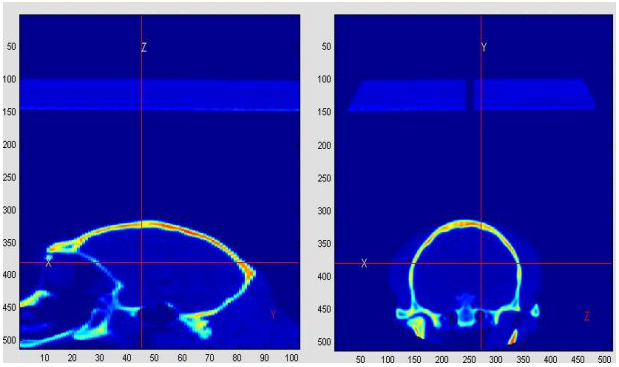

Fig. 5 Example of X-ray slices showing the selected target point. In this case the target point was 1 centimeter away from the geometric focal point.

D. Calculation of acoustical properties of the skull

It has been shown in a previous study [2] that the bone porosity can be derived from the raw CT data in Housfield Unit (HU):

$$\Phi = 1 - \frac{HU}{1000} \quad (3)$$

Acoustical properties (density, speed and acoustical absorption) of the skull are then deduced from the porosity map. Density is directly given by the porosity:

$$d = d_{water}\Phi + d_{bone}(1-\Phi) \quad (4)$$

d_{water} is the density of water and d_{bone} is the density of cortical bone.

The speed of sound is harder to deduce from the skull porosity. The diploe and the inner and outer tables have different mechanical properties[9]. Acoustic waves propagating in the fluid and the solid media are coupled, which is correctly described by the Biot theory if the wavelength is negligible compared to the size of the heterogeneities. At 1.5 MHz, the wavelength is unfortunately of the order of magnitude of the heterogeneities. However, Carter and Hayes[10] showed that the elastic modulus of bone is proportional to the apparent density cubed, which suggests a linear relationship between velocity and porosity:

$$c = c_{water}\Phi + c_{bone}(1-\Phi) \quad (5)$$

c_{water} is the speed of sound of water and c_{bone} is the speed of sound of cortical bone.Thanks to ex vivo measurements performed on monkeys piece of skull at the Laboratoire d'Imagerie Paramétrique (LIP, France), the following parameters have been set for the present study on monkeys:

$c_{water} = 1500\ m.s^{-1}$
$c_{bone} = 2900\ m.s^{-1}$
$d_{water} = 1000\ kg.m^{-3}$
$d_{bone} = 2200\ kg.m^{-3}$

E. Propagation from a virtual source point to the therapy probe through the skull

Once the source is chosen and correctly positioned and the skull's acoustical properties are calculated, the propagation of the wave from the source to the prototype through the skull has to be simulated. A full 3D finite difference code developped in the lab is used. Figure 6 shows an example of a propagation through the skull bone.

Fig. 6 Propagation from virtual source point through sull bone using finite difference code.

As monkey skull bone are smaller than human one the propagation is only calculated with finite difference code to an arbitrary plane of transducers just in front of the skull. The propagation from this plane to the prototype is realised by a simple ray tracing code. This boil down taking only account of the diffraction in an homogeneous media. For human skulls the simulation will have to be split into parts because of limited memory of computers.

F. Repositioning and therapy treatment

For the treatment, the monkey is shaved with depilatory cream for a better contact and placed in the stereotactic frame at the same position than in the X-ray scanner. The frame is positioned on the front part of the

probe. The water cooling balloon is filled and coated with echographic gel to ensure a good ultrasonic transmission. Figure 7 shows a picture of the treatment.

Fig. 7 Therapy treatment of a monkey. The monkey is placed in the stereotactic frame which is fixed on the front part of the prototype.

Once the simulation has been performed, the global amplitude of the emission signals is adjusted to reach 1200W.cm^{-2} at focus. The amplitude is thus set to 45% of the maximum amplitude available on the prototype (20% of the maximum acoustic power). Indeed, due to the smaller absorption rate in the monkey skull compared to a human skull, the prototype designed for human treatments is overpowered for mokeys. The same energy is also delivered on the contralateral hemisphere but without any correction (the simulation process was performed in the same way except that the targeted location was symmetric and the simulation medium was water, without any skull bone). Therapeutic sequences are optimized to avoid skin burns. For a point, a serie of ten shots of 10 seconds was achieved at a quite low intensity and between two shots a waiting time of 20 seconds was set in order to let the skull cool down. With these sequences skin burn was observed.

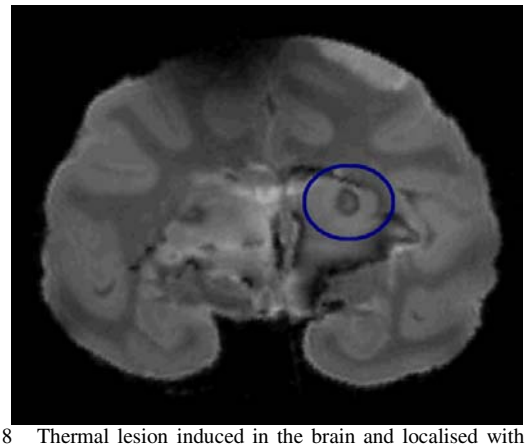

Fig. 8 Thermal lesion induced in the brain and localised with a T2 sequence in a 7T Brucker MRI.

Figure 8 shows an MRI image of the lesion induced in the brain and figure 9 the repositioning between MRI image and CT localisation. Note that this fusion between MRI and CT images is rough as the MRI was achieved on the formalized brain one week after the treatment.

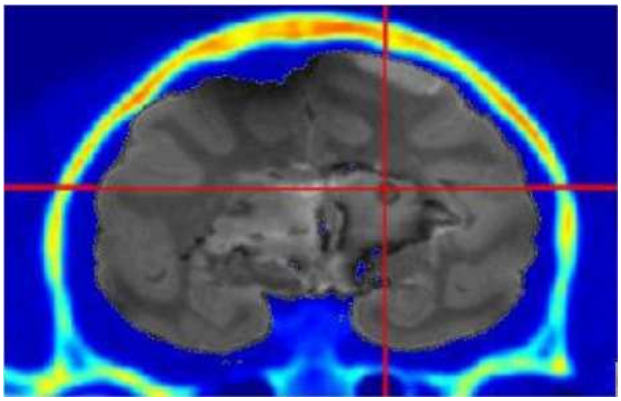

Fig. 9 Repositioning between MRI image and the point source chosen on the CT-scan.

IV. Conclusion

A totally non invasive protocol for transcranial HIFU was proposed and tested. Acoustical properties of the skull can be deduced from CT-scans and the first results are very promising. A lesion has been induced in the brain at the expected location with the non invasive correction. A symmetric location was also targeted on the same monkey on the other hemisphere without performing any correction, by simply steering electronically the beam. In each case, the same total energy was emitted. No lesion has been found without correction, which means that there was no effect without correction or that this effect was significantly lower than with correction Ongoing investigations deal with more in-vivo data.

V. References

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