

UNIVERSITAT
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Acoustic holograms for biomedical ultrasound applications

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Universitat Politècnica de València / Consejo Superior de Investigaciones Científicas

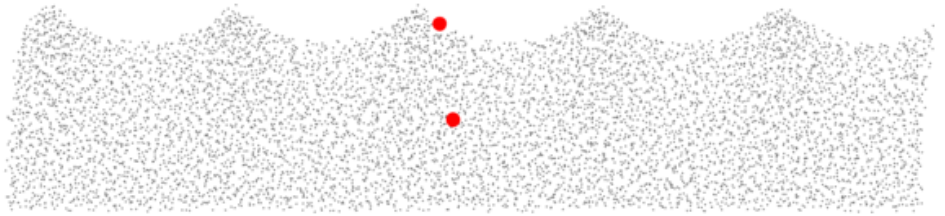
Acoustics Research Seminar, University of Salford, April 21, 2021

How can we use mechanical waves for therapy?

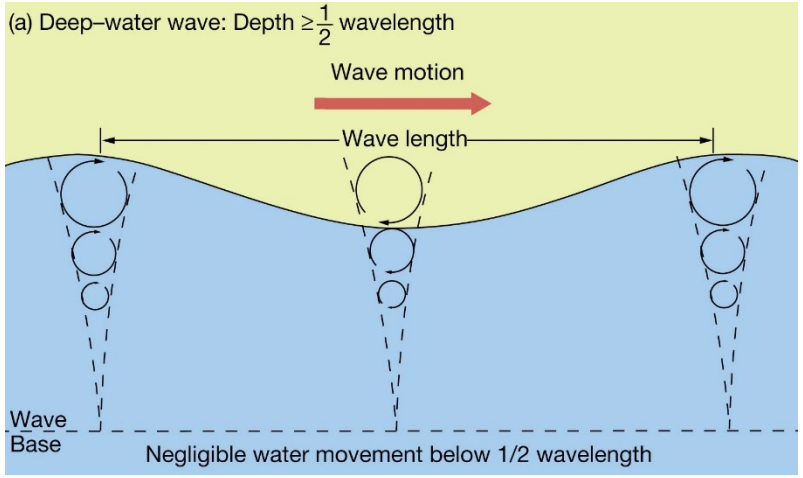
Mechanical waves

Wave-matter interaction

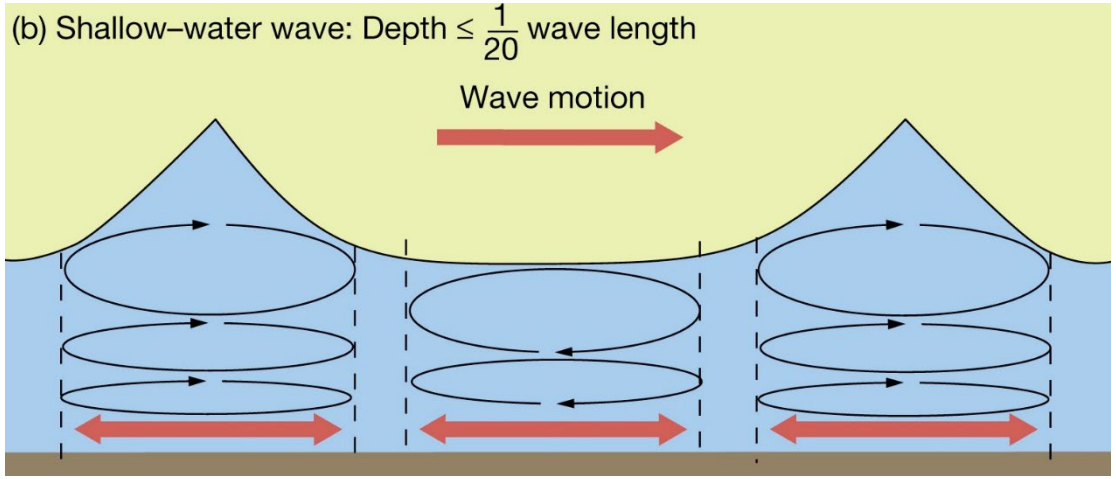
- Waves carry energy and momentum.
- When a wave interacts with matter, it can transfer the energy and/or momentum to the medium



Deep-water waves



Shallow water waves



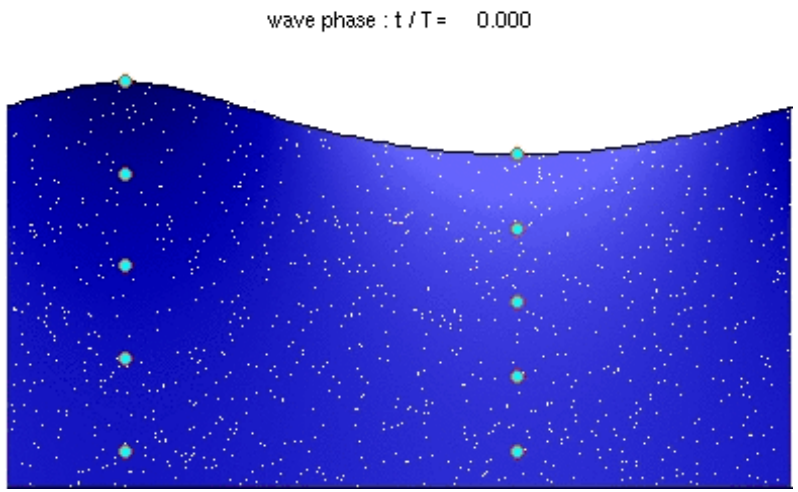
Mechanical waves

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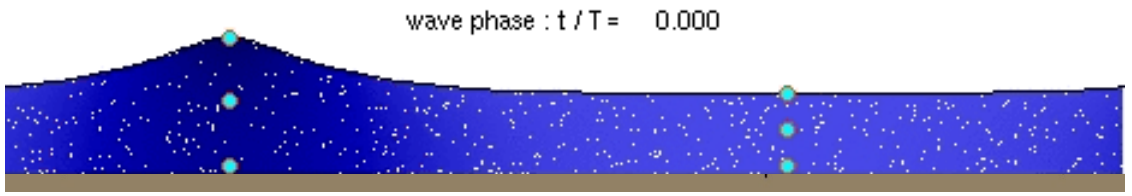
- Waves carry energy and momentum.
- When a wave interacts with matter, it can transfer the energy and/or momentum to the medium



Can we create localized “tsunamis” in the human body?



Deep-water waves



Shallow water waves

Ultrasound

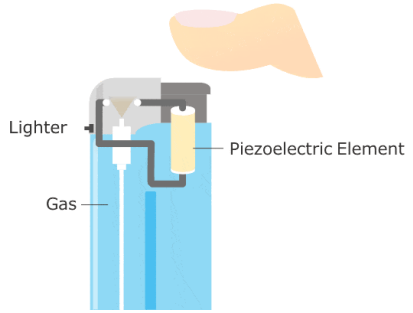
What is ultrasound

- Just a longitudinal mechanical wave,
- Acoustic wave with a frequency above 20 kHz



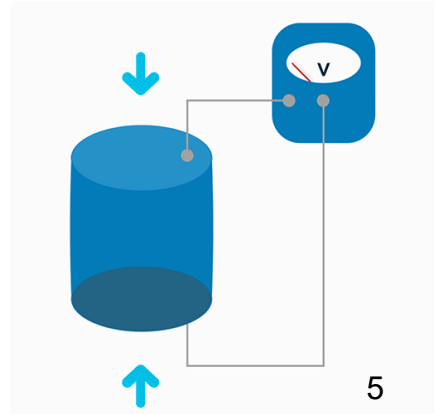
How is ultrasound generated?

- Mainly using piezoelectric effect.
- A deformation is produced if an electric field is applied



How is ultrasound detected?

- Also using piezoelectric effect.
- An electric field is generated when the material is deformed



Biological effects of ultrasound

Wave-matter interaction

- Waves carry energy and momentum.
- When a wave interacts with matter, it can transfer the energy and/or momentum to the medium

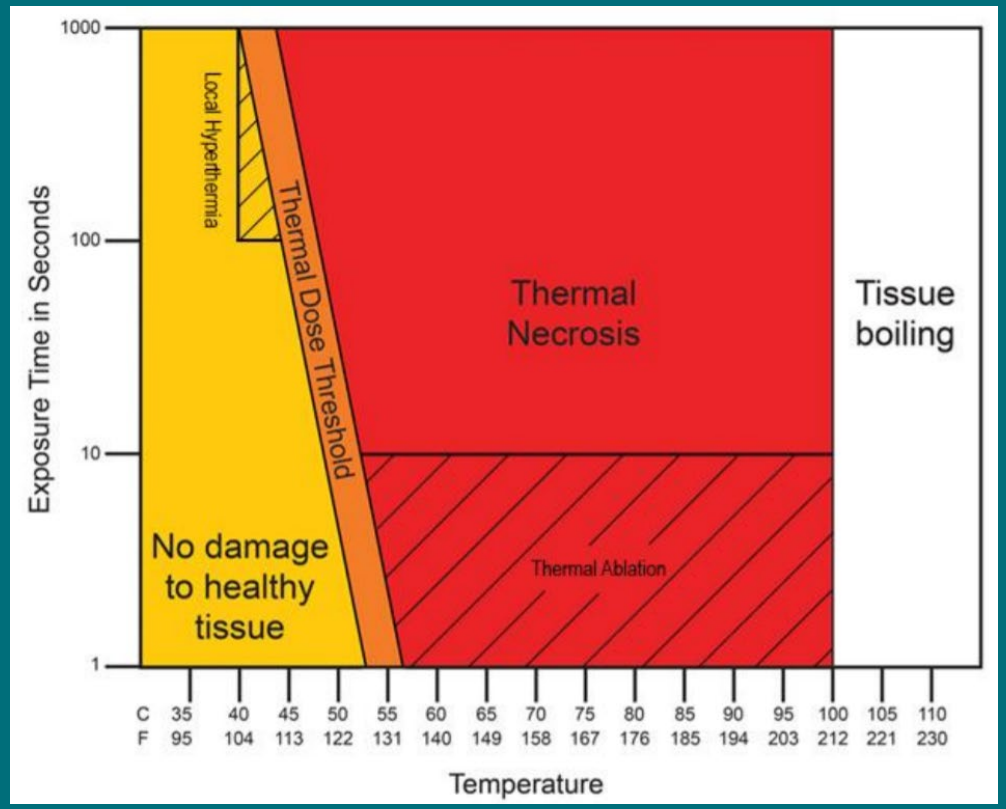
a) Thermal effects

- Temperature rise
- Sonoluminescence

b) Mechanical effects

- Acoustic radiation force
- Streaming (in fluids) and deformation (in solids)
- Cavitation (non-inertial and inertial)

Temperature rise in tissue



Biological effects of ultrasound

Wave-matter interaction

- Waves carry energy and momentum.
- When a wave interacts with matter, it can transfer the energy and/or momentum to the medium

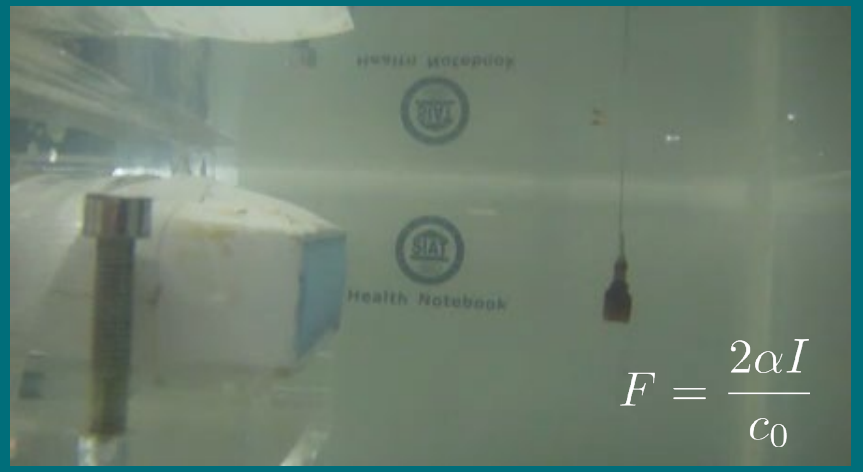
a) Thermal effects

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b) Mechanical effects

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- Cavitation (non-inertial and inertial)

Acoustic radiation force



Light radiation pressure



Biological effects of ultrasound

Wave-matter interaction

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- When a wave interacts with matter, it can transfer the energy and/or momentum to the medium

a) Thermal effects

- Temperature rise
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b) Mechanical effects

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Acoustic streaming



Biological effects of ultrasound

Wave-matter interaction

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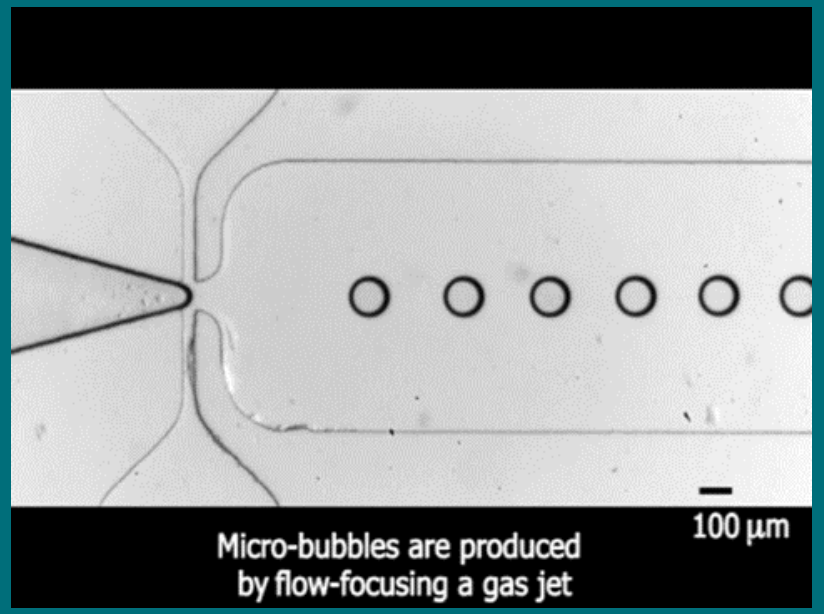
a) Thermal effects

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b) Mechanical effects

- Acoustic radiation force
- Streaming (in fluids) and deformation (in solids)
- Cavitation (non-inertial and inertial)

Stable cavitation



Inertial cavitation



(Bubble cloud for histotripsy)

Biological effects of ultrasound

Wave-matter interaction

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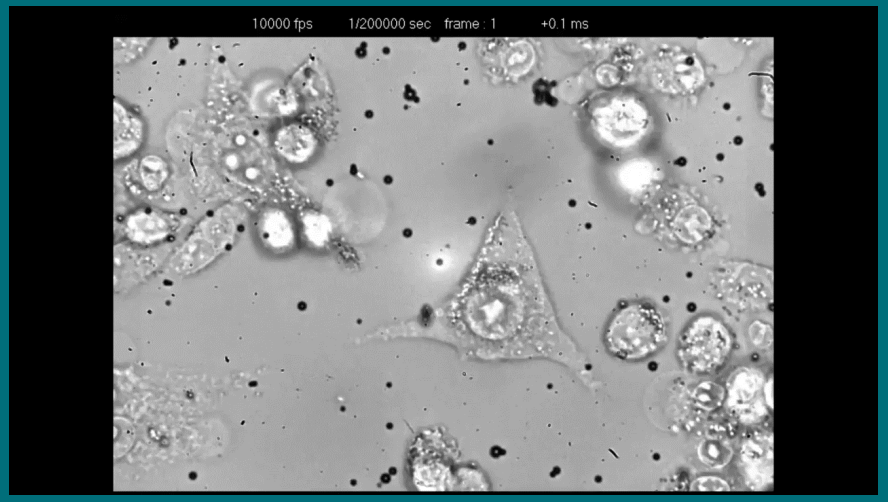
a) Thermal effects

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Acoustic cavitation



Gas microbubbles and cancer cells interact under the influence of low-energy, clinically safe ultrasound. The microbubbles are seen to enter, bounce ons, drill into, a
u



Biological effects of ultrasound

Tissue destruction

- Stone fragmentation
- Clot lysis
- Localized thermal destruction of tissues
- Localized mechanical destruction of tissues

Drug delivery

- Sonoporation
- Increasing vascular permeability
- Vasodilation
- Drug delivery carriers, nanodroplets
- Blood-brain barrier opening

Other effects

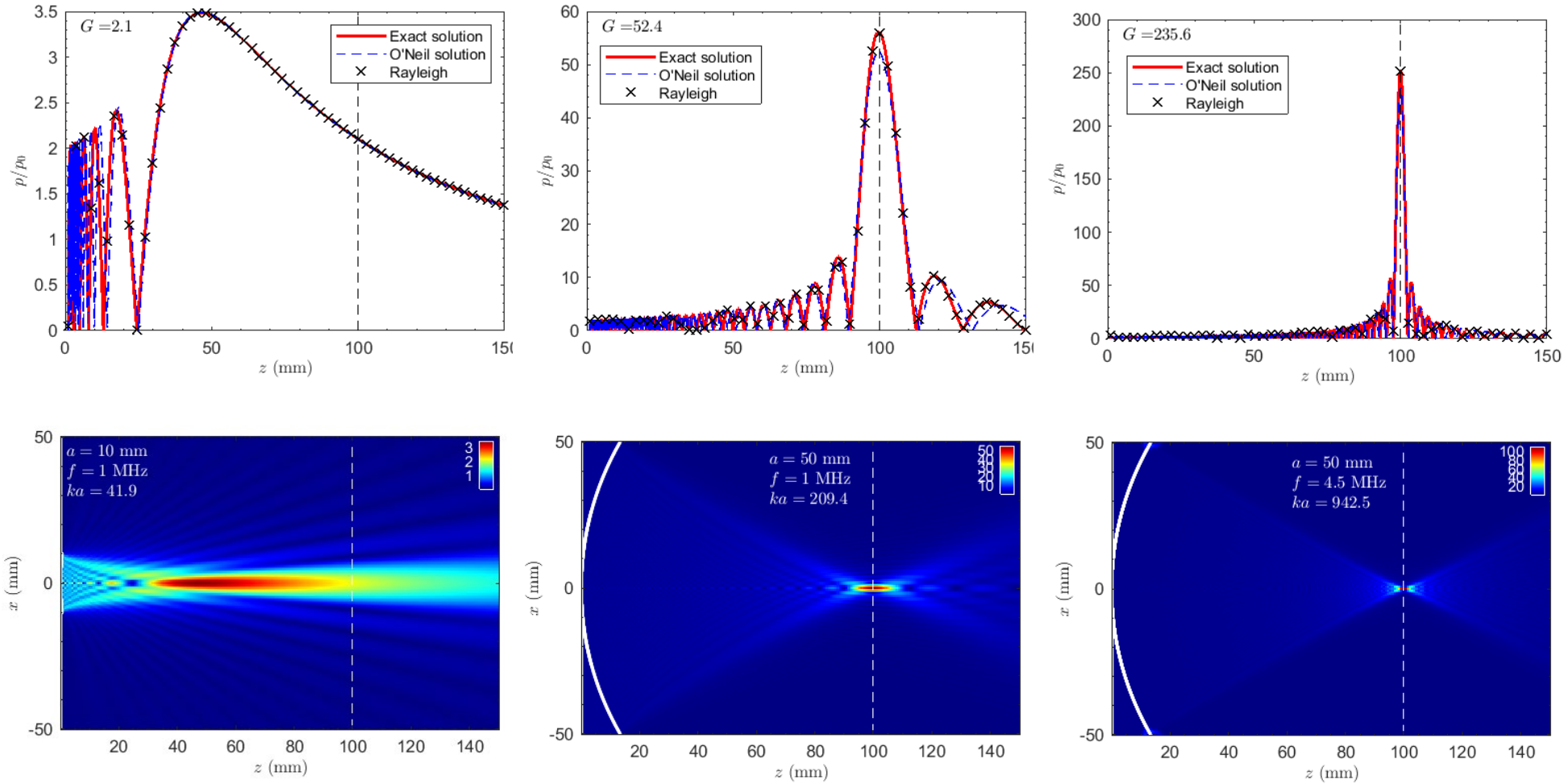
- Vasoconstriction
- Hemostasis, coagulation of internal bleeding
- Immunomodulation
- Increased sensitivity to chemotherapy
- Increased sensitivity to radiotherapy
- Sensitization to immunotherapy and gene therapy
- Neuromodulation (stimulation / suppression)
- Biomarker amplification
- Stem cell guidance
- Other specific effects

