UNIVERSITAT POLITÈCNICA DE VALÈNCIA

"Hear for Tomorrow". Hearing Conservation Association / Institute of Acoustics. Royal Academy of Engineering. 30th March 2022

Brain therapy using acoustic holograms

Noé Jiménez, PhD

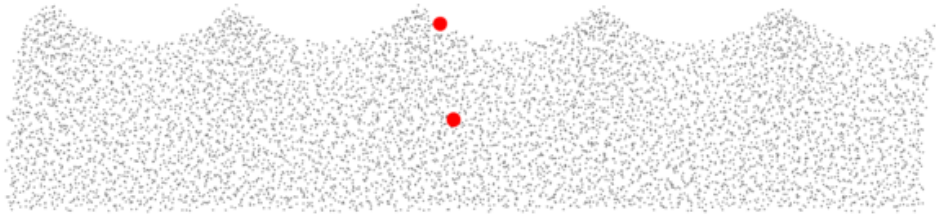
JdC-I Postdoc, Instituto de Instrumentación para Imagen Molecular,
Universitat Politècnica de València / Consejo Superior de Investigaciones Científicas
(València, Spain)

How can we use mechanical waves for therapy?

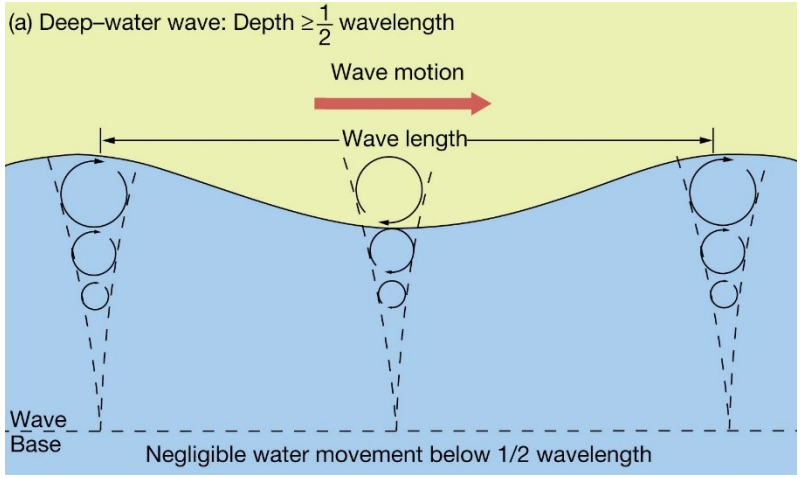
Mechanical waves

Wave-matter interaction

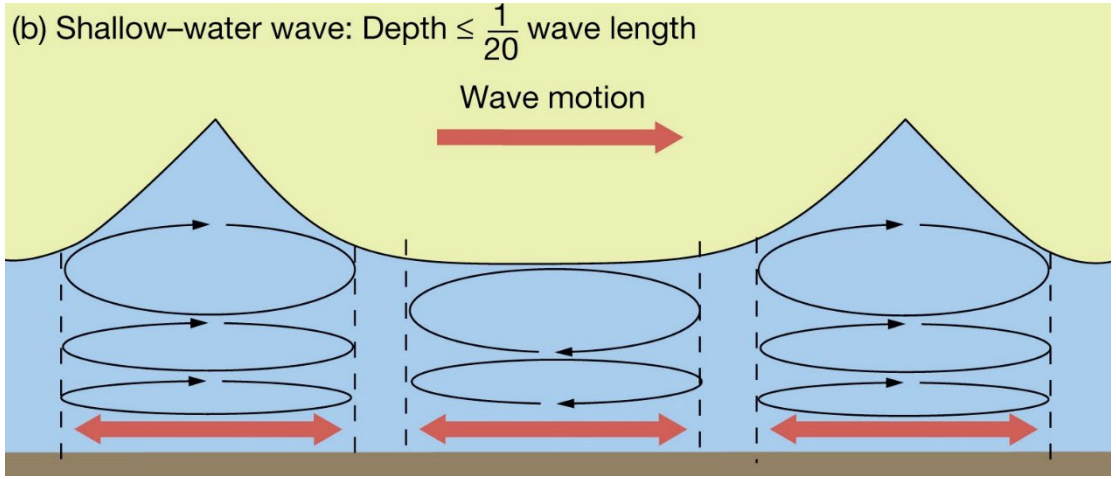
- Waves carry energy and momentum.
- When a wave interacts with matter, it can transfer the energy and/or momentum to the medium