How to treat (only) diseased tissues

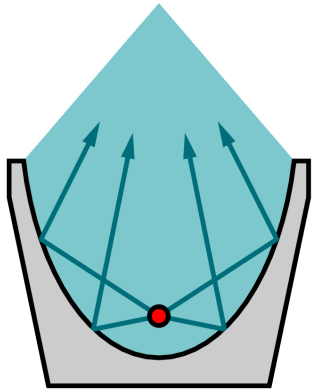

gentle motion
(in acoustics)
violent motion
(in acoustics)
almost at rest
(in acoustics)

Focused ultrasound

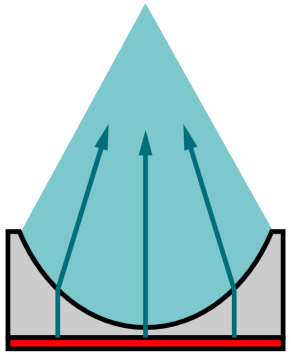
Focused ultrasound allows to increase and localize mechanical energy



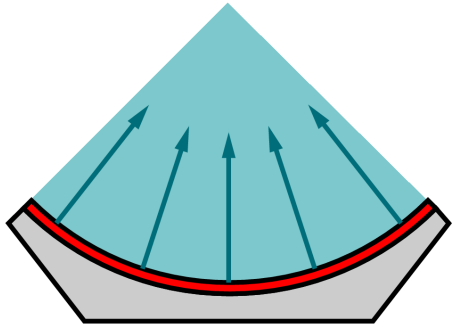
Focused ultrasound



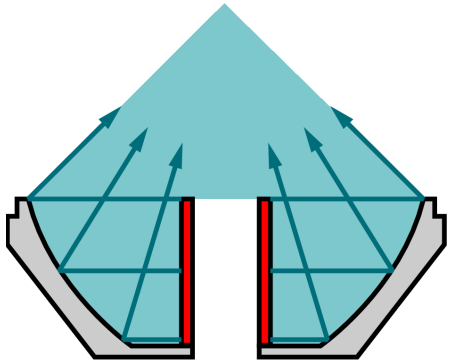
Elliptical reflectors



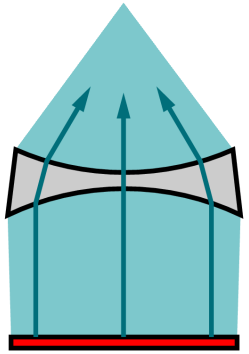
Elliptical lenses



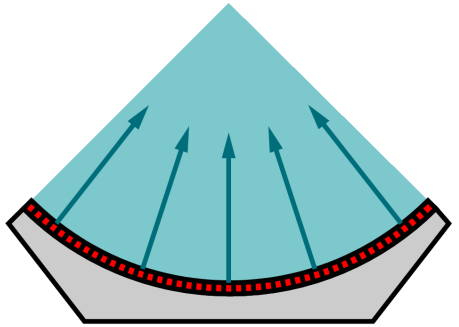
Spherical radiators



Parabolical reflectors

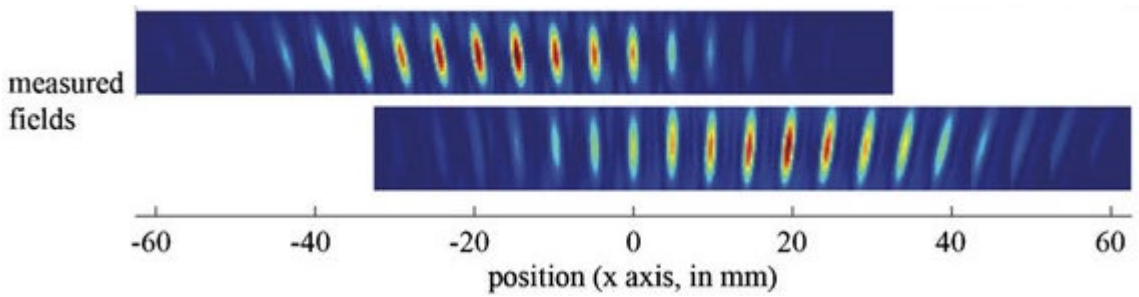


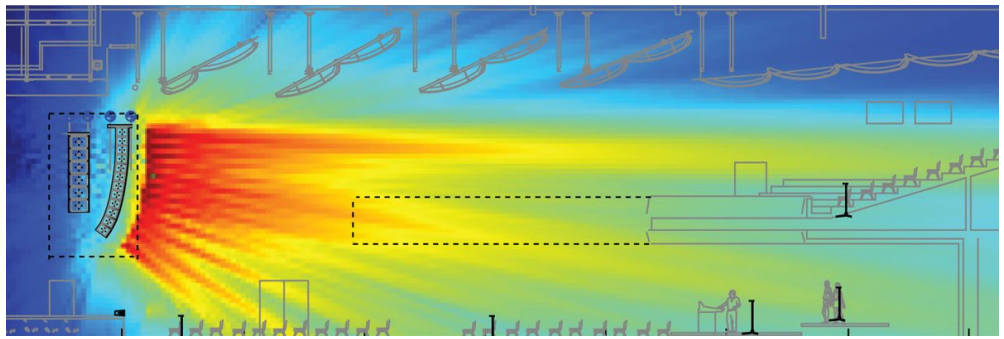
Convex lenses



Phased arrays

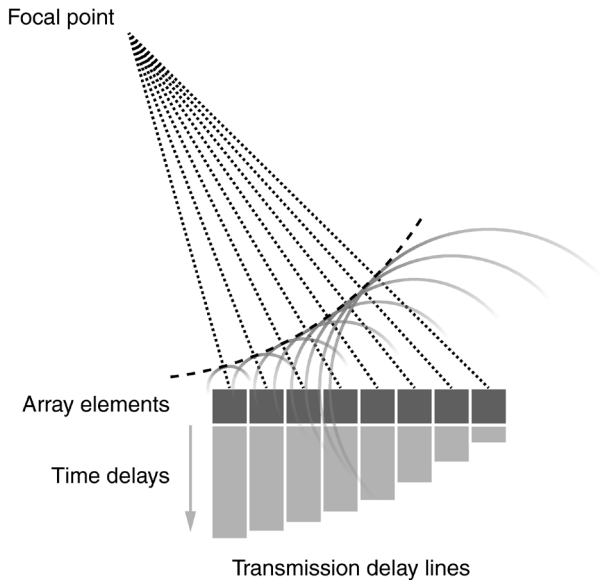
Focused ultrasound

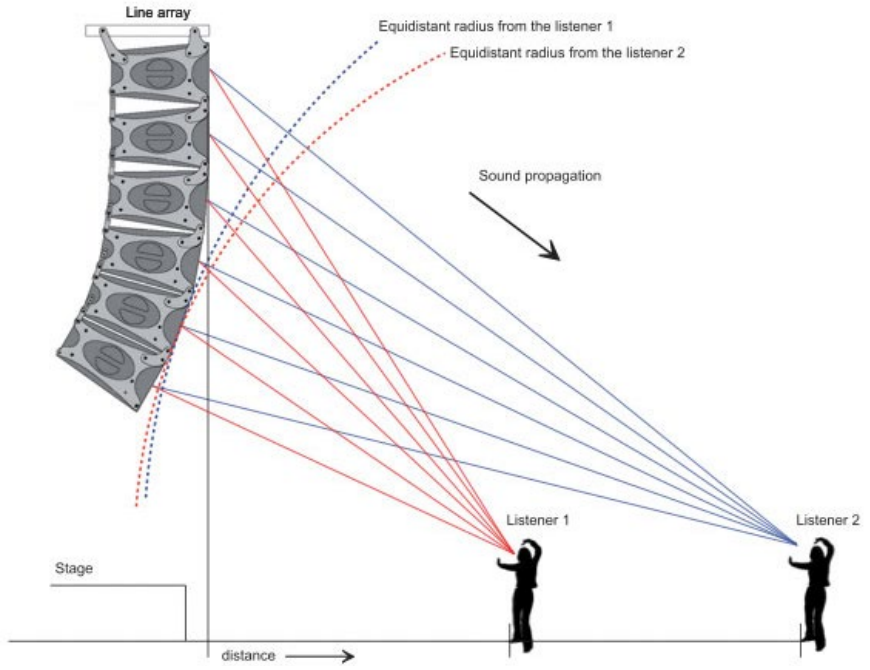






Histosonics Gen1 (USgFUS)





Thermal tissue ablation

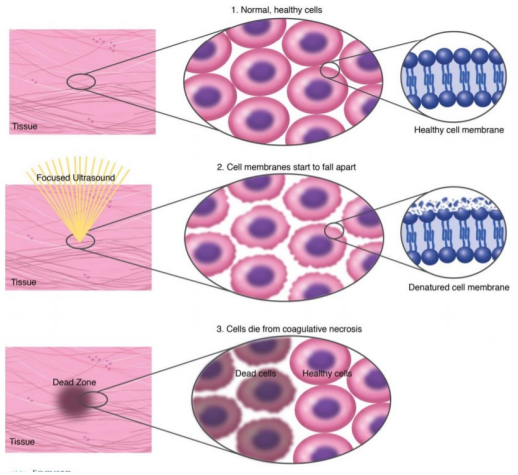
High Intensity Focused Ultrasound (HIFU)

Therapy

- Long-duration ultrasound pulse is applied at high intensity.
- Temperature rises to 56-100°C.
- Protein denaturation.
- Lesion size: 10 x 3 x 3 mm (of the order of a grain of rice).

Result

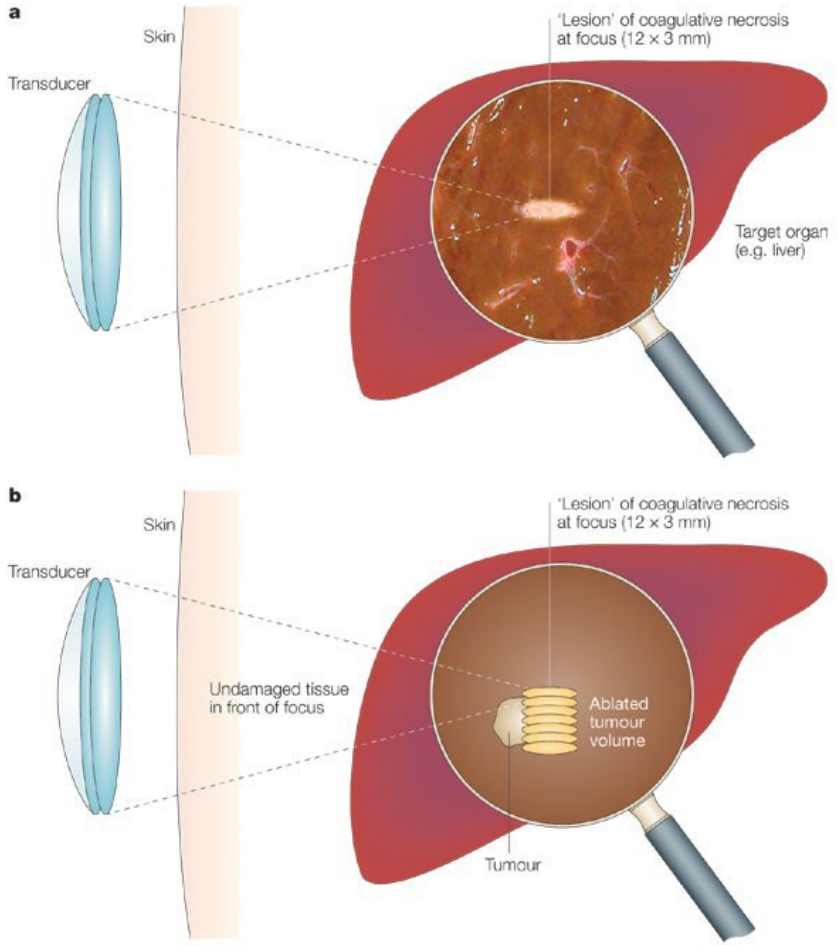
- localized cell necrosis.



Normal tissue

Thermal ablation

Result



Kennedy, J. E. (2005). Nature reviews cancer, 5(4), 321-327.

Thermal tissue ablation

High Intensity Focused Ultrasound (HIFU)

Applications

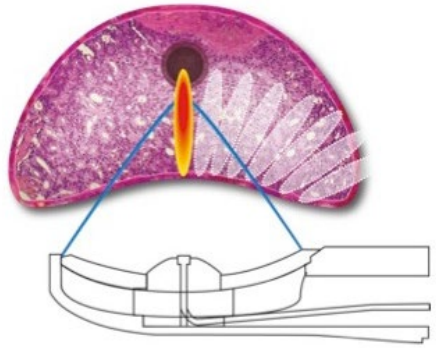
- Prostate cancer
- Uterine fibrosis
- Liver cancer
- Bone metastases, etc.

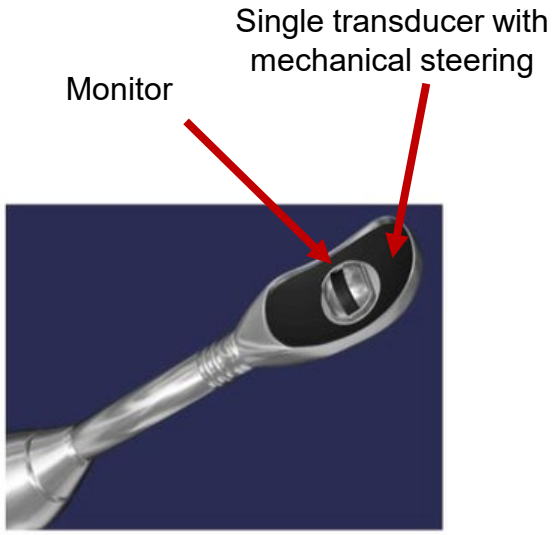
Mechanism

- Localized thermal tissue ablation

Monitoring

- MRI (MRgFUS)
- US (USgFUS)





ExAblate (MRgFUS)



Ablatherm (USgFUS)



… and in the brain?

Thermal tissue ablation

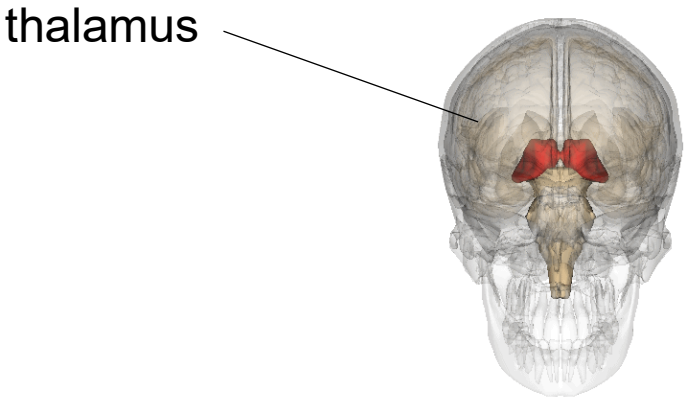
Thalamotomy for essential tremor

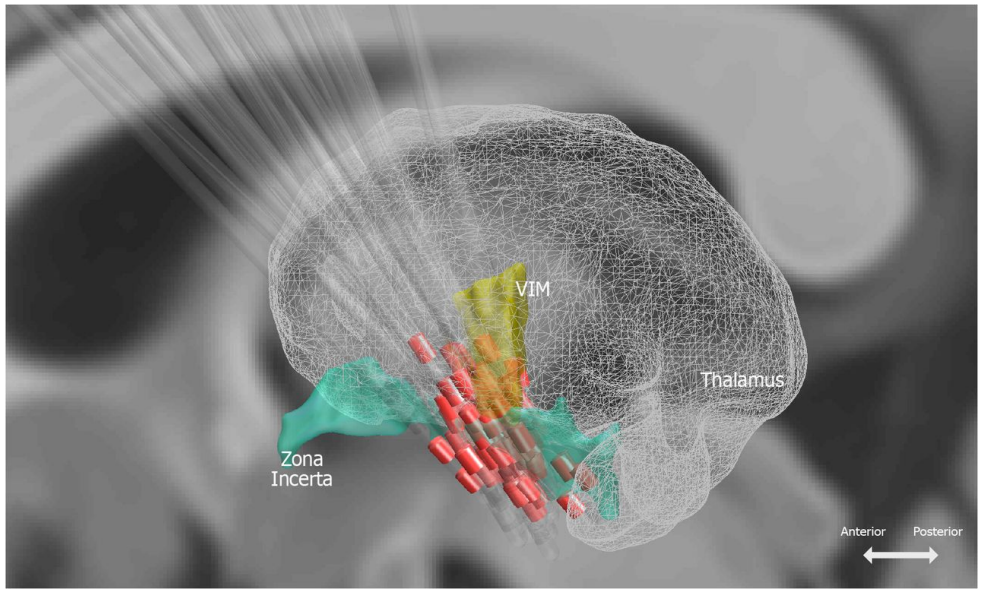
Problem

- Most common movement disorder, benign disease.
- Impairment of patients' ability to eat, shave, write, perform household activities and work.