Deep-water waves



Shallow water waves



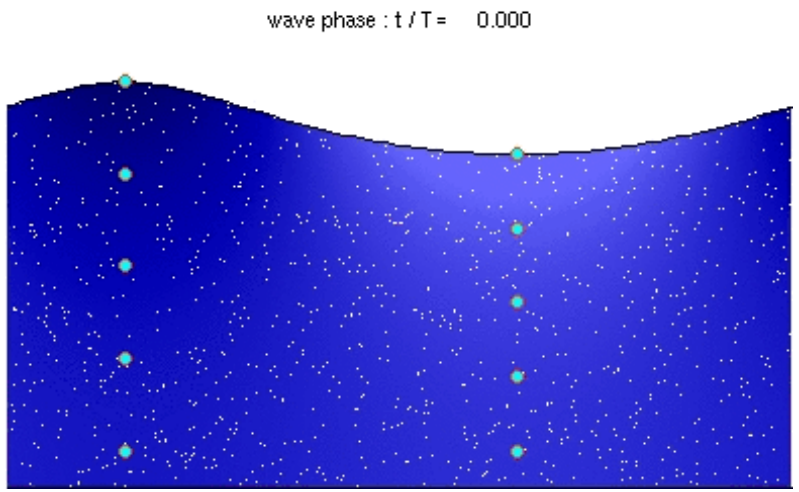
Mechanical waves

Wave-matter interaction

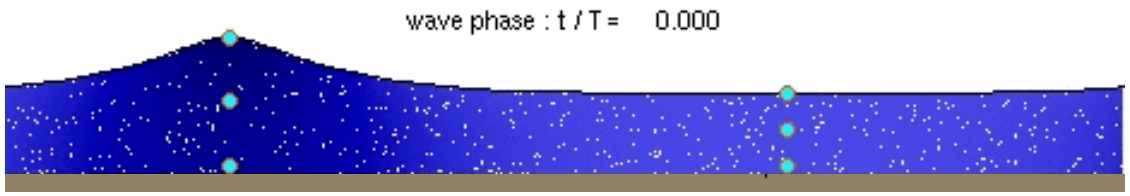
- Mechanical waves carry energy and momentum.
- When a mechanical wave interacts with matter, it can transfer the energy and/or momentum to the medium



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



Deep-water waves



Shallow water waves

Ultrasound

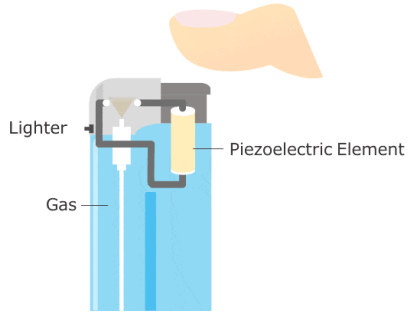
What is ultrasound

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



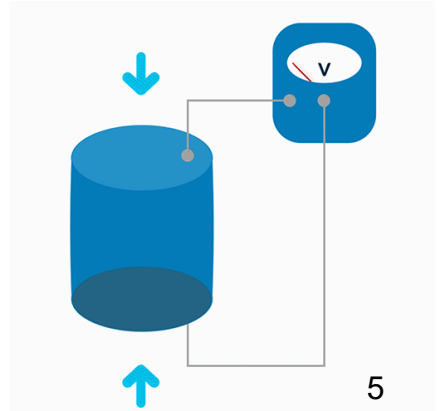
How is ultrasound generated?

- 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



Mechanisms of interaction between ultrasound and matter

Interaction

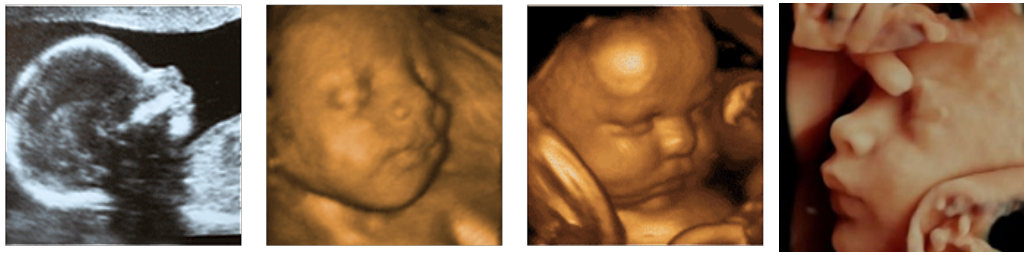
Low amplitude ultrasound

- The energy and amount of movement is very small
- Medical image / NDT

High amplitude ultrasound

- Possibility of acting on the environment
- Therapeutic / Industrial applications

Low amplitude ultrasound



GE Healthcare (2019)

High amplitude ultrasound

Effects of ultrasound on matter

a) Thermal Effects

- Temperature rise
- Sonoluminescence

b) Mechanical Effects

- Radiation force
- Flow (in fluids) and deformations (in solids)
- Cavitation (inertial and non-inertial)

University of Michigan (2019)

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 derived 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
- Many other specific effects …

How to treat (only) diseased tissues


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

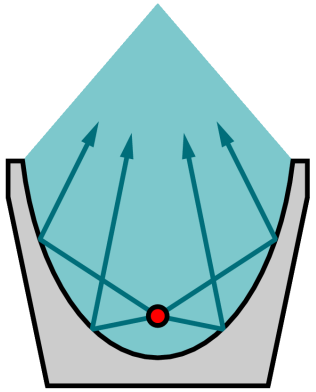
Focused ultrasound

Focused ultrasound allows to increase and localize mechanical energy

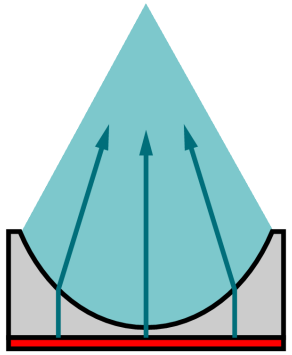




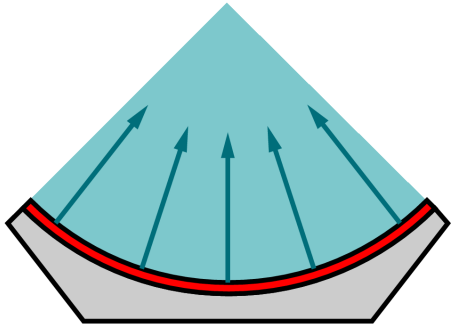
Focused ultrasound



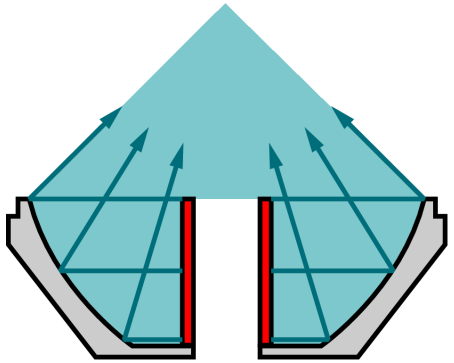
Elliptical reflectors



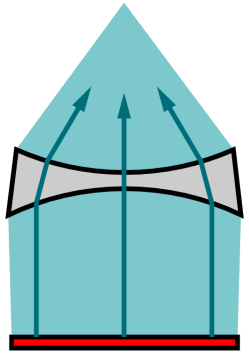
Elliptical lenses



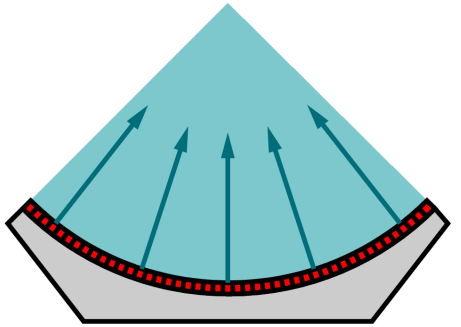
Spherical radiators



Parabolical reflectors



Convex lenses



Phased arrays

Thermal tissue ablation

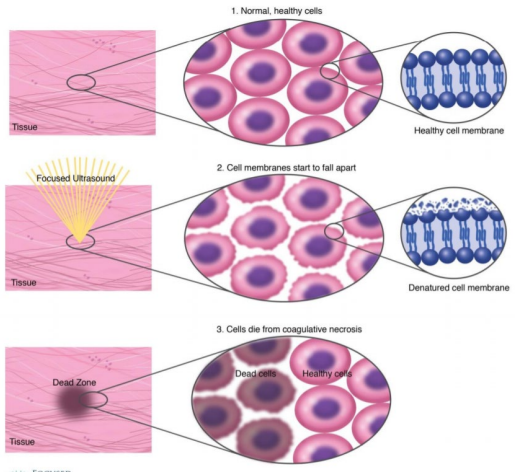
High Intensity Focused Ultrasound (HIFU)

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

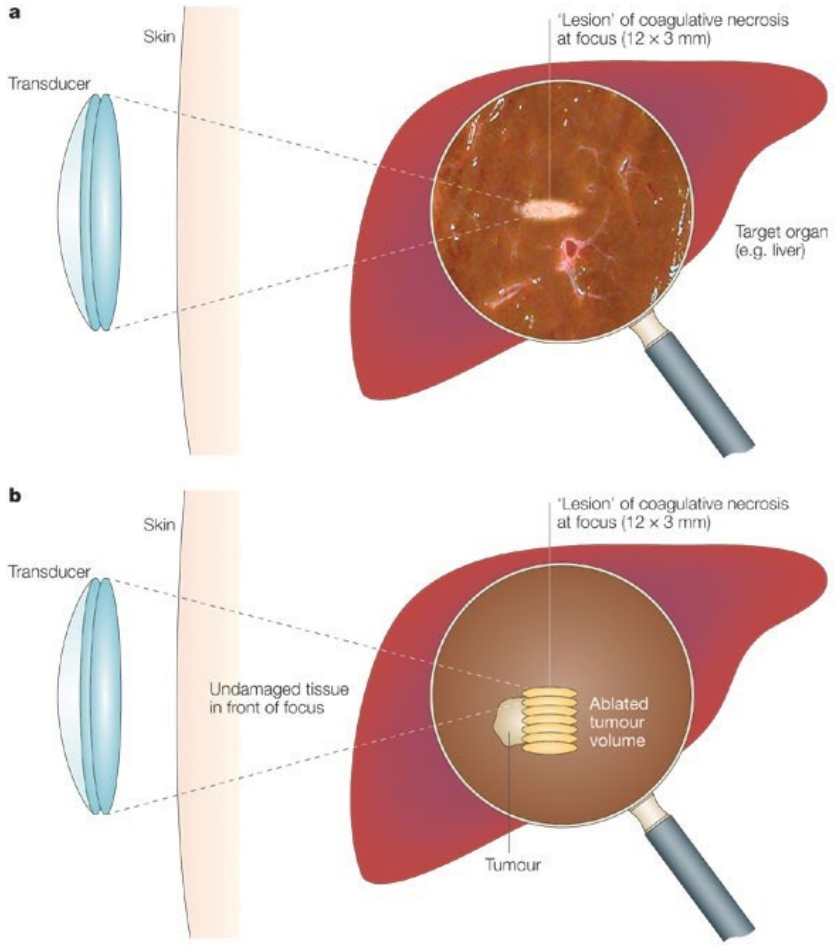
- localized cell necrosis.