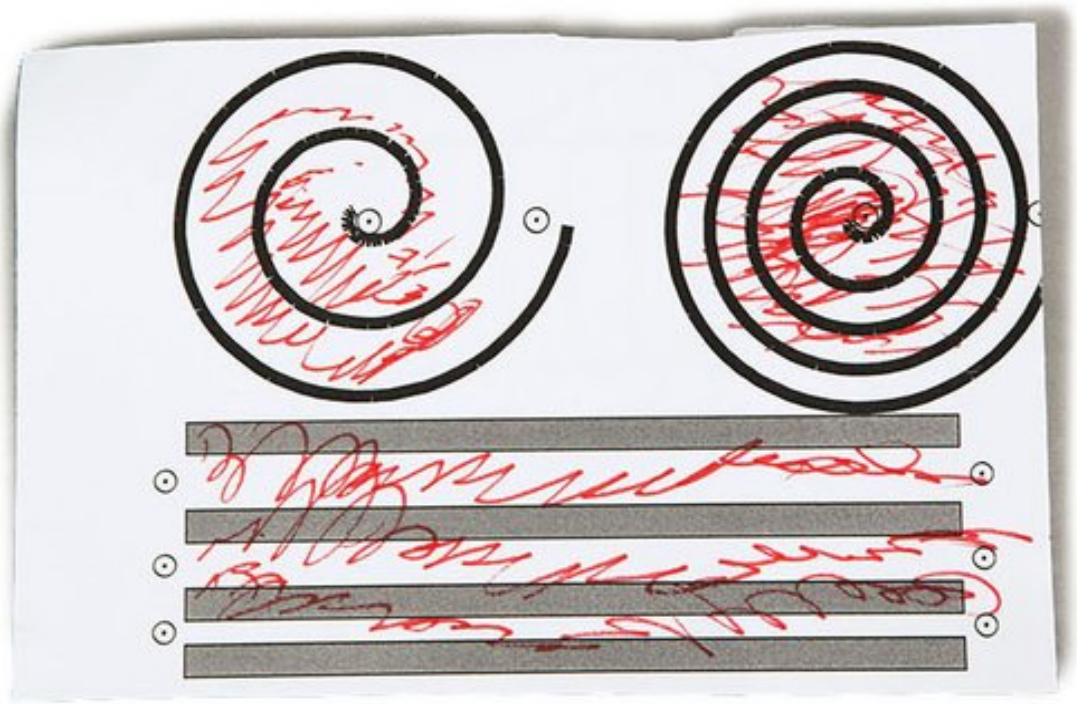
Treatment

- Ablation of the thalamus (VIM, ventralis intermedius)
- Using US: the patient is awake and requires no anesthesia, no scalp incisions, or insertion of electrodes into the brain and no holes in the skull (burr holes)





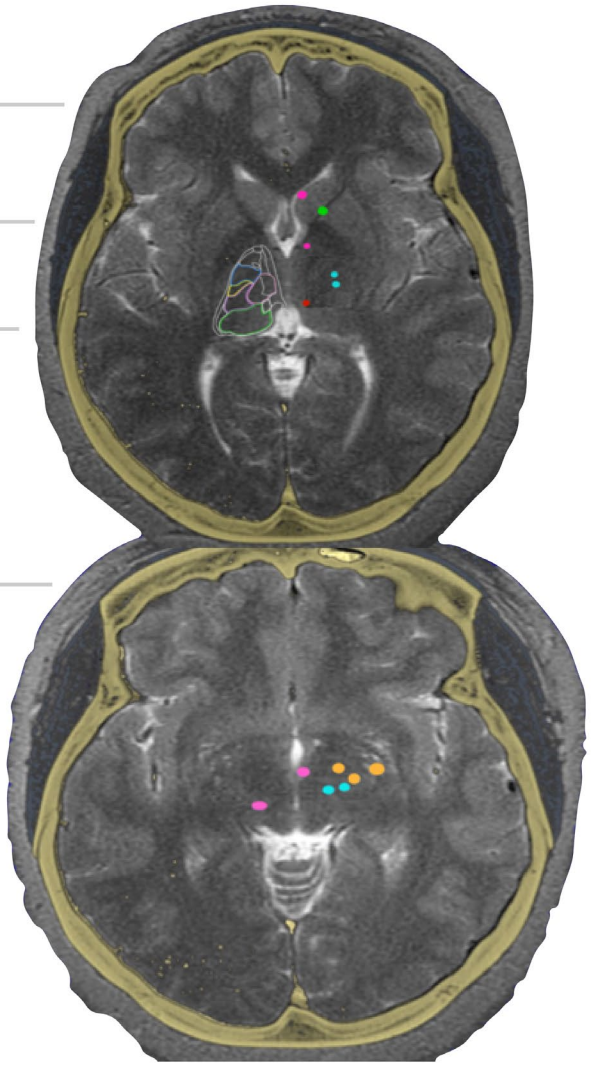
Thermal tissue ablation





Thermal tissue ablation

Disease	Thermal ablation targets
Obsesive-compulsive disorder	ALIC
Neuropathic pain	CLN
Epilepsy	SEGA Anterior Nucleus HH Temporal Lobe
Essential tremor	Vo VIM ZI CTT
Parkinson's disease	PTT GPi STN



FDA Approved

The US Food and Drug Administration has approved focused ultrasound for this condition. Patients can seek commercial treatment at participating sites.

International Approval

Focused ultrasound is approved to treat this condition outside the US. Patients can seek commercial treatment at participating international sites.

Clinical Trials

Focused ultrasound for this condition is being researched in clinical trials.

Early Stage

Focused ultrasound research is in the laboratory phase and is not yet available for patients.

https://www.fusfoundation.org/diseases-and-conditions/neurological

Localized drugs and gene delivery

Blood-brain barrier opening

Problem

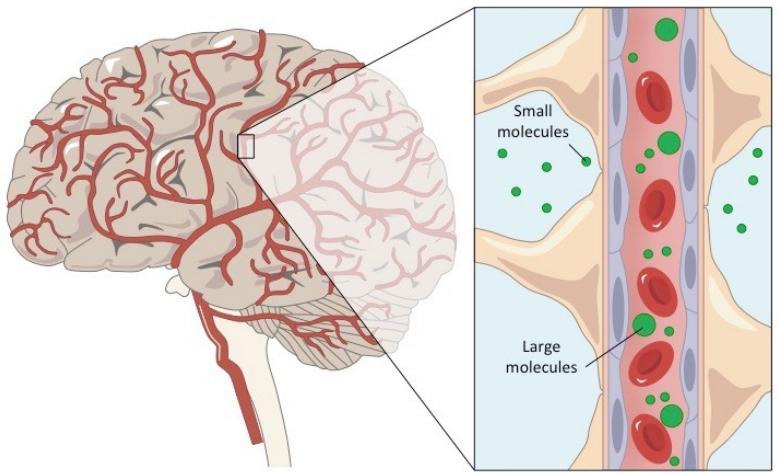
- Tight junctions in the endothelium prevent the passage of heavy molecules into the CNS
- Protection against infections, viruses
- Blocks drug delivery

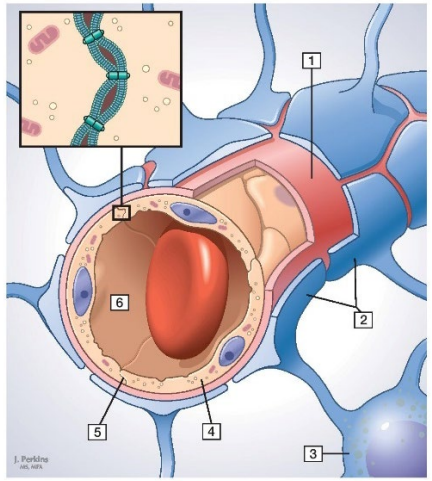
Treatment

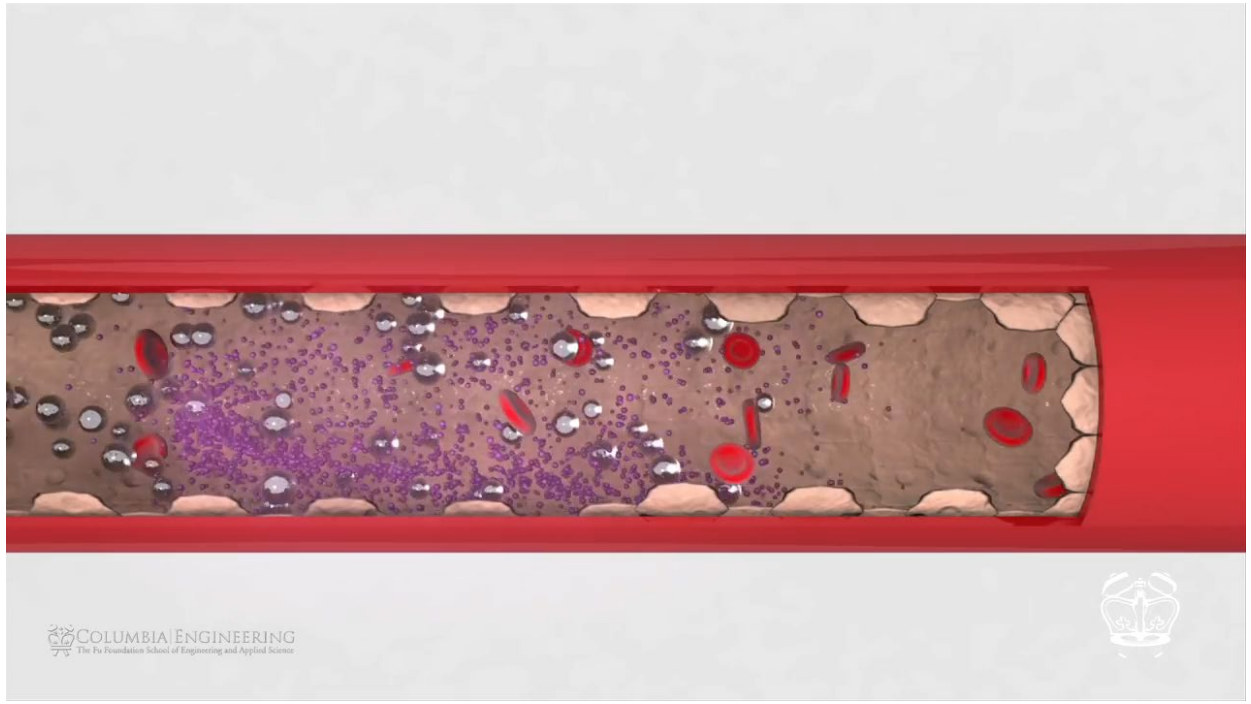
- Medium intensity focused US + microbubbles
- Localized, transient, non-invasive and safe way blood-brain barrier opening

Application

- Localized chemotherapy
- Therapies for Alzheimer's, Parkinson's, etc....







Neuromodulation

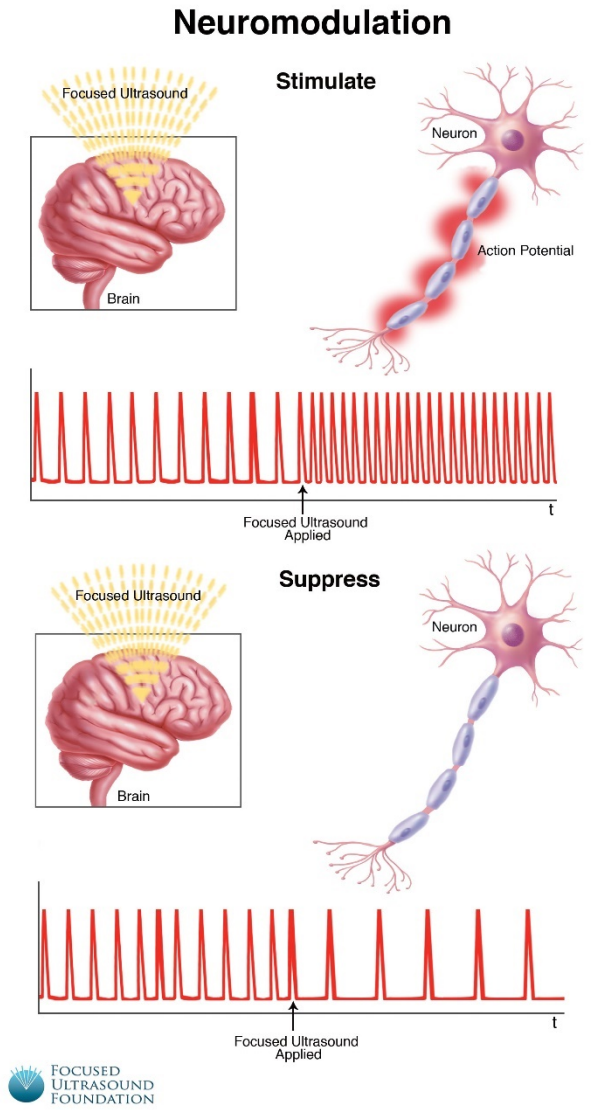
FUS Mediated Localized Neuromodulation

Stimulation

- Stimulate neuronal activity in a localized manner
- Applications
  - Mapping of neuronal networks, CNS research
  - Somatosensory, visual?

Suppression

- Suppress nerve stimuli in a localized manner
- Applications
  - Epilepsy
  - Chronic pain treatment
  - Depression
  - Essential tremor



Neuromodulation

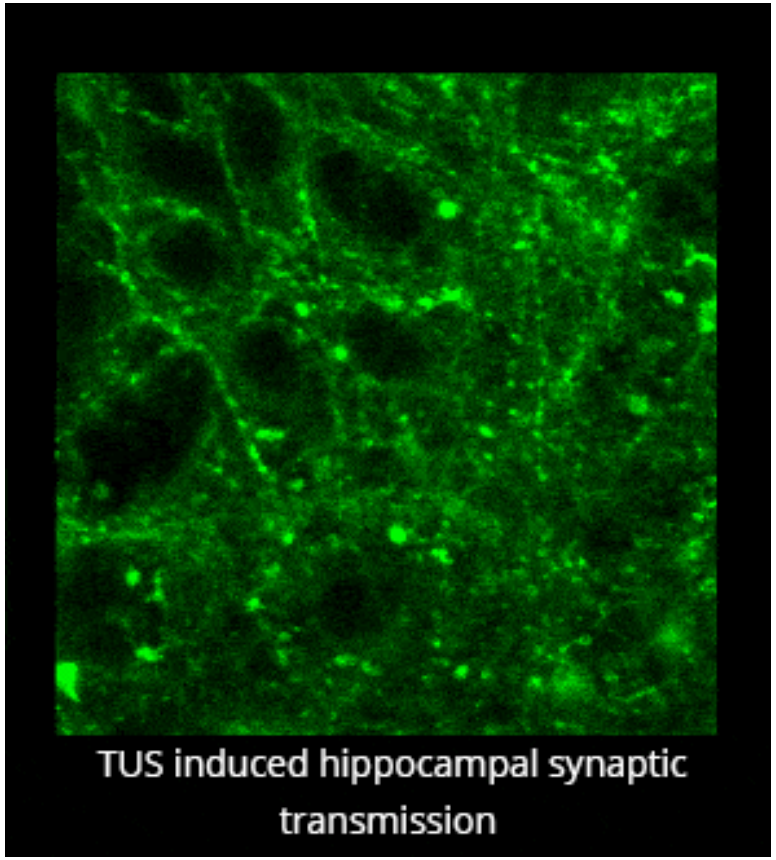
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TUS induced hippocampal synaptic transmission

Focusing ultrasound in the brain

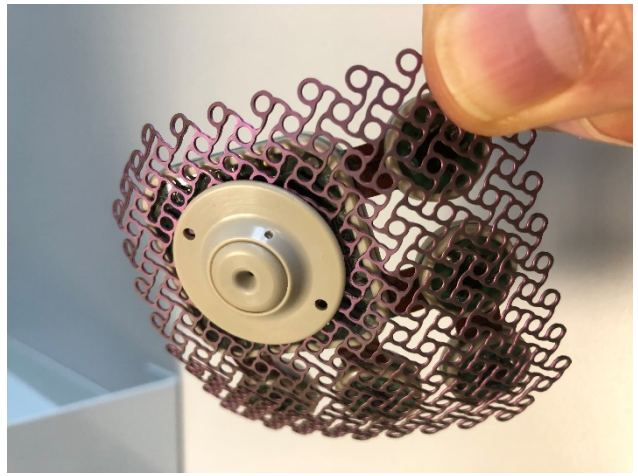


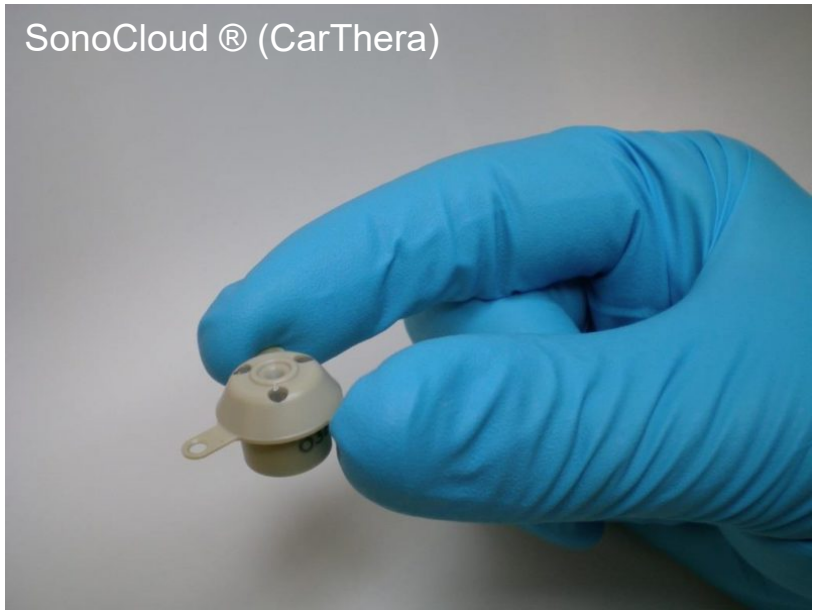
Transcraneal ultrasound systems

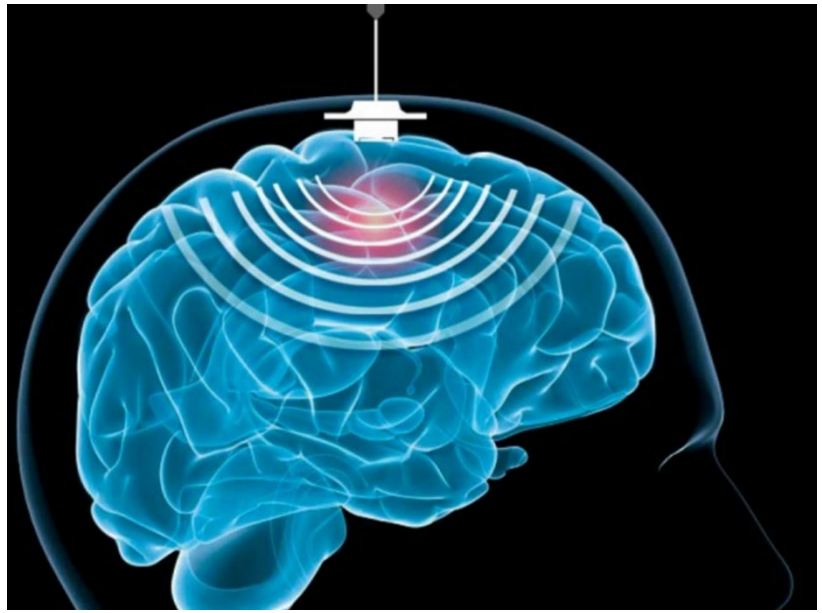
Intracranial implants

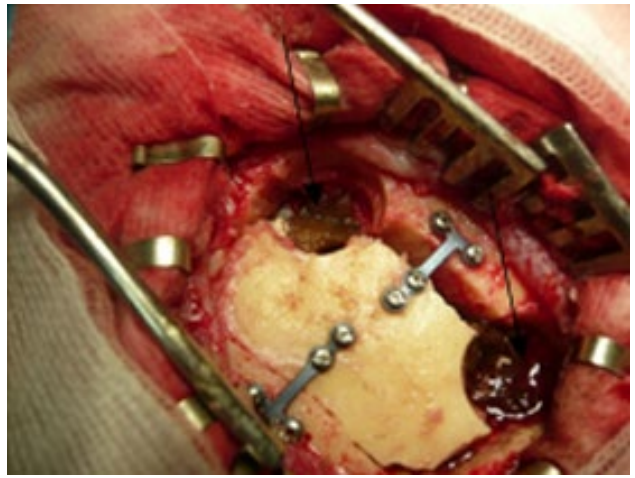
- Blood-brain barrier opening
- Chemotherapy
- Implanted in a burr hole (diagnostic biopsy or post tumor resection glioblastoma)
- Invasive, poor focusing