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

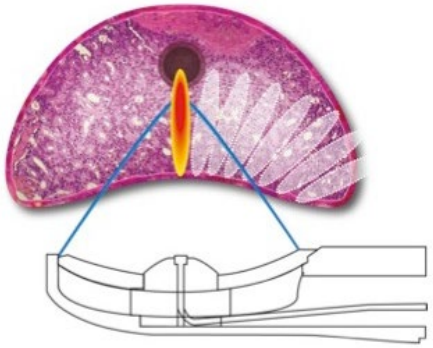
- Localized thermal tissue ablation

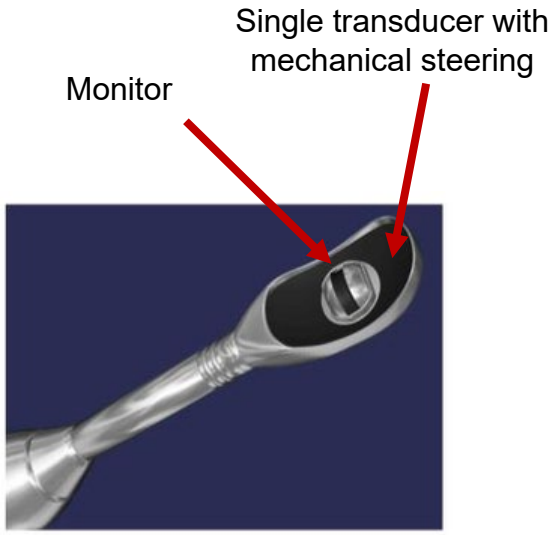
Monitoring

- MRI (MRgFUS)
- US (USgFUS)

ExAblate (MRgFUS)







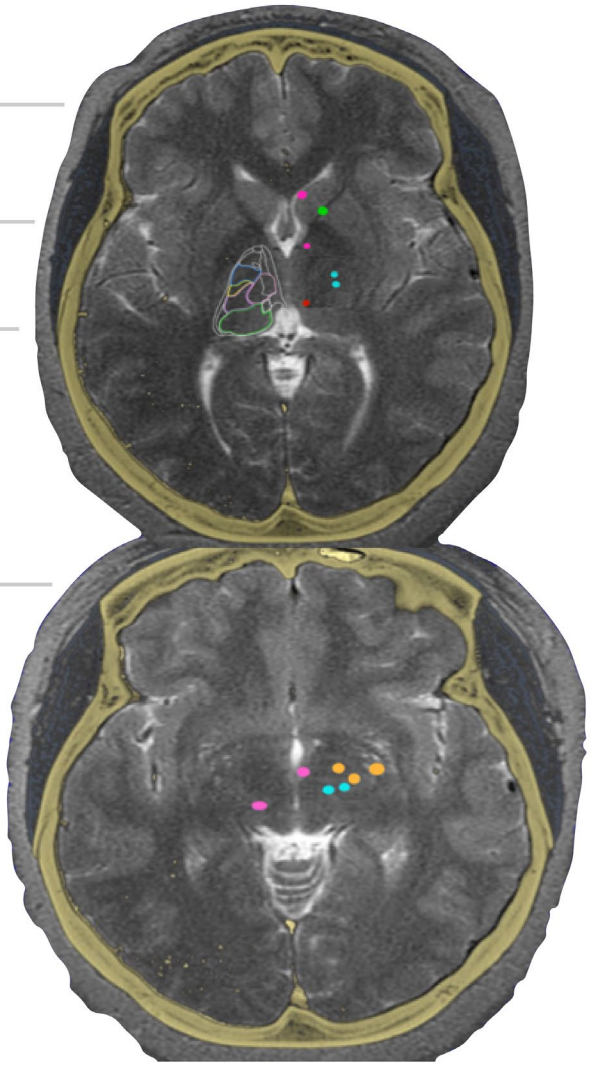
Ablatherm (USgFUS)



… and in the brain?