CarThera
Advanced Brain Therapy Through Innovation







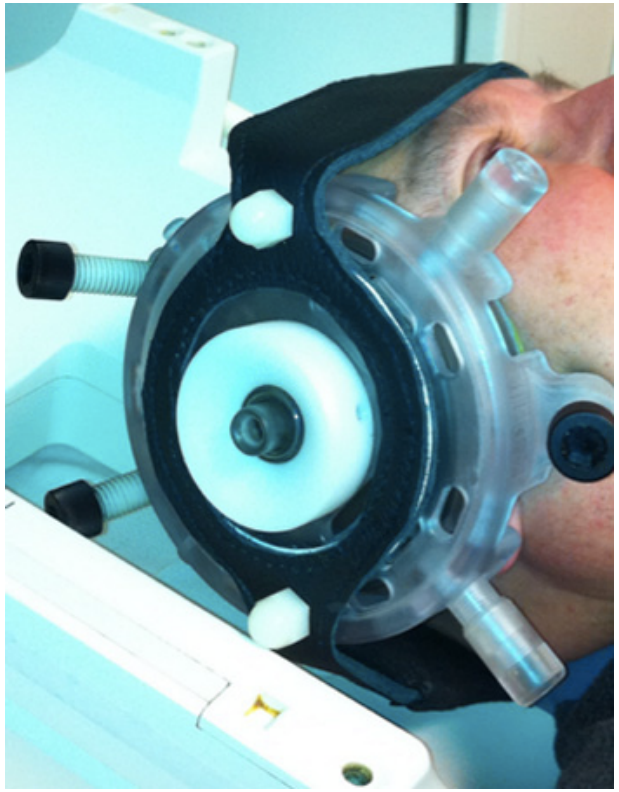


Transcraneal ultrasound systems

Single element transducer

- Simple, cheap
- MRI compatible
- Neuromodulation
- No aberration correction (500 kHz)
- Uncontrolled focusing





BRAINSONIX CORPORATION



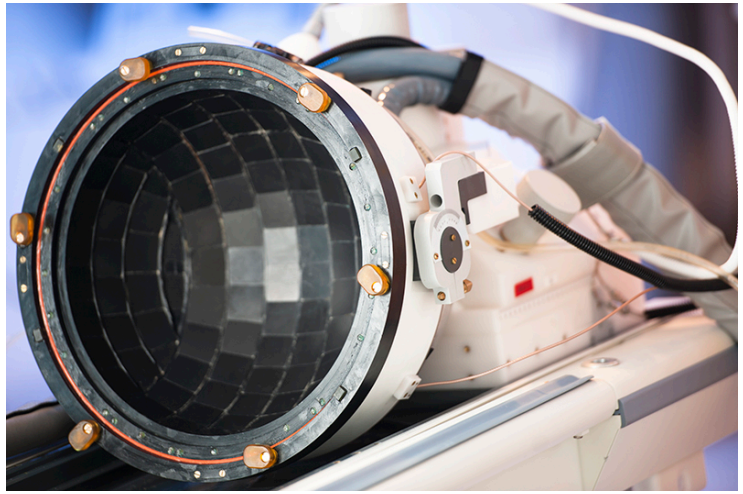
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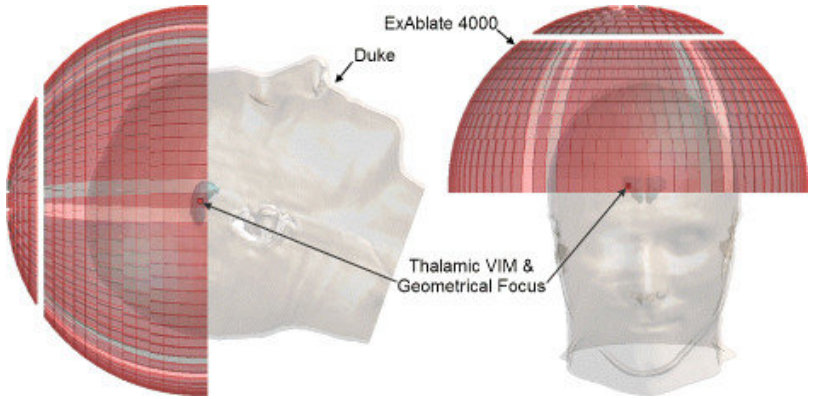
Magnetic resonance-guided focused ultrasound (MRgFUS)

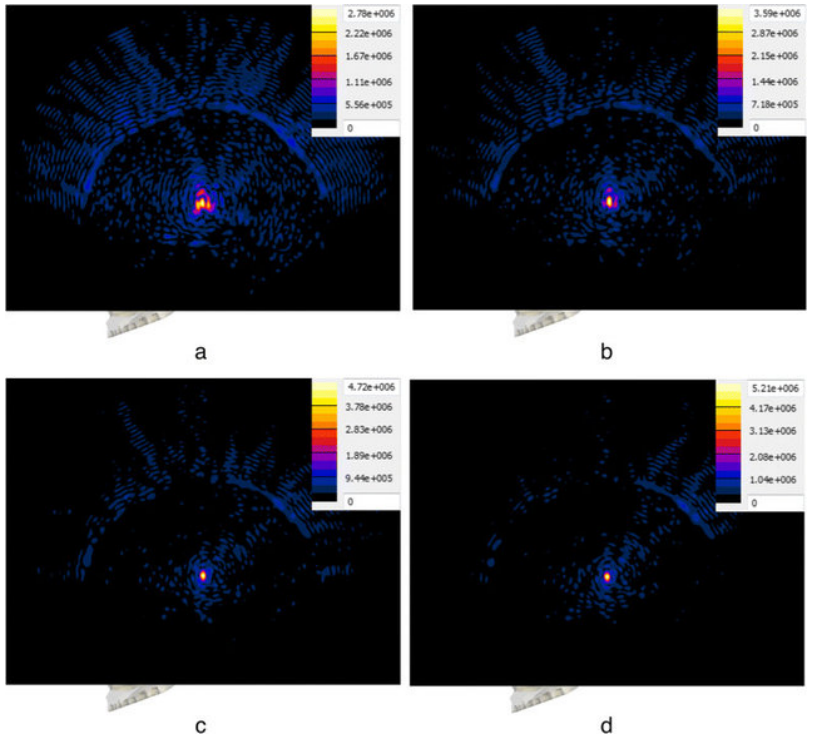
- Phased array
  - Skull aberrations can be mitigated
  - Focal steering
  - MRI guided
- Thermal ablation (650 kHz)
- BBB Opening (220 kHz)
- Expensive

INSIGHTEC









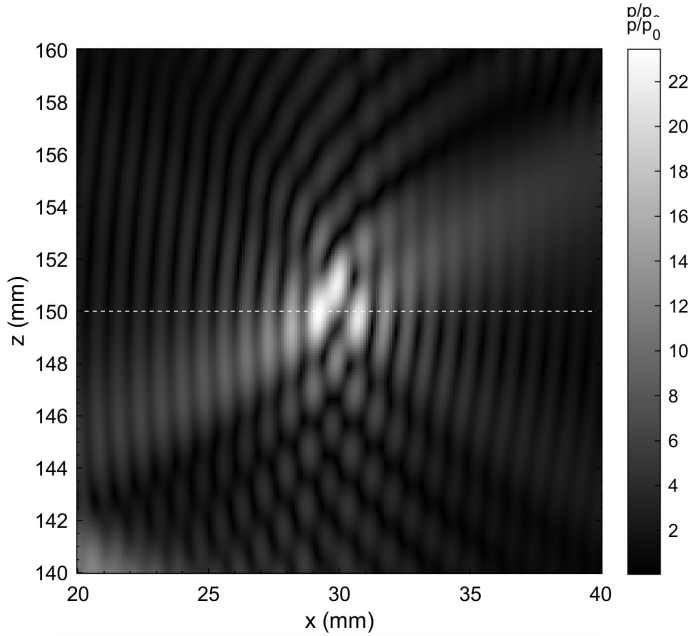
Focusing challenges

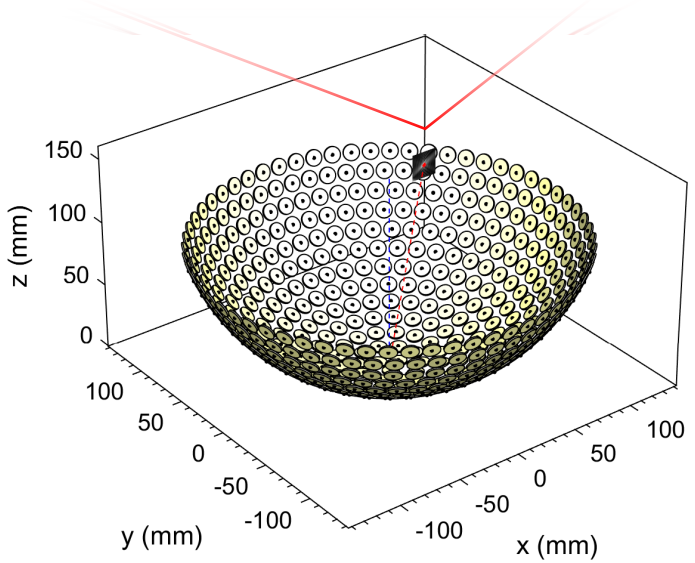
Focusing

- Phased arrays provide good focusing and aberration correction near the center, but....
- Elements are separated (much) more than half a wavelength apart
- Diffraction grating lobes appear (as in audio line arrays)
- Focusing capabilities are limited.

Example

- InsightTech's Exablate Neuro 4000
- 1024 elements covering the entire head
- Good focus near the geometric center (e.g., thalamus)
- Poor focus on other nuclei or CNS cortex



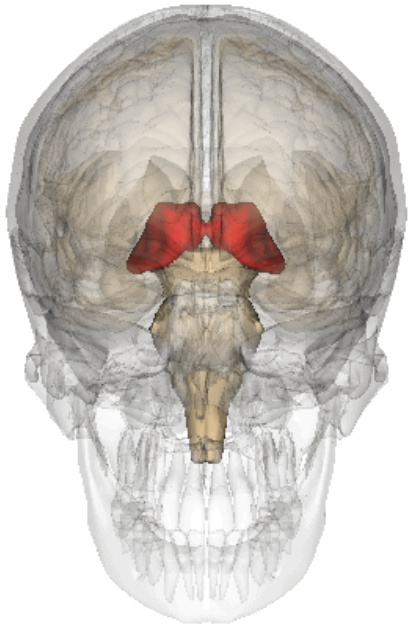


Focusing challenges

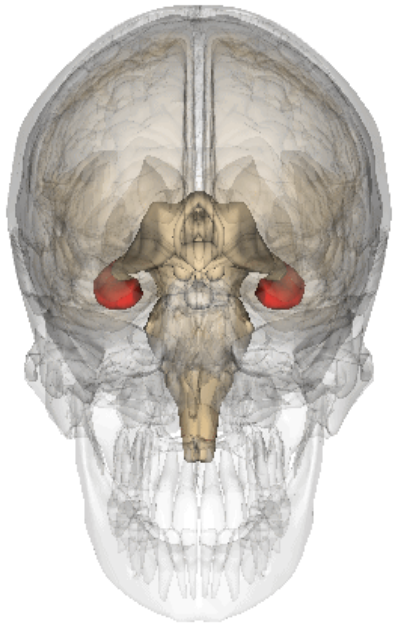
Complex target morphology

- Can we adapt the beam to the therapeutical target?

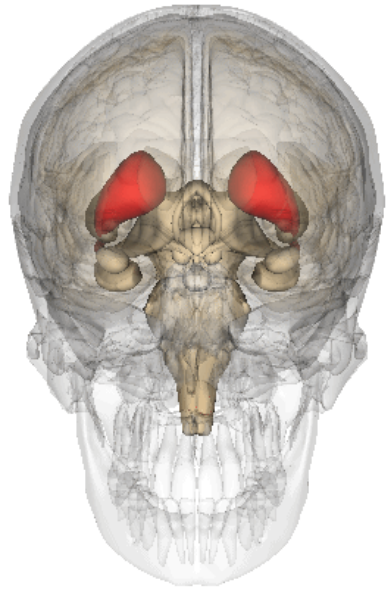
Thalamic nuclei



Hippocampus



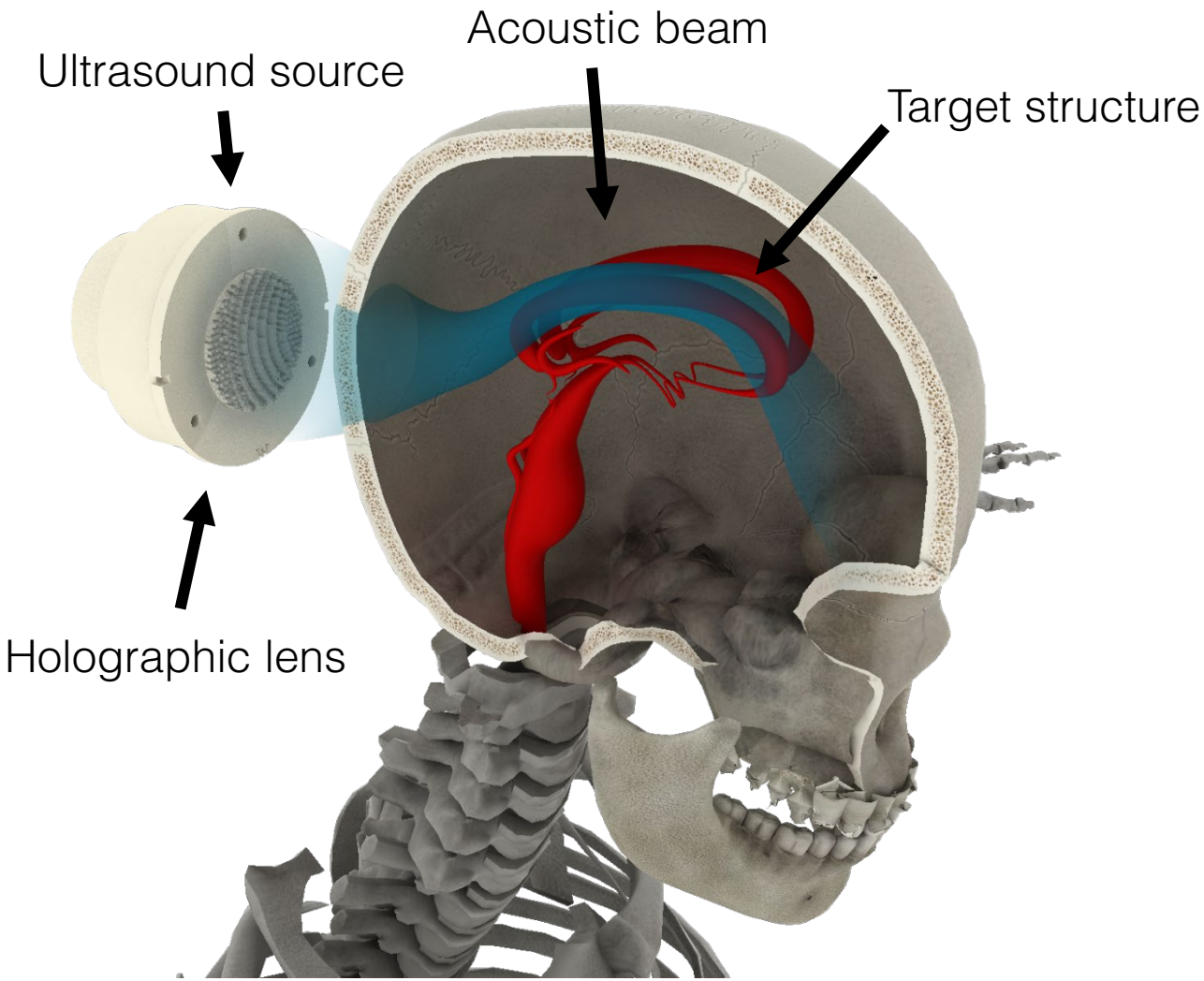
Caudate nucleus



http://www.brainfacts.org/3D-Brain

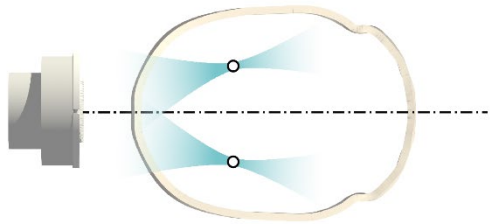
Acoustic holograms

Acoustic holograms

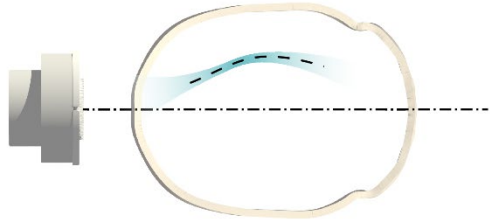


Configurations

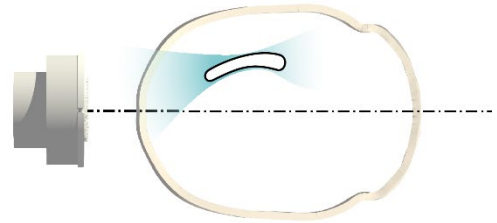
1) Multiple point



2) Self-bending beams



3) Volumetric treatments

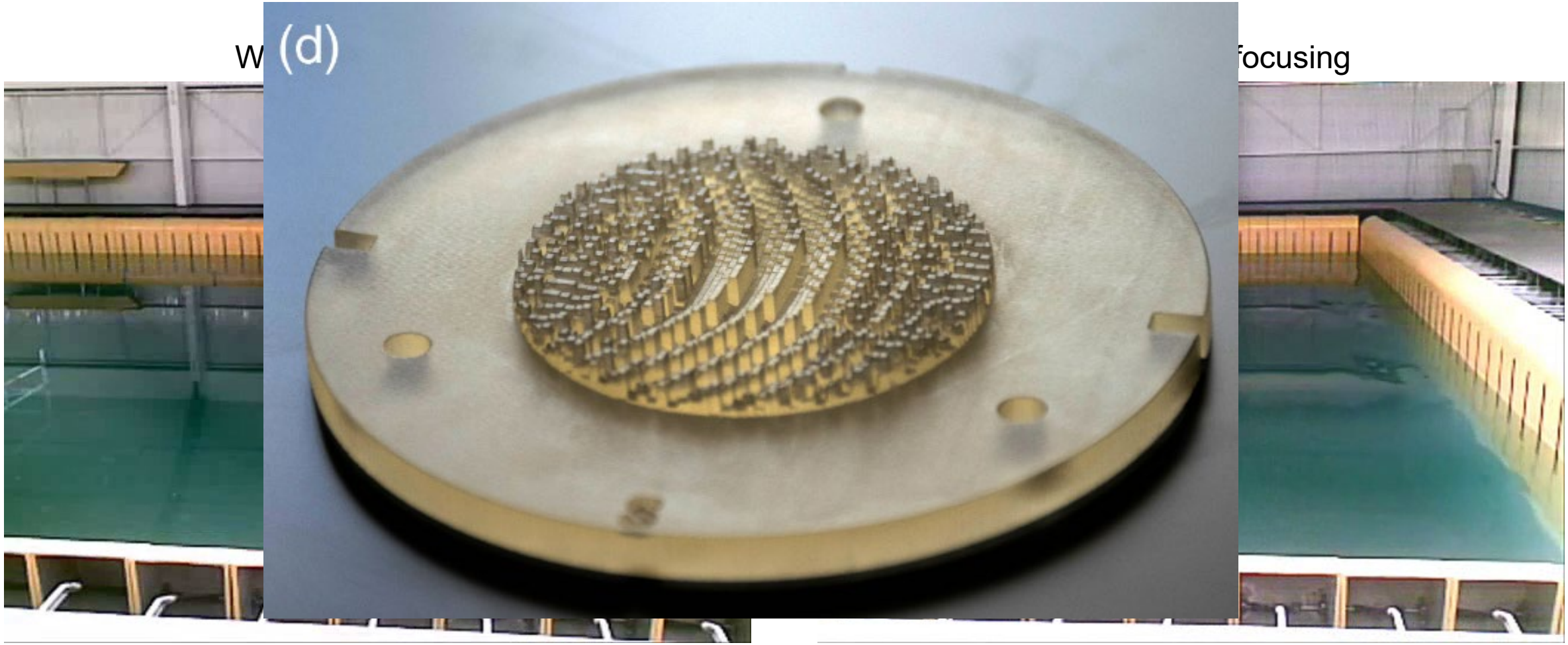


Jiménez-Gambín, et al. Phys Rev Appl 12 014016 (2019)

Acoustic holograms

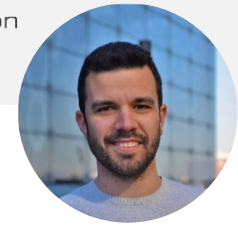
Time-reversal symmetry

- Acoustic wave equation show time-reversal symmetry



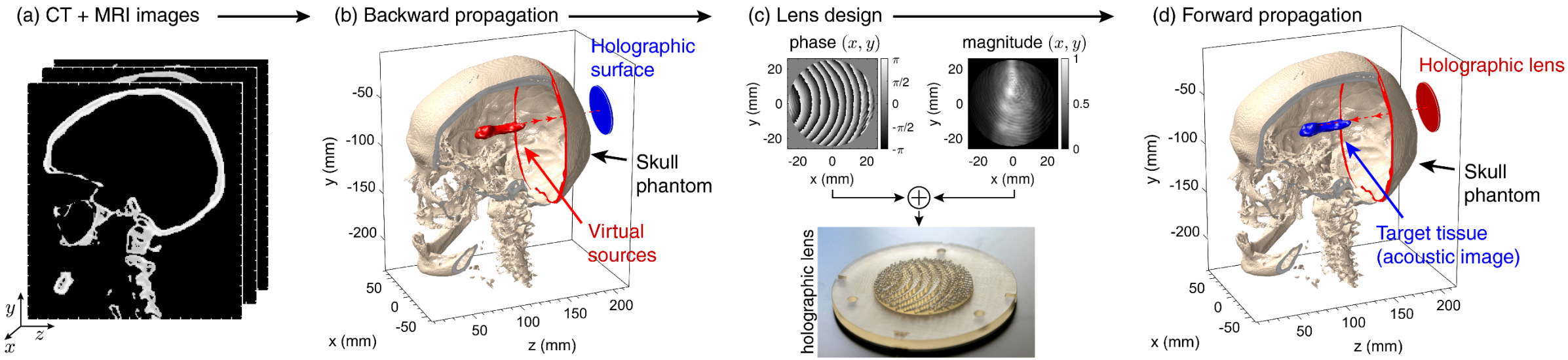
Acoustic holograms

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Protocol

- **Planning**: MRI (soft tissue segmentation) + X-ray CT (bone properties)
- **Backward propagation**: Time reversal simulation (phase conjugation)
- **Lens design**: 3D printing
- **Forward propagation**: validation and treatment



Jiménez-Gambín, et al. Phys Rev Appl 12 014016 (2019)

Acoustic holograms

Hologram design

- Record field at the holographic surface

$$P_H = P_H(x, y),$$

- Each pixel vibrates longitudinally (elastic Fabry-Perot resonator)

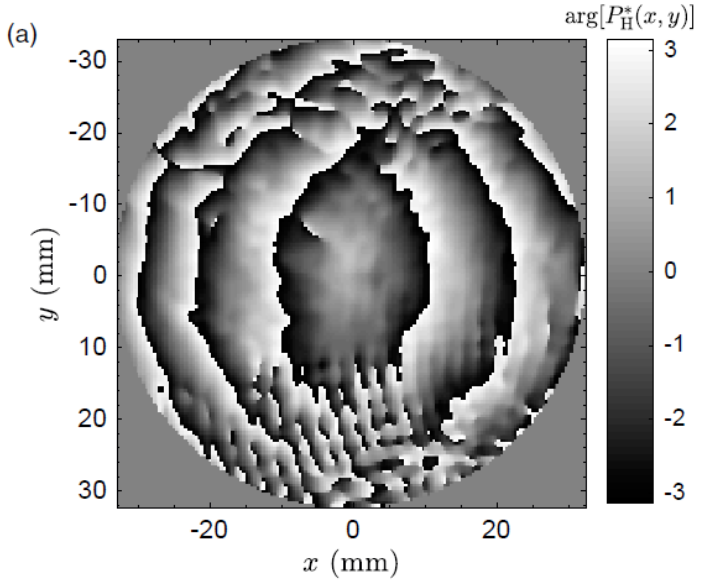
$$T(x, y) = \frac{2Ze^{-ik_0(d-h(x,y))}}{2Z\cos(k_L h(x, y)) + i(Z^2 + 1)\sin(k_L h(x, y))},$$

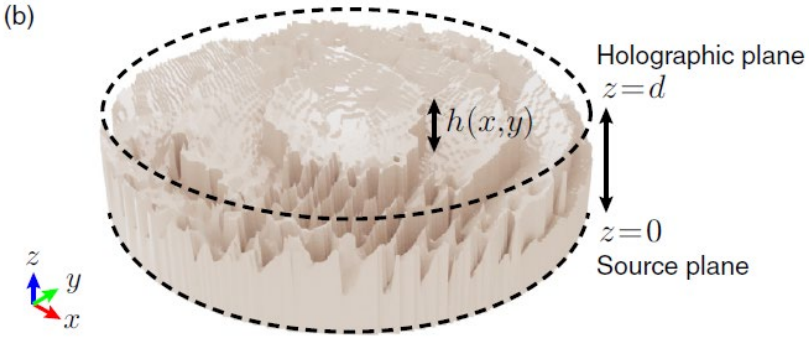
- Find the heigh function $h(x, y)$, producing

$$\arg[T(x, y)] = \arg[P_H^*(x, y)],$$

where * is complex conjugation (time-reversal in frequency domain)

- Then build your .STL file and 3D-print it!



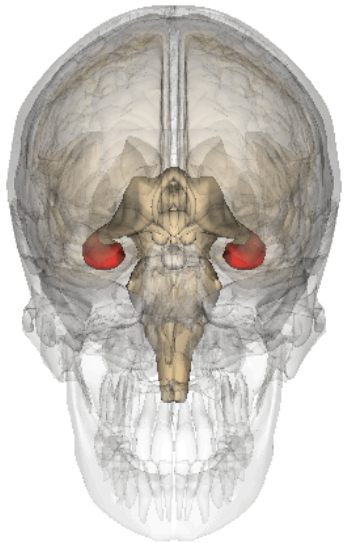


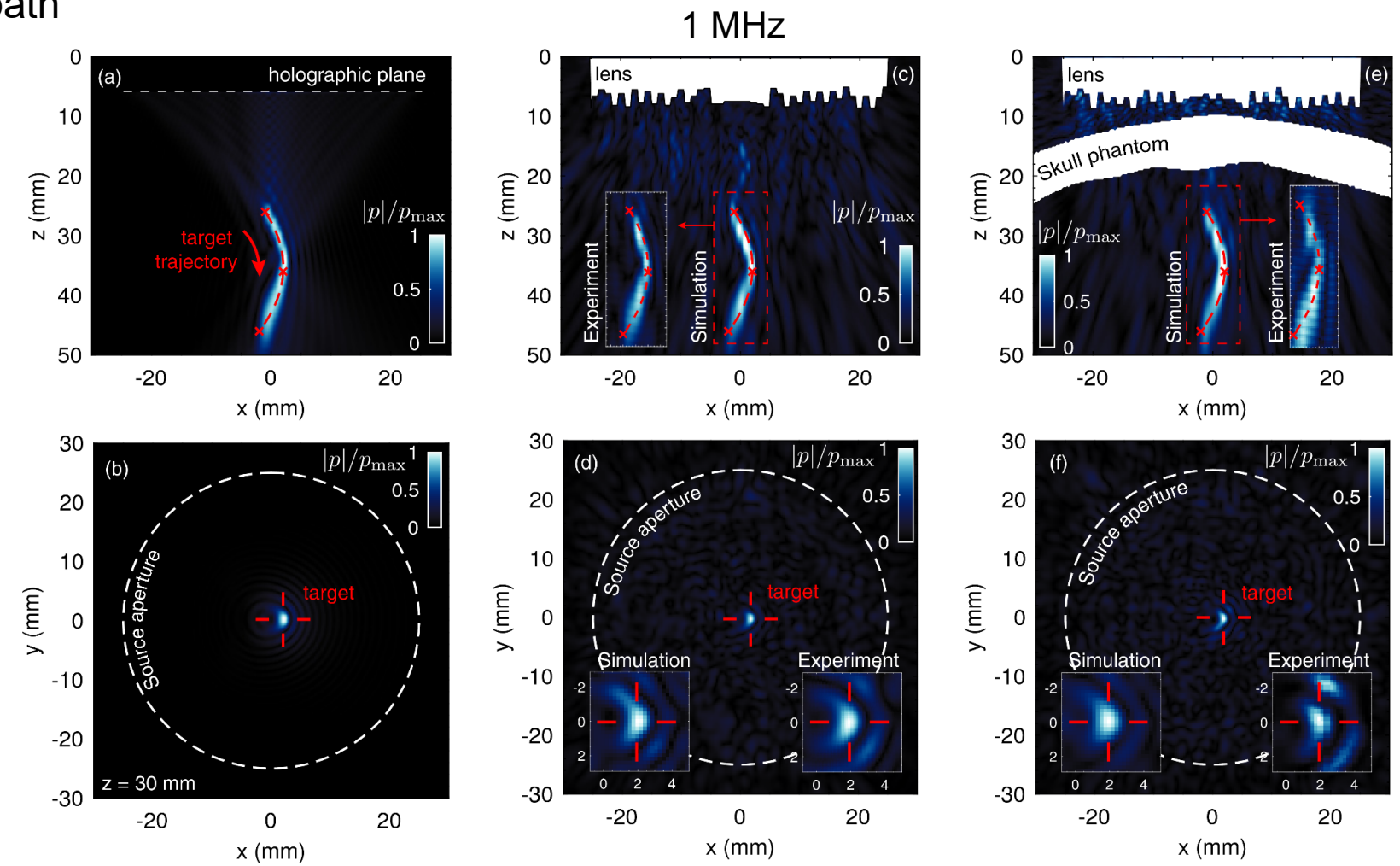
Jiménez-Gambín, et al. Phys Rev Appl 12 014016 (2019)

Acoustic holograms

Self-bending beams

- Beam can follow an arbitrary path
- Aberration-free propagation
- Diffraction limited beams

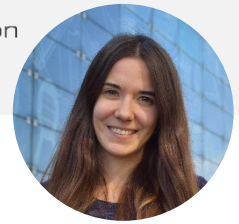




Jiménez-Gambín, et al. Phys Rev Appl 12 014016 (2019)

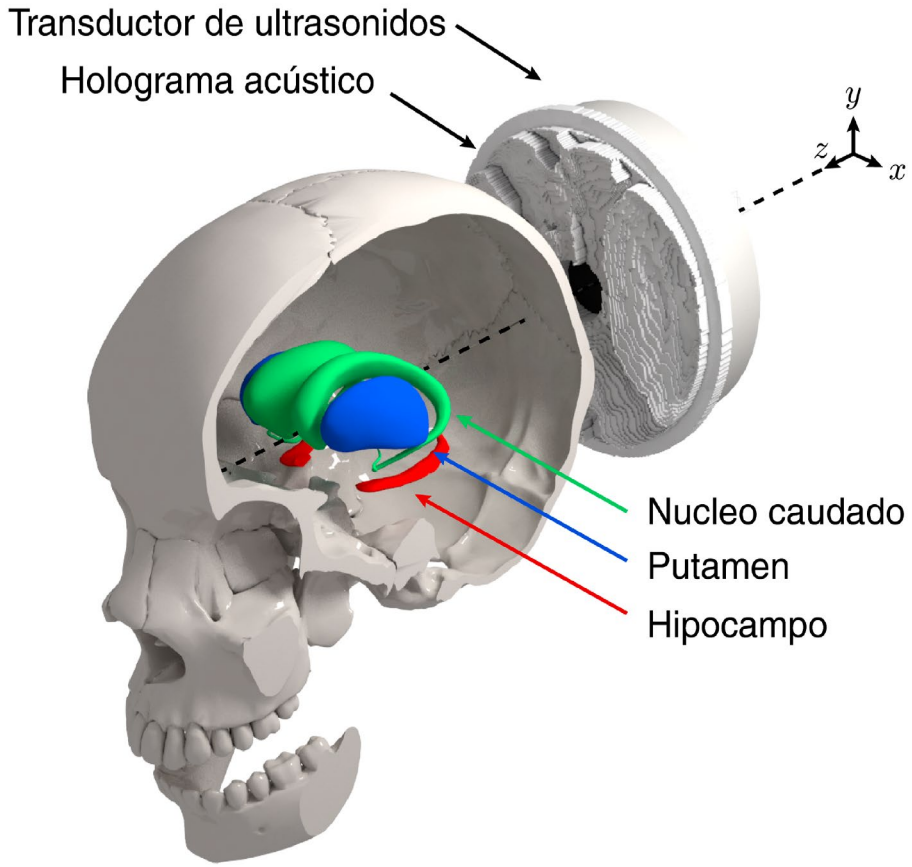
Acoustic holograms

Instituto de Instrumentación para Imagen Molecular

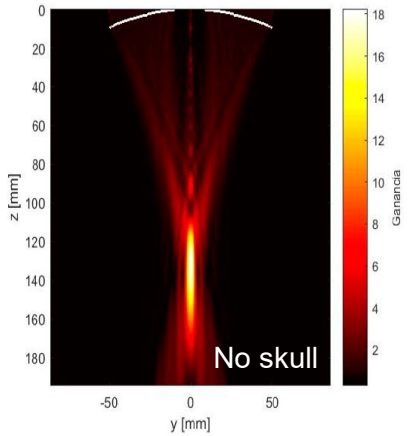


Bilateral focusing

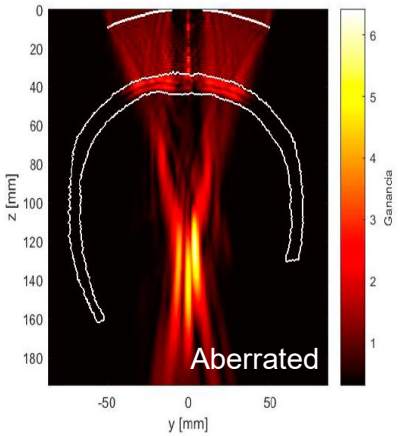
- Targeting at complex bilateral shapes



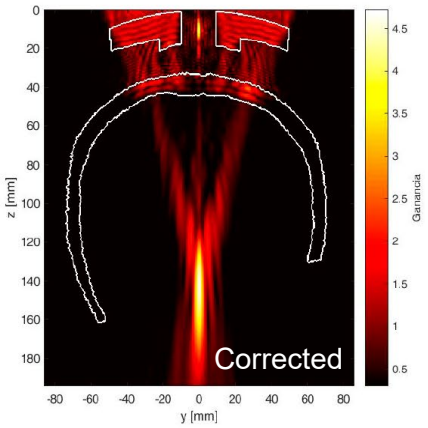
FUS transducer (500 kHz)



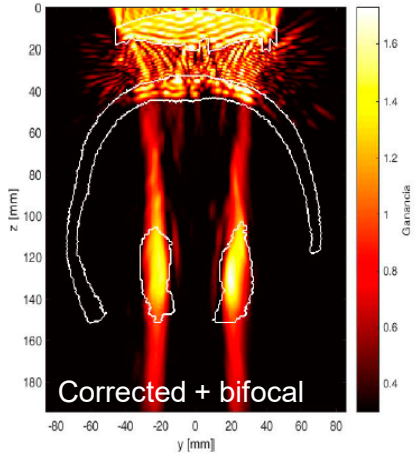
FUS transducer + skull



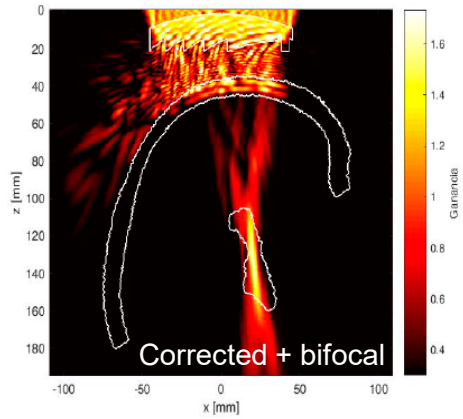
Hologram + skull



Bilateral focusing at hippocampus (coronal)



Bilateral focusing at hippocampus (sagittal)



Acoustic holograms

Using the temporal window

- Low thermal dose and deep-brain focusing



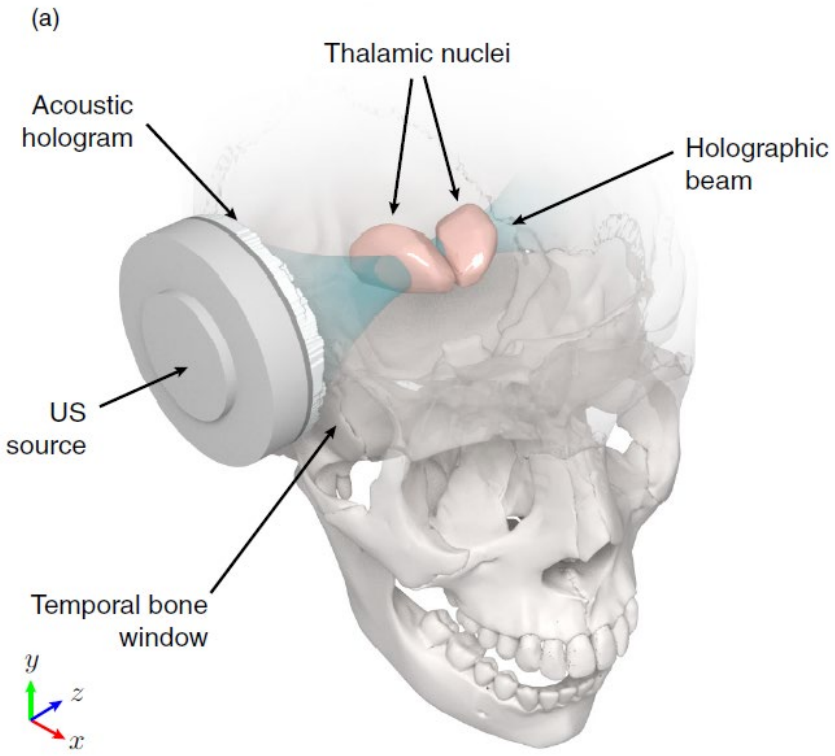
Acoustic holograms

Instituto de Instrumentación para Imagen Molecular

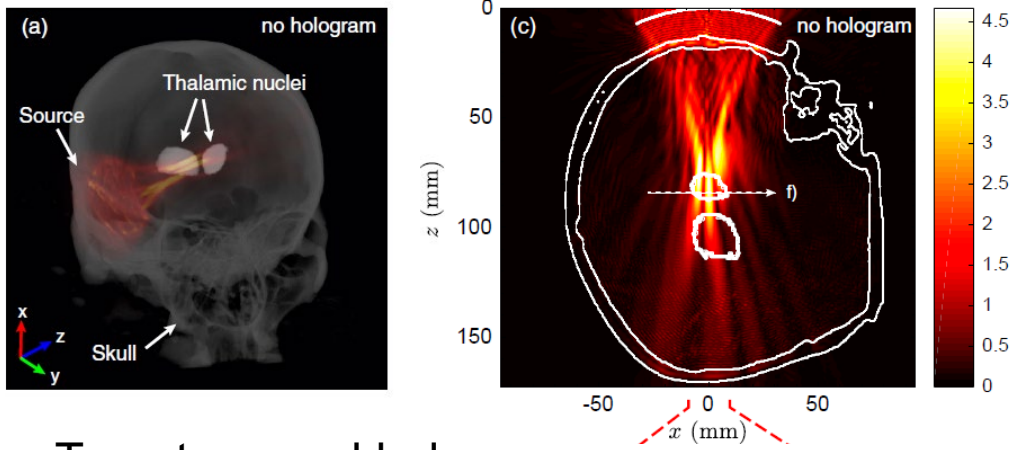


Using the temporal window

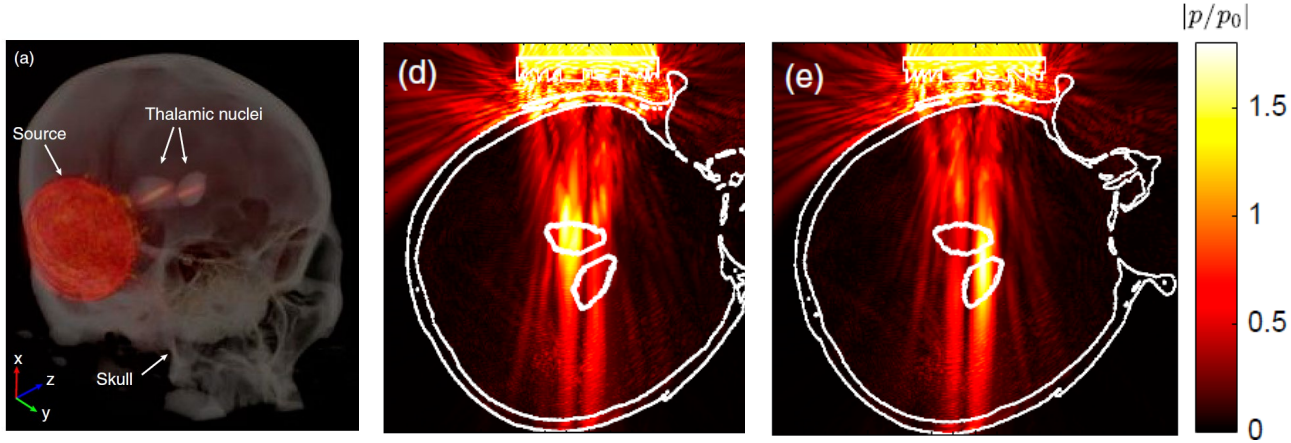
- Low thermal dose and deep-brain focusing