Thermal tissue ablation

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

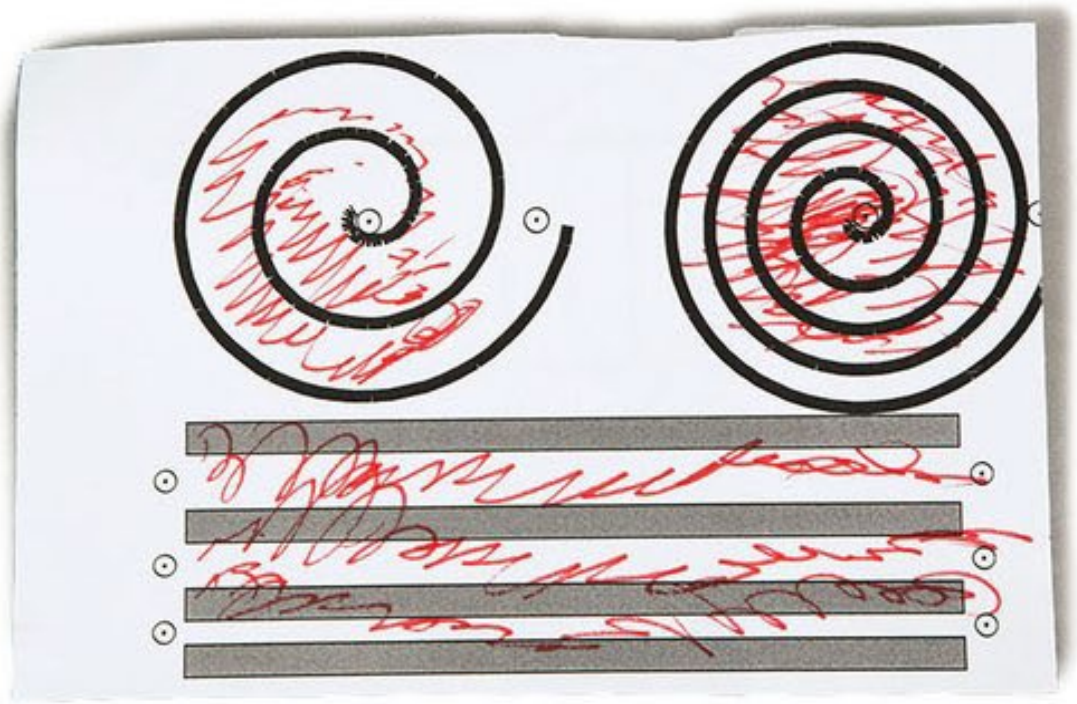
Focused ultrasound for this condition is being researched in clinical trials.

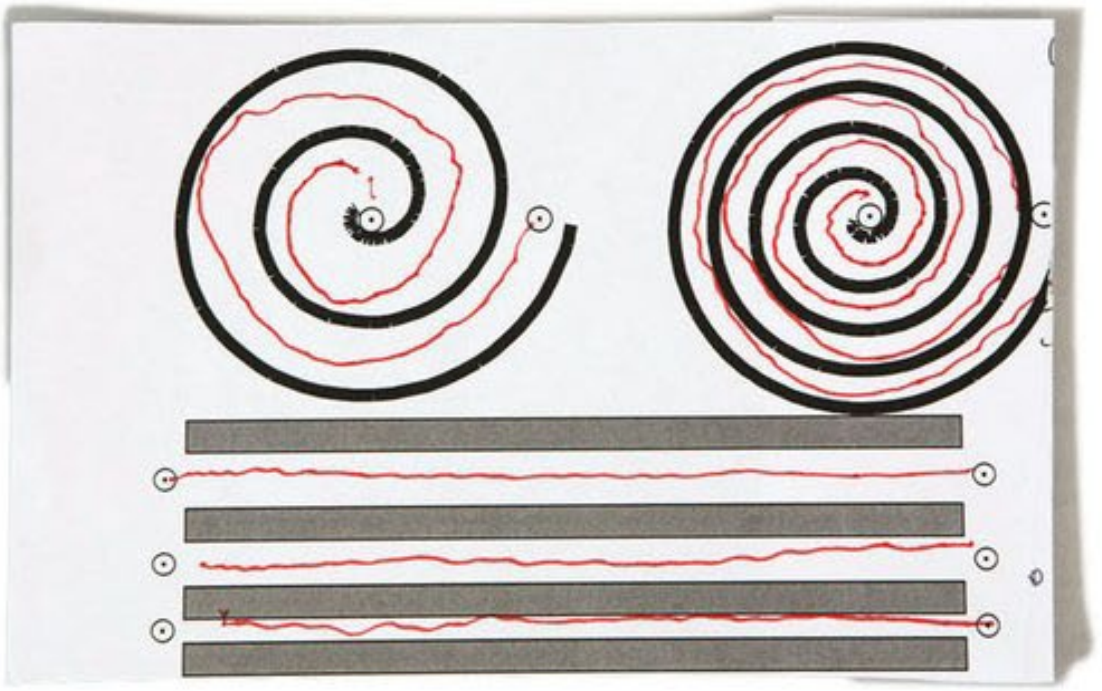
Early Stage

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

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

Thermal tissue ablation





Localized drugs and gene delivery

Blood-brain barrier opening

Problem

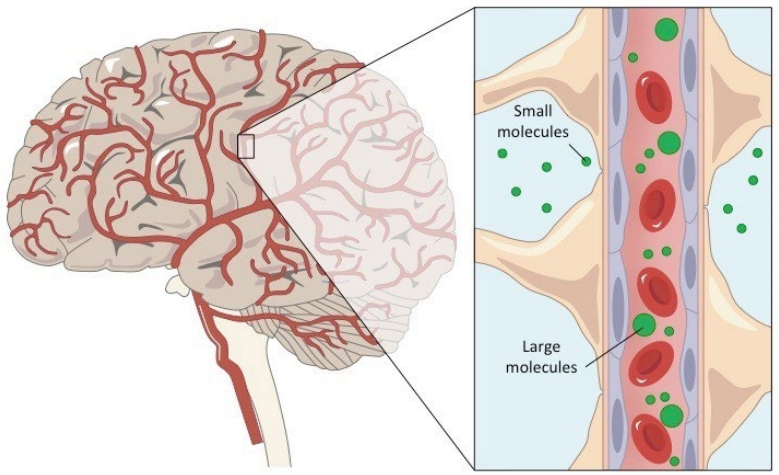
- Tight junctions in the endothelium prevent the passage of heavy molecules into the CNS
- Protection against infections, viruses
- Blocks drug delivery

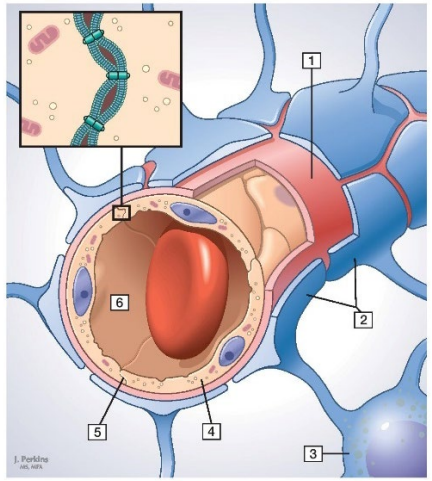
Treatment

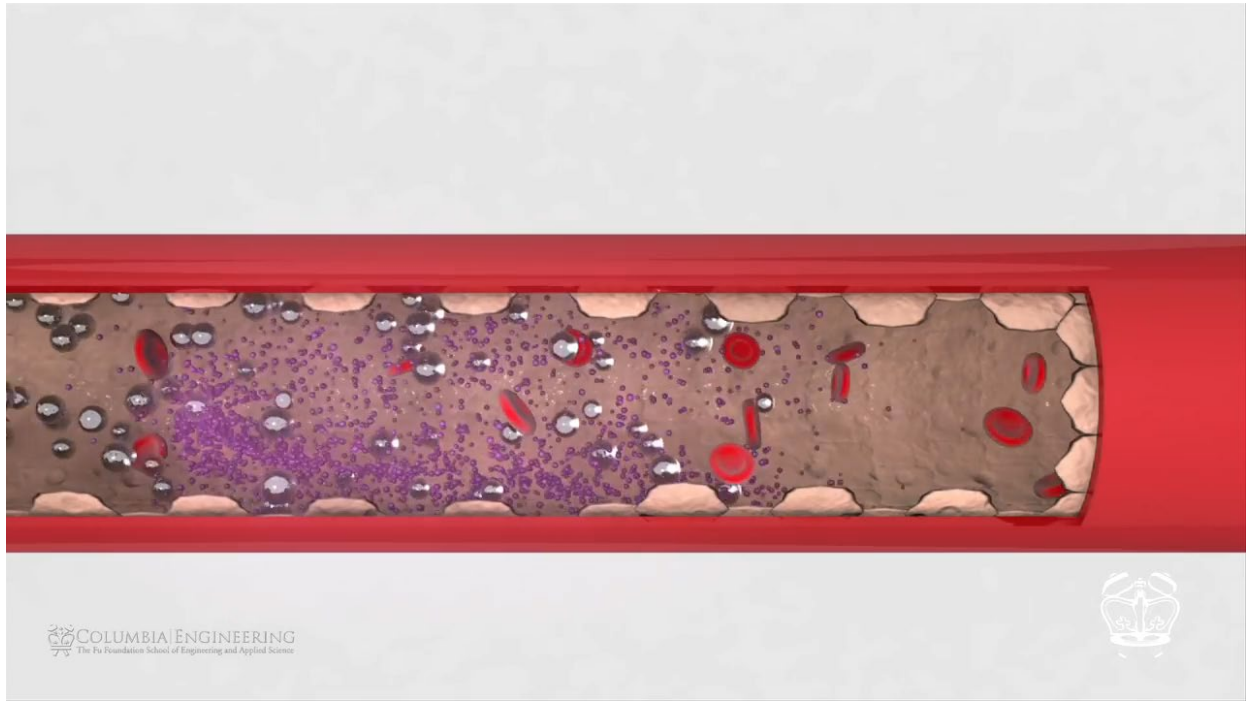
- Medium intensity focused US + microbubbles
- Localized, transient, non-invasive and safe way blood-brain barrier opening