- Standard focused transducer (650 kHz)



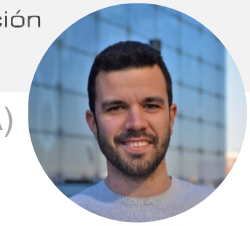
- Transtemporal hologram



Diana Andres, et al. “Acoustic holograms for deep-brain targeting through the temporal bone window”, preprint 2021

In-vivo validation

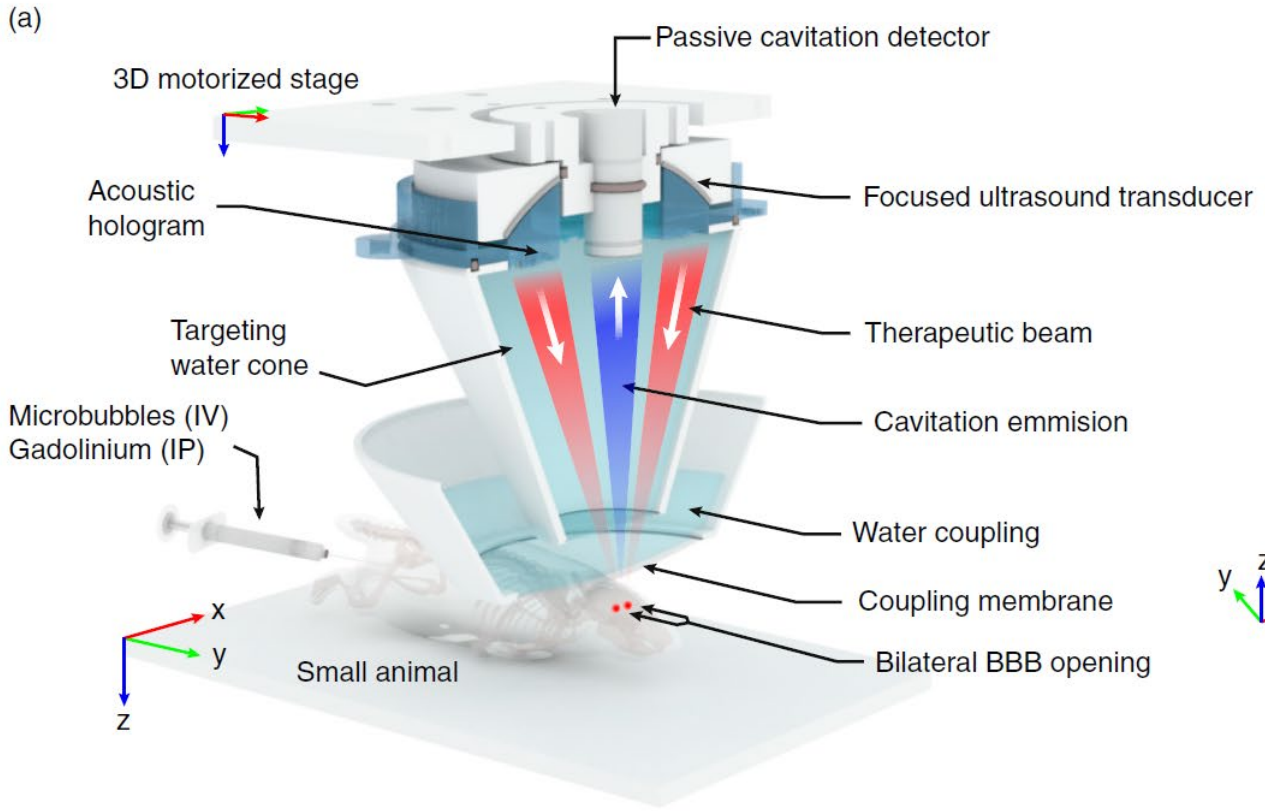
Instituto de Instrumentación para Imagen Molecular

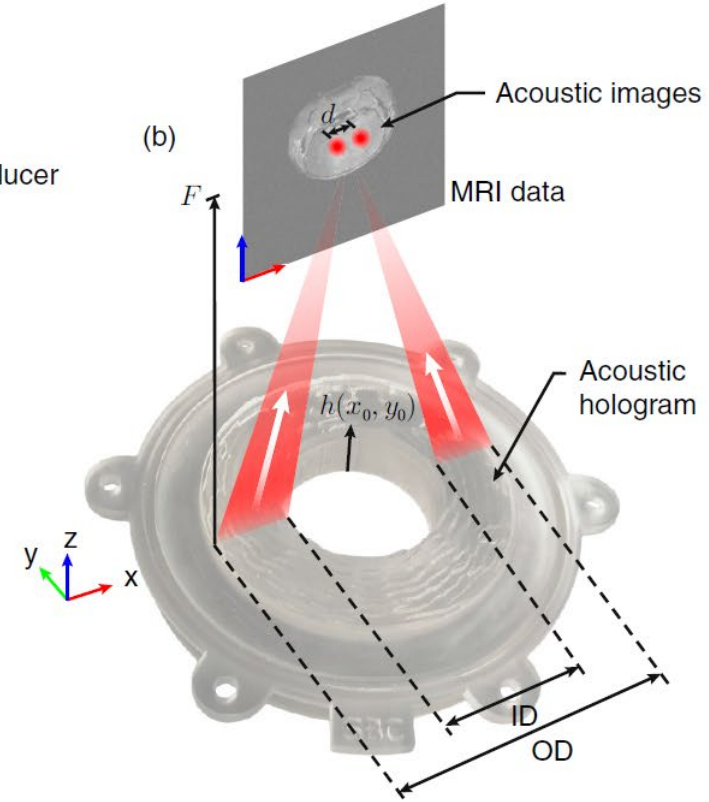


In collaboration with E.E. Konofagou, Columbia University (NYC, USA)

Bilateral blood-brain barrier opening

- First in-vivo application of acoustic holograms

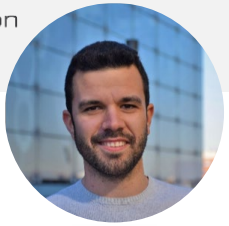




Sergio Jiménez-Gambín, et al. “Acoustic holograms for bilateral blood-brain barrier opening in a mouse model”, Submitted 2021

In-vivo validation

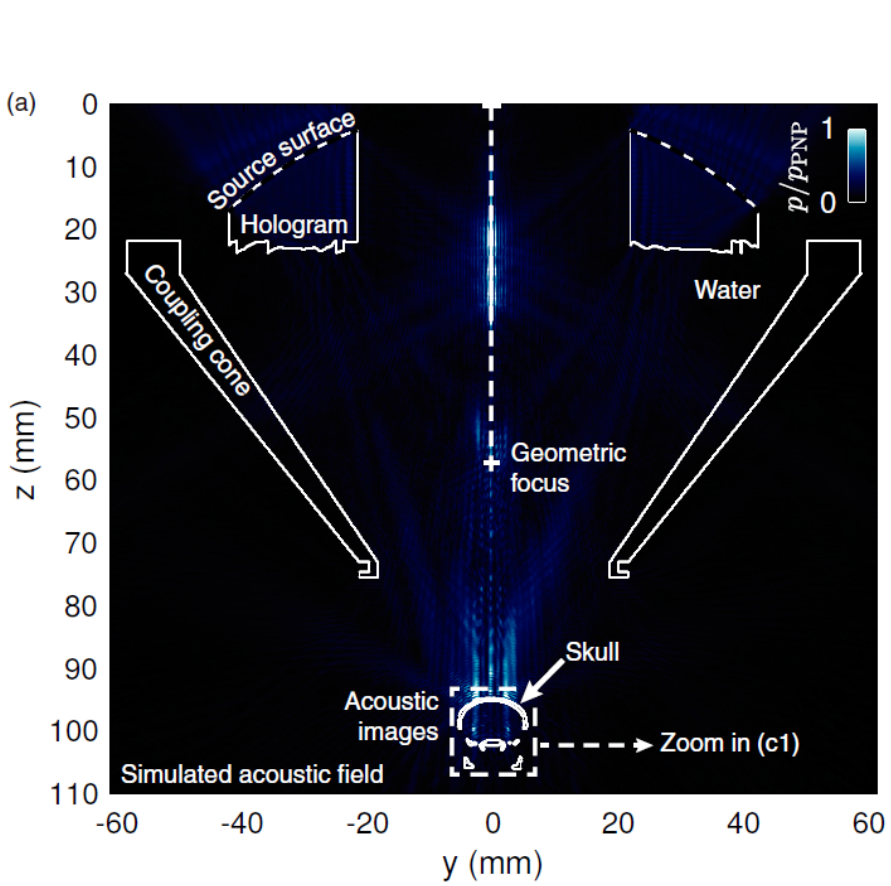
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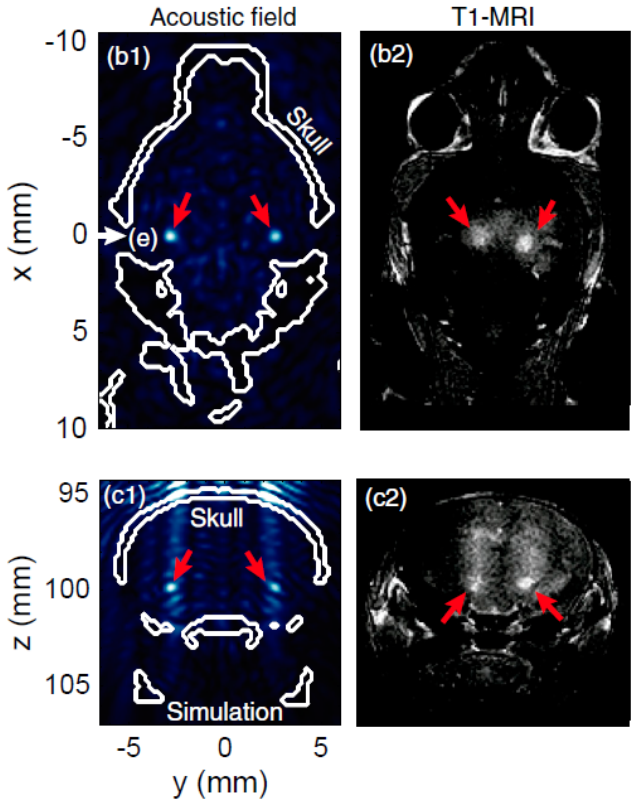


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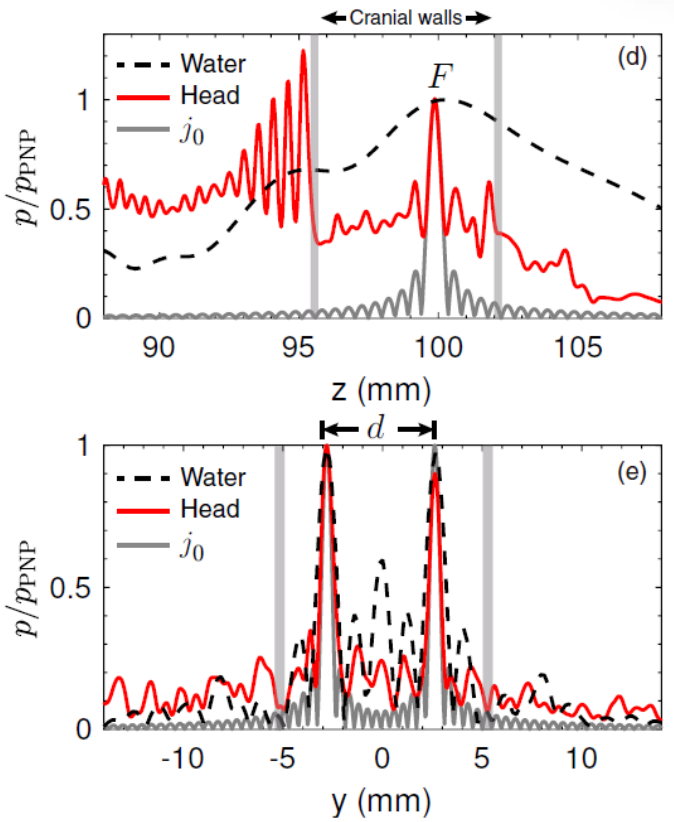
Bilateral blood-brain barrier opening

- First in-vivo application of acoustic holograms



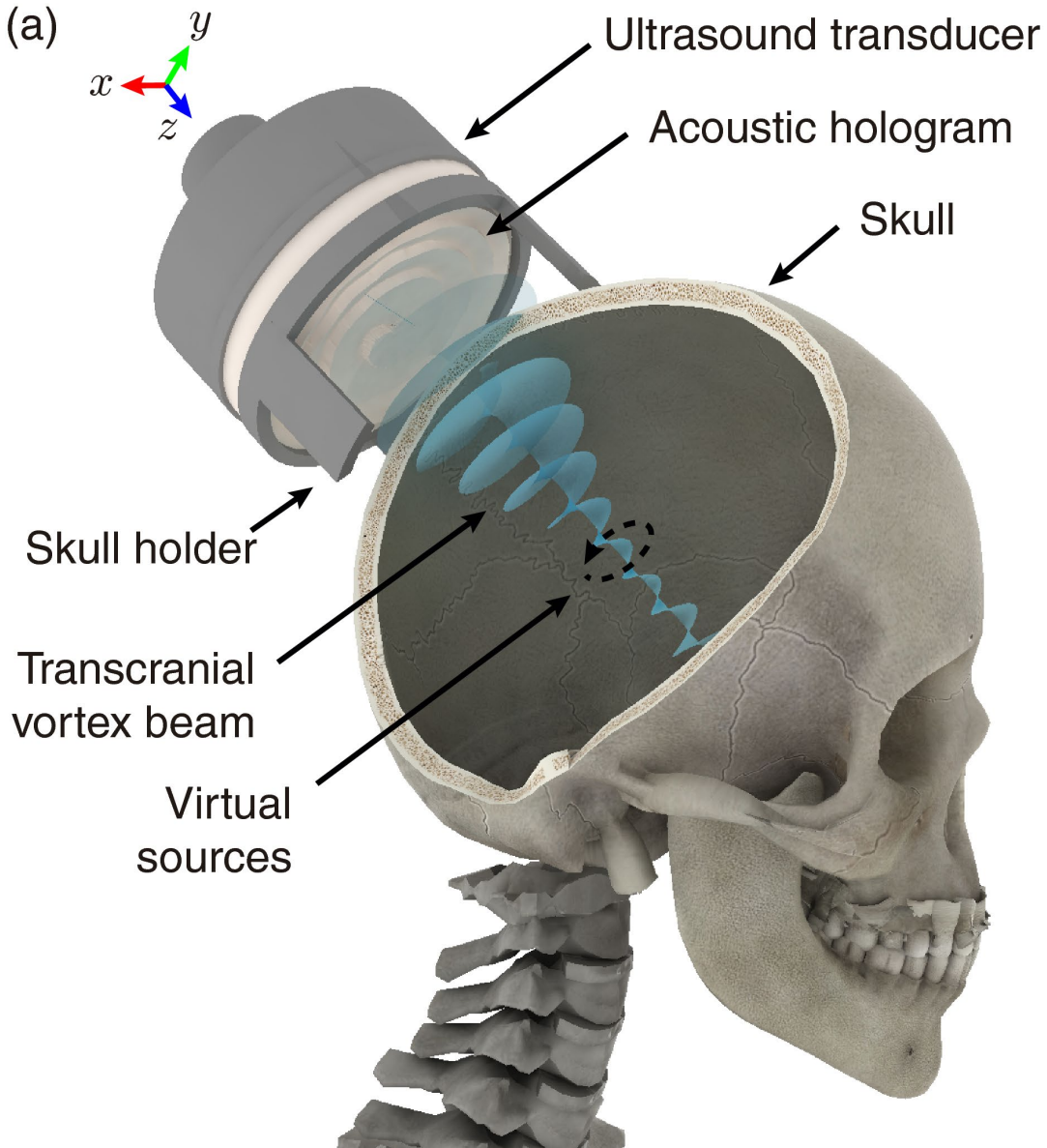


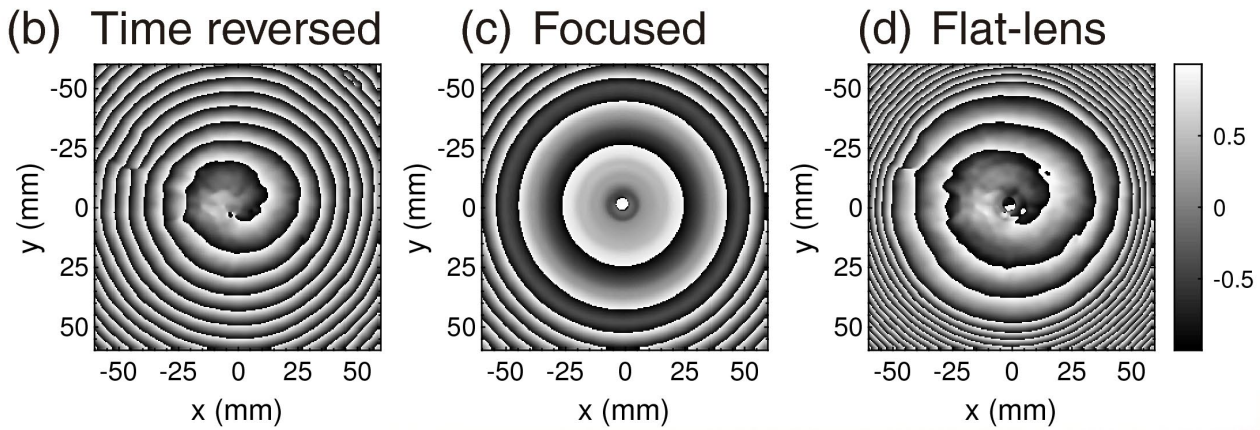
1.6 MHz

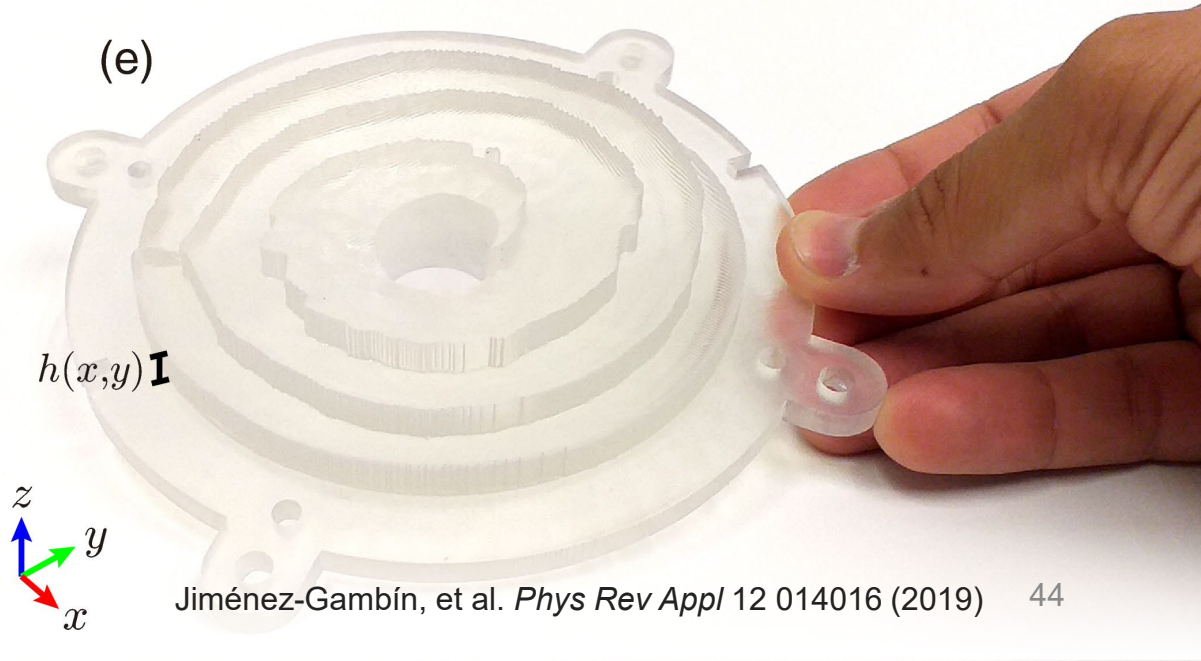


Sergio Jiménez-Gambín, et al. “Acoustic holograms for bilateral blood-brain barrier opening in a mouse model”, Submitted 2021