Application

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







Courtesy of Columbia University

Neuromodulation

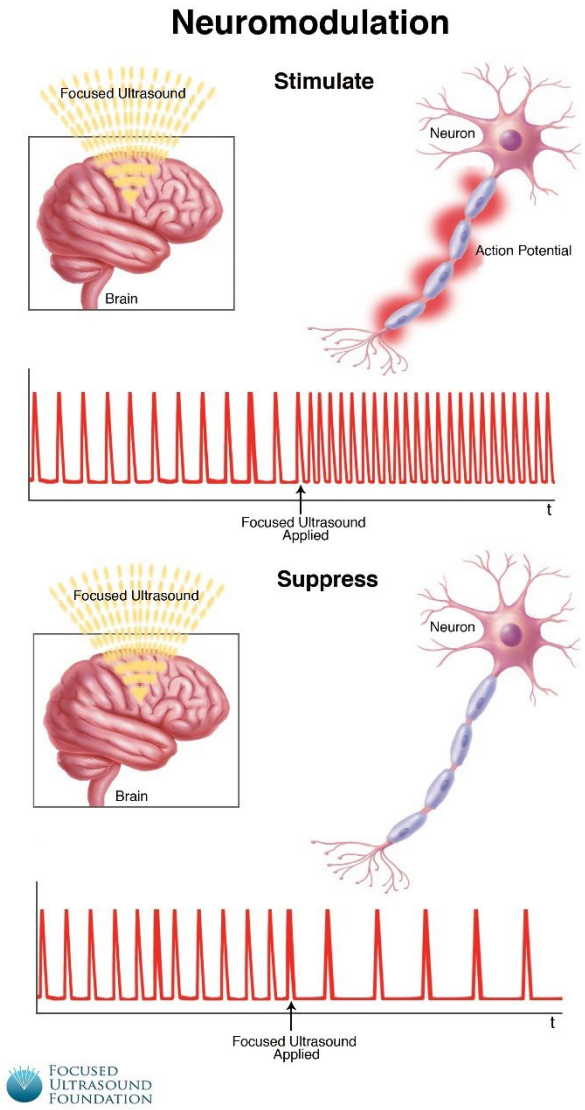
FUS Mediated Localized Neuromodulation

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



Focused Ultrasound Foundation (2020)

Tyler, W. J. et al. PLoS ONE 3, e3511 (2008).
Legon, W. et al. Nat. Neurosci. 17, 322–329 (2014).
Yoo, Sangjin, et al. Nature Communications 13.1 (2022): 1-13.

Neuromodulation

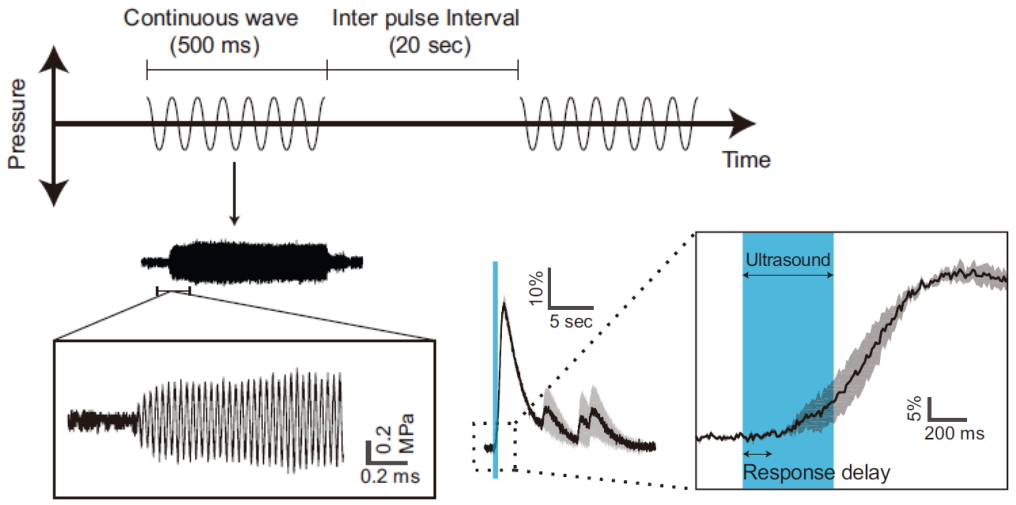
FUS Mediated Localized Neuromodulation

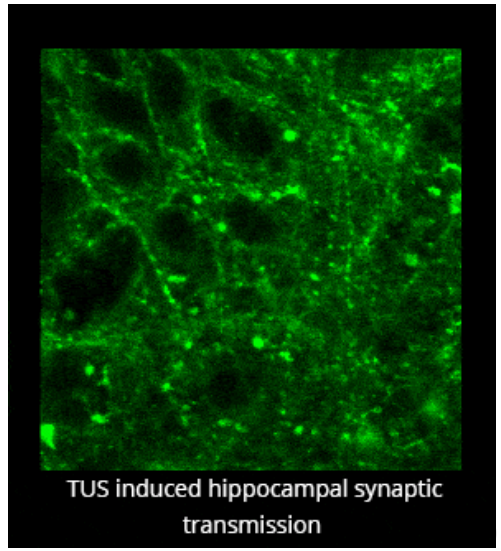
Stimulation

- 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




TUS induced hippocampal synaptic transmission

Tyler, W. J. et al. PLoS ONE 3, e3511 (2008).
Legon, W. et al. Nat. Neurosci. 17, 322–329 (2014).
Yoo, Sangjin, et al. Nature Communications 13.1 (2022): 1-13.