Acoustic vortices in the brain





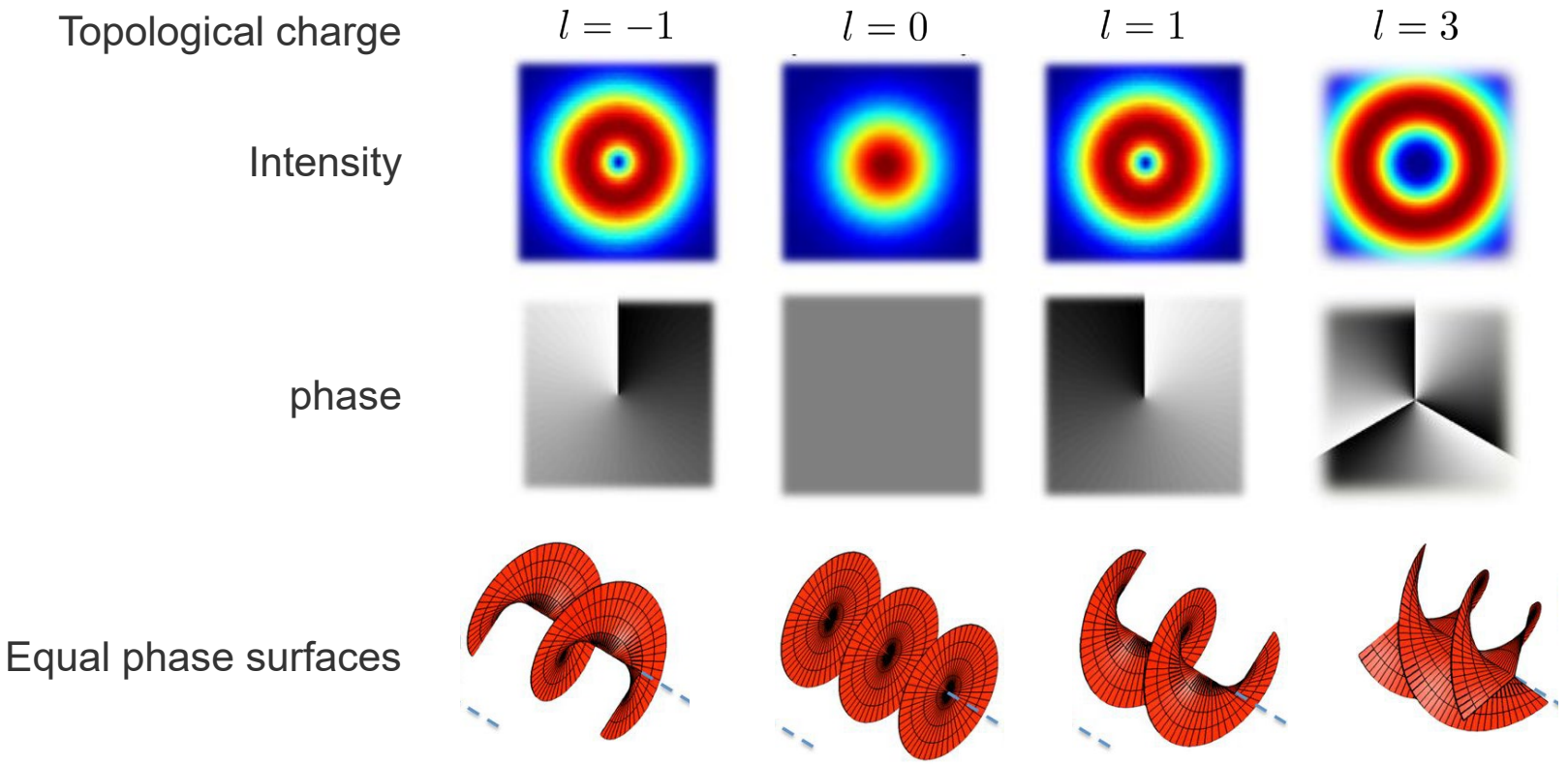


Jiménez-Gambín, et al. *Phys Rev Appl* 12 014016 (2019)

Acoustic vortices in the brain

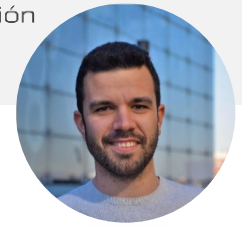
Acoustic vortex beams

- Beams presenting a phase dislocation at the axis
- The phase of the field rotates l times with each azimuthal turn
- Example, Bessel beam : $p(\theta, r, z) = P_0 J_l\left(k_r r\right) \exp\left(-ik_z z\right) \exp\left(il\theta\right)$



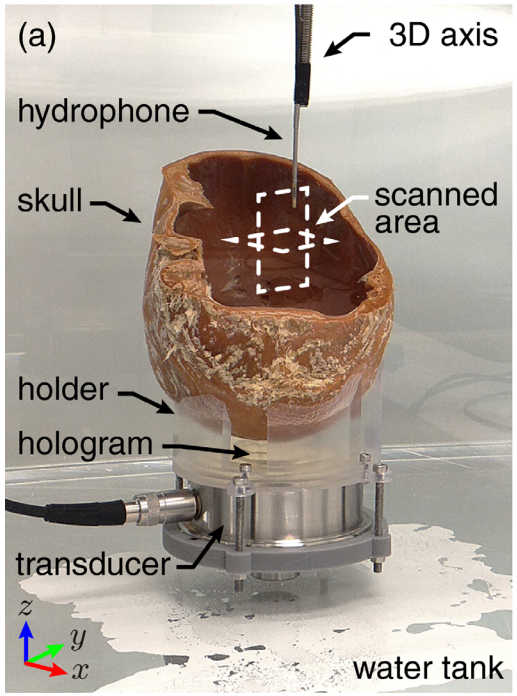
Acoustic vortices in the brain

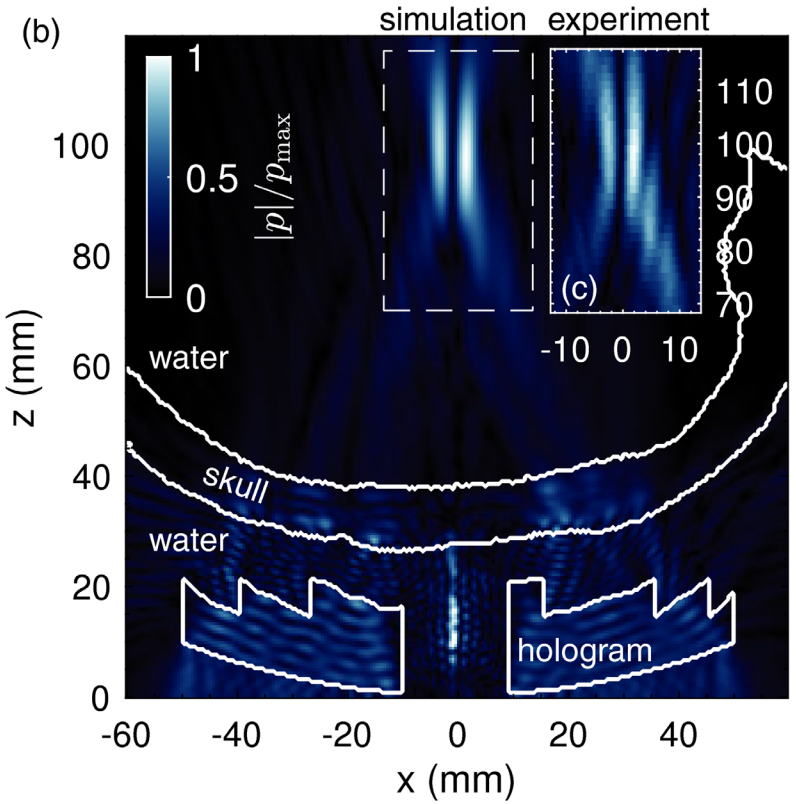
Instituto de Instrumentación para Imagen Molecular

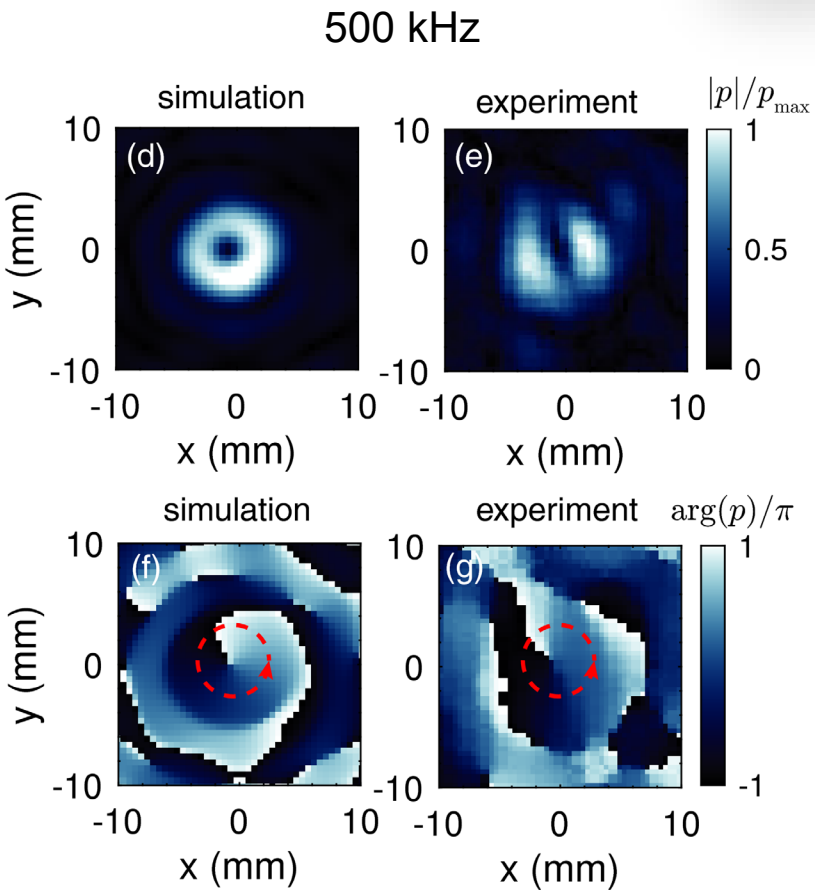


Aberration correction ex-vivo

- A phase dislocation is restored using a focused vortex beam





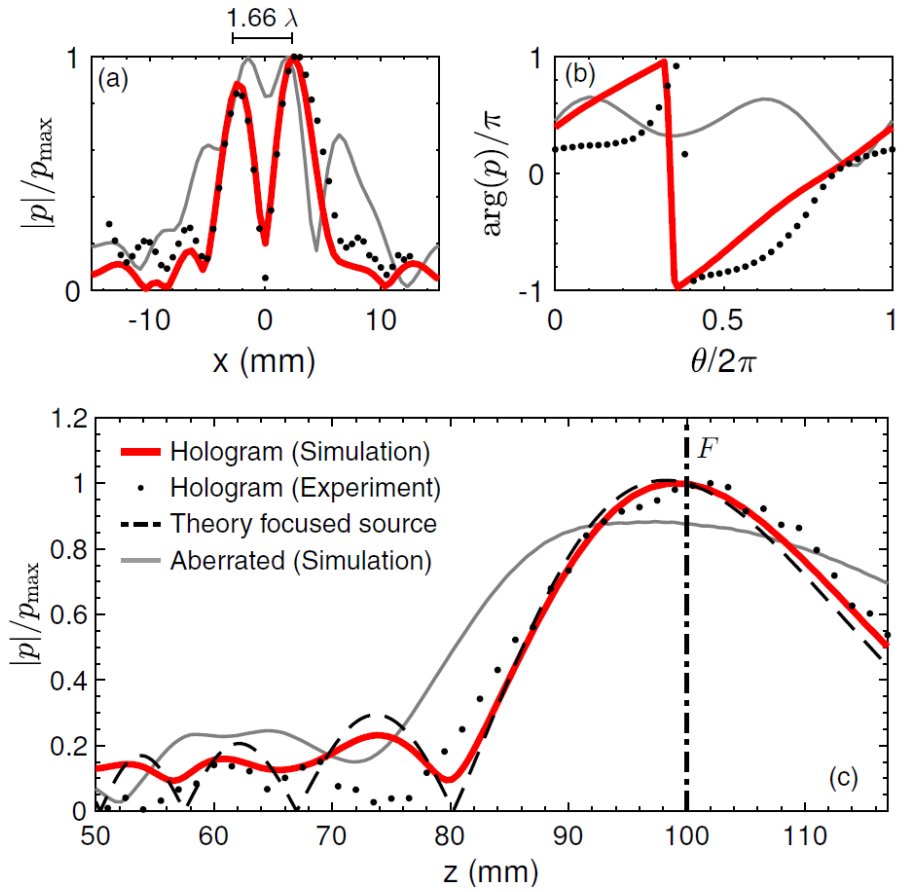


Jiménez-Gambín, et al. *Phys Rev Appl* 12 014016 (2019)

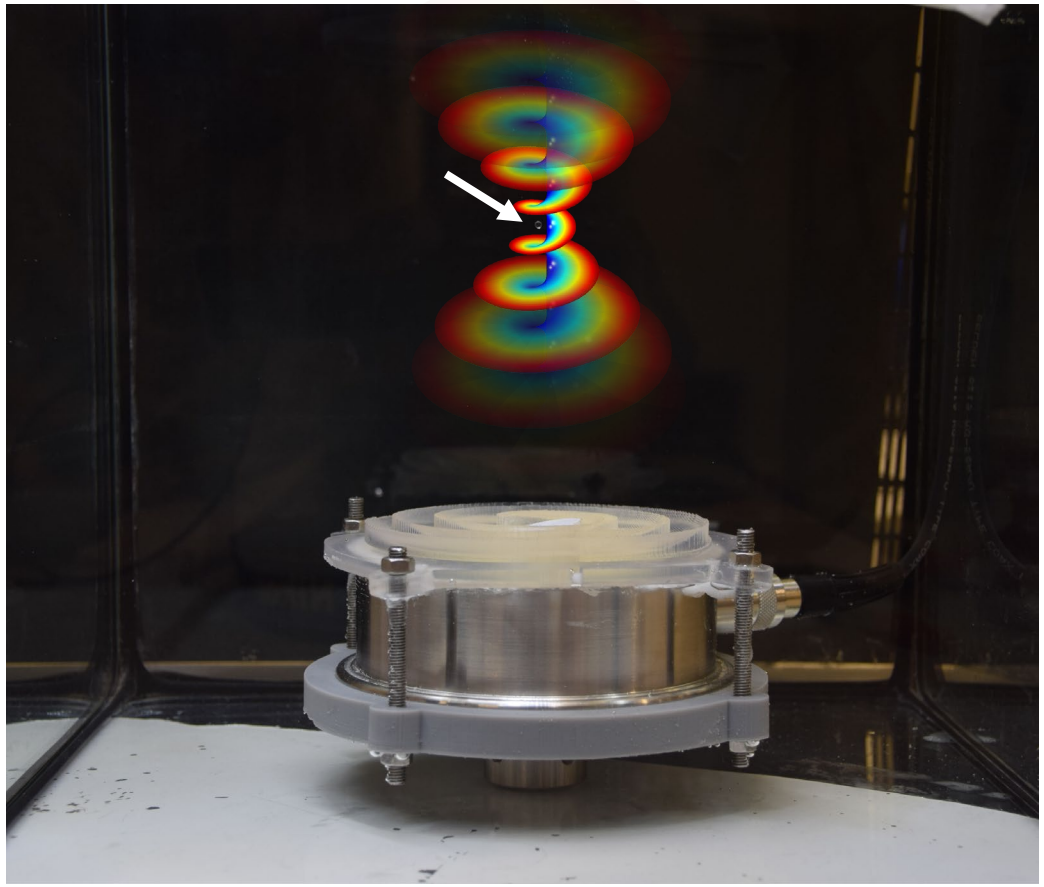
Acoustic vortices in the brain

Aberration correction

- Topological charge can be tuned



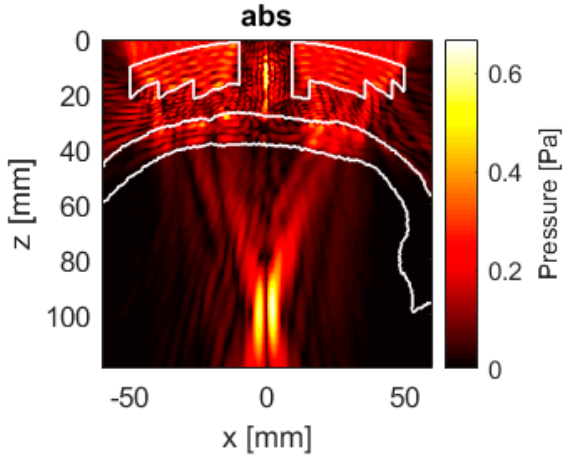
- Particle trapping: potential for clot manipulation

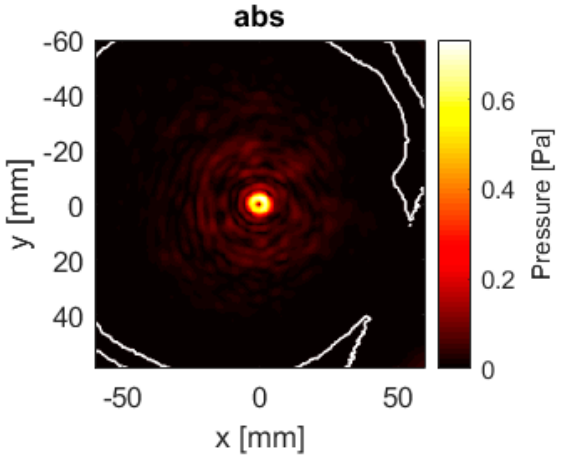


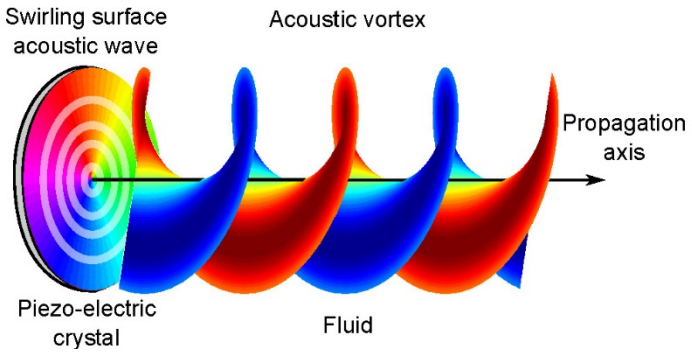
Jiménez-Gambín, et al. *Phys Rev Appl* 12 014016 (2019)

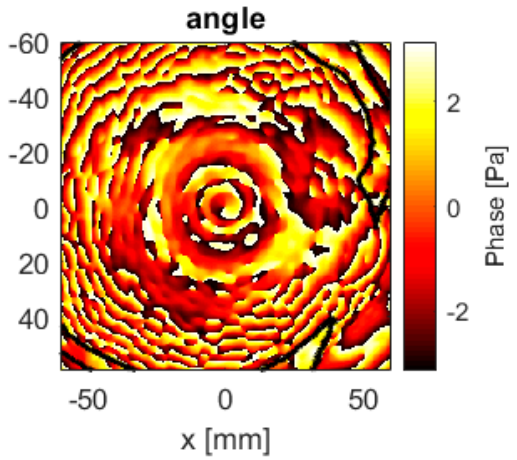
Vortex beams

Vortex focusing by holograms











Thermal holograms

Instituto de Instrumentación para Imagen Molecular

In collaboration with Jonathan Vappou, CNRS (France)



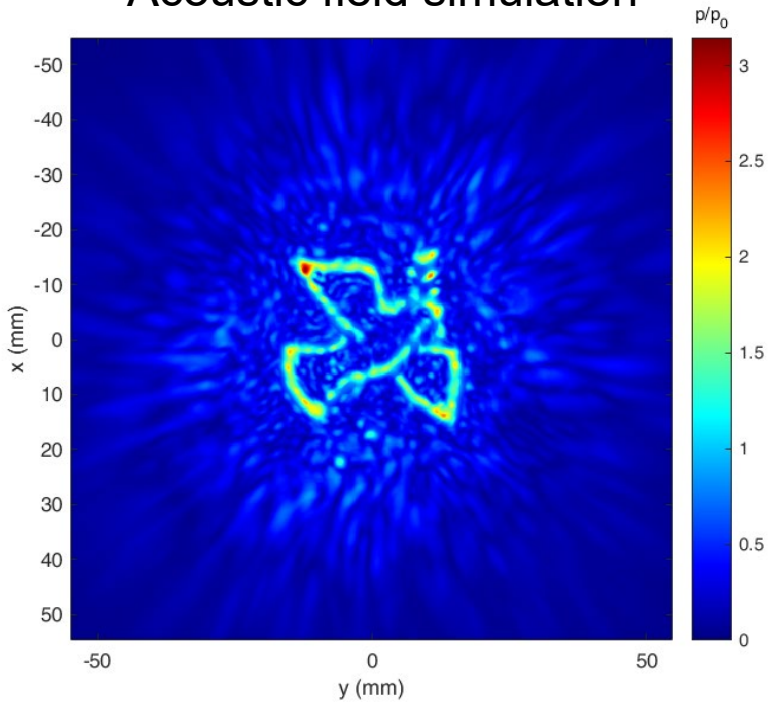
Thermal patterns for ultrasound hyperthermia

- Mild and local rise temperature
- Activate immune system
- Enhance drug administration
- Enhance chemotherapy

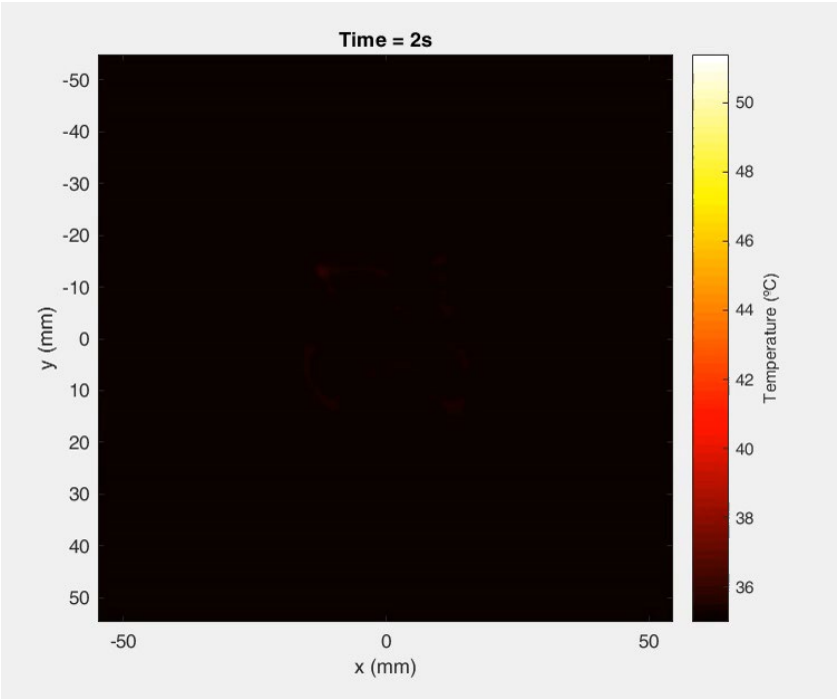
Image



Acoustic field simulation



Thermal simulation



Thermal holograms

Instituto de Instrumentación para Imagen Molecular

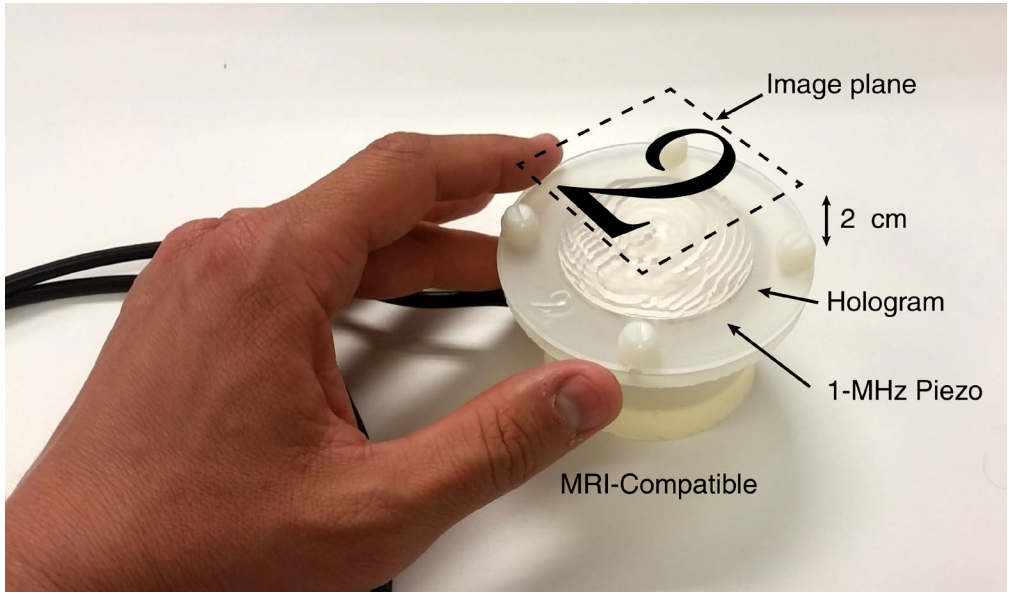
In collaboration with Jonathan Vappou, CNRS (France)



Thermal patterns for ultrasound hyperthermia

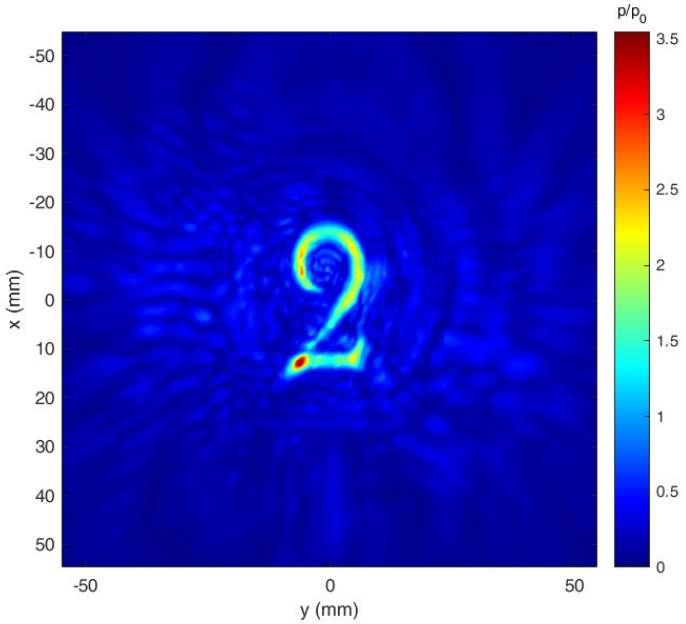
- Mild and local rise temperature
- Activate immune system
- Enhance drug administration
- Enhance chemotherapy

Experimental setup

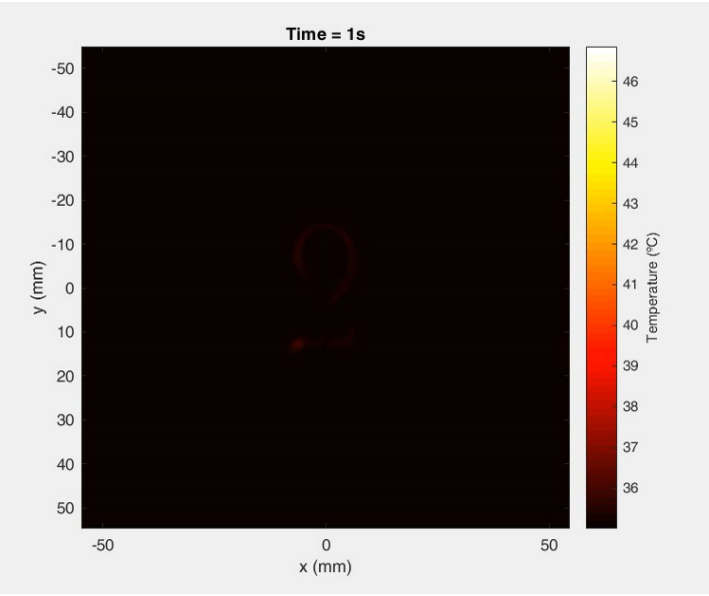


Thermal camera

Simulation (field)



Simulation (thermal)



Thermal holograms

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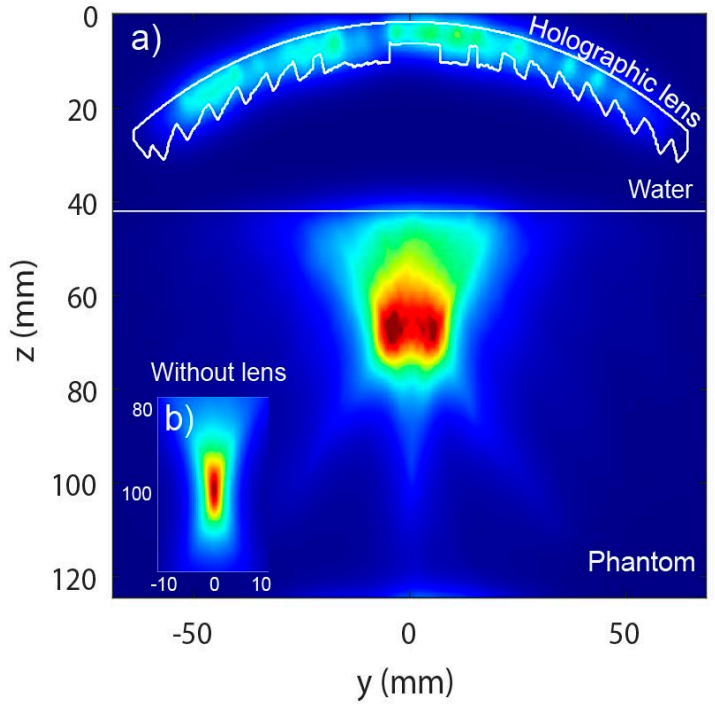
In collaboration with Jonathan Vappou, CNRS (France)



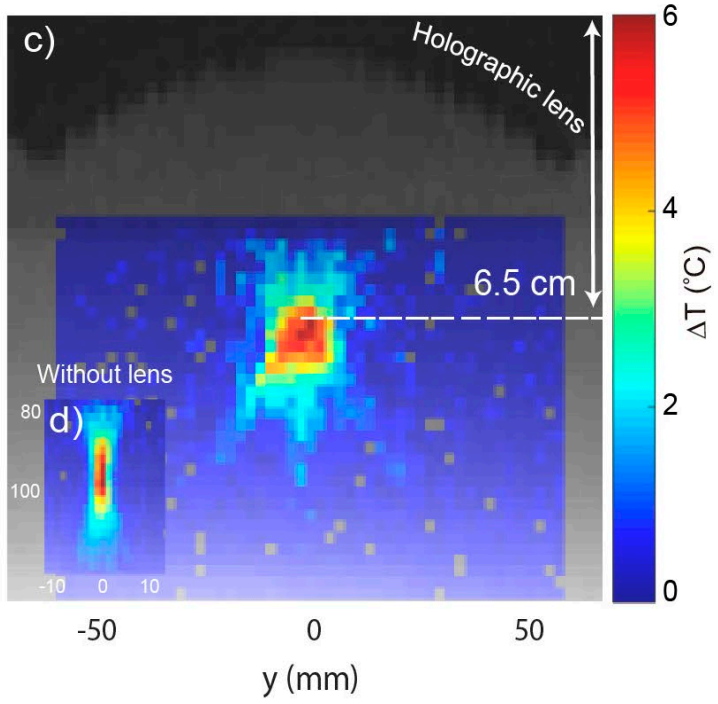
Thermal patterns for ultrasound hyperthermia

- Mild and local rise temperature
- Activate immune system
- Enhance drug administration
- Enhance chemotherapy

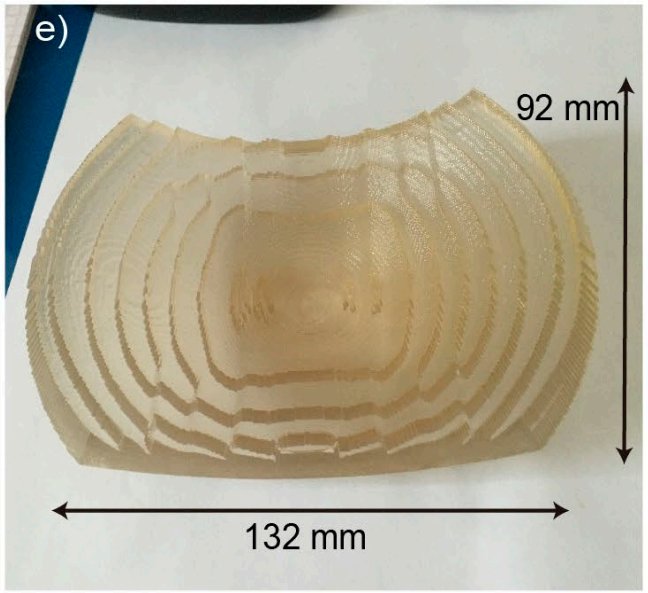
Thermal simulation



1.5-Tesla MRI thermometry



Experimental setup



Conclusions

Transcranial focused ultrasound

- Allow the treatment of several neurological disorders (*thermal and mechanical mechanisms, and their bioeffects*)
- Noninvasive: *waves*
- Non-ionizing: *mechanical waves*
- High localization: *focalization*
- Allow real-time monitoring: *USgFUS, cavitation mapping, MRgFUS*
- High portability

Acoustic holograms

- Aberrations due to stiff layers such as bones are corrected
- Sharp acoustic images are restored
- Low-cost systems: patient specific
- Towards active **spatial-sound modulators**



Publications

Papers

- S. Jiménez-Gambín, A. N. Pouliopoulos, N. Jiménez, J. M. Benlloch, E. E. Konofagou, F. Camarena. *First in-vivo Demonstration of Bilateral Blood-Brain Barrier Opening Using Acoustic Holograms in Mice*. Submitted (2021)
- S. Jiménez-Gambín, N. Jiménez, F Camarena. Transcranial focusing of ultrasonic vortices by acoustic holograms. *Physical Review Applied*, *14*(5), 054070 (2020)
- S. Jiménez-Gambín, N. Jiménez, J.M. Benlloch, F. Camarena. *Holograms to focus arbitrary ultrasonic fields through the skull. Physical Review Applied*, 12 (1), pp. 014016, (2019)
- S. Jiménez-Gambín, N. Jiménez, J.M. Benlloch, F. Camarena. *Generating Bessel beams with broad depth-of-field by using phase-only acoustic holograms*. Scientific Reports, 9 (1), pp. 20104, (2019)
- M. Ferri, J.M. Bravo, J. Redondo, S. Jiménez-Gambín, N. Jiménez, F. Camarena, J.V. Sánchez-Pérez. *On the Evaluation of the Suitability of the Materials Used to 3D Print Holographic Acoustic Lenses to Correct Aberrations.* Polymers, 11 (9), pp. 1521, (2019)
- N. Jiménez V Romero-García, L M. García-Raffi, F. Camarena, and K. Staliunas. *Sharp acoustic vortex focusing by Fresnel-spiral zone plates.* Applied Physics Letters 112, 204101 (2018)
- N Jiménez, F Camarena, J Redondo, V Sánchez-Morcillo, Y Hou, EE Konofagou. *Time-Domain Simulation of Ultrasound Propagation in a Tissue-Like Medium*. Acta Acustica united with Acustica, 102 (5), pp. 876–892, (2016)

Patent

- WO2020084181A1 / ES2755516: N. Jiménez, S. Jiménez-Gambín, J.M. Benlloch, F. Camarena. Método de fabricación de una lente y dispositivo de ultrasonidos que comprende dicha lente (2018)

Acknowledgments

Instituto de Instrumentation para Imagen Molecular

- Sergio Jimenez-Gambín (PhD candidate)
- Diana Andrés (PhD candidate)
- Nathalie Lamothe (PhD candidate)
- Francisco Camarena (Prof. UPV)
- José María Benlloch (Prof. CSIC)
- Elisa Konofagou (Columbia University, NY, USA)
- Antonios N. Pouliopoulos (Columbia University, NY, USA)
- Jhonathan Vappou (CNRS, France)



Funding

- MCIU: Juan de la Cierva – Incorporación, IJC2018-037897-I, Plan Nacional Retos: PID2019-111436RB-C22.
- Agència Valenciana de la Innovació: INNVAL10/19/016, INNCON/2020/009.
- Generalitat Valenciana: ACIF/2017/045.
- European Union: IDIFEDER/2018/022

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Acoustic holograms for biomedical ultrasound applications

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Acoustics Research Seminar, University of Salford, April 21, 2021