Focusing ultrasound in the brain

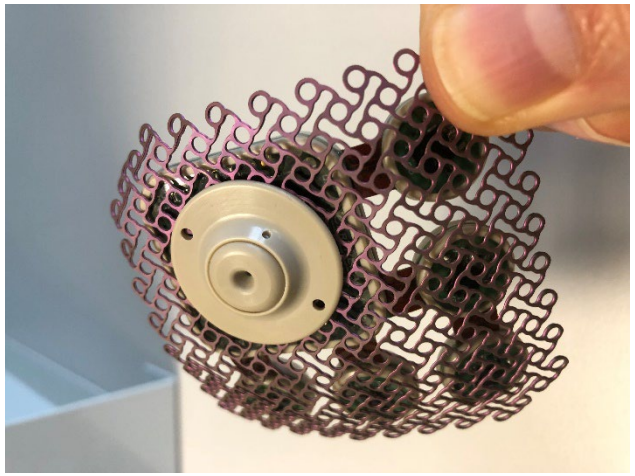


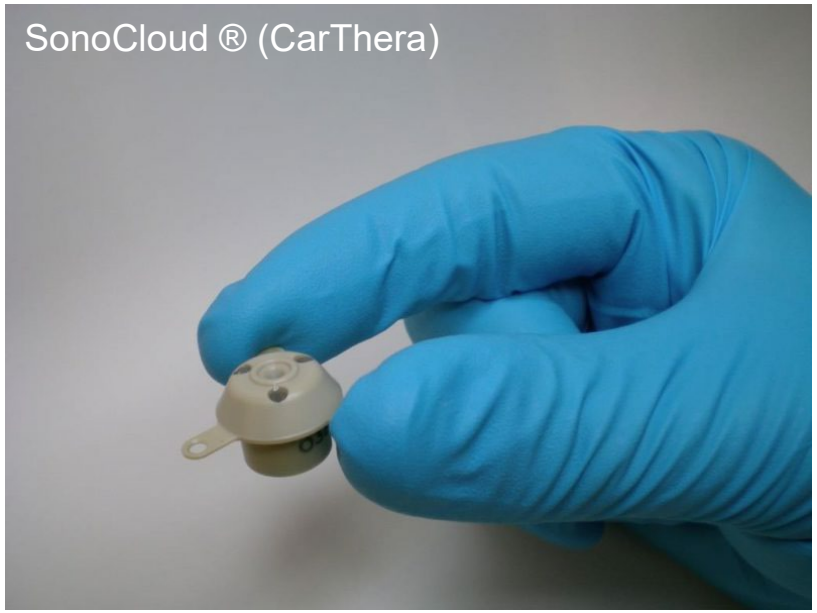
Transcraneal ultrasound systems

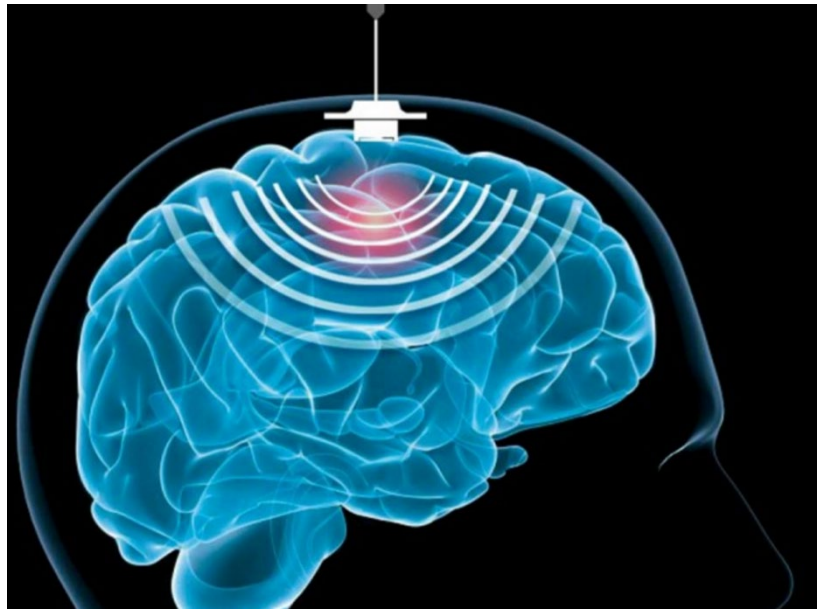
Intracranial implants

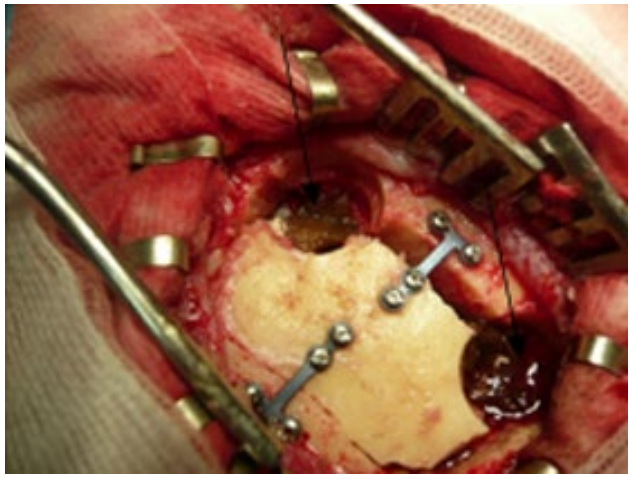
- Blood-brain barrier opening
- Chemotherapy
- Implanted in a burr hole (diagnostic biopsy or post tumor resection glioblastoma)
- Invasive, poor focusing

CarThera
Advanced Brain Therapy Through Innovation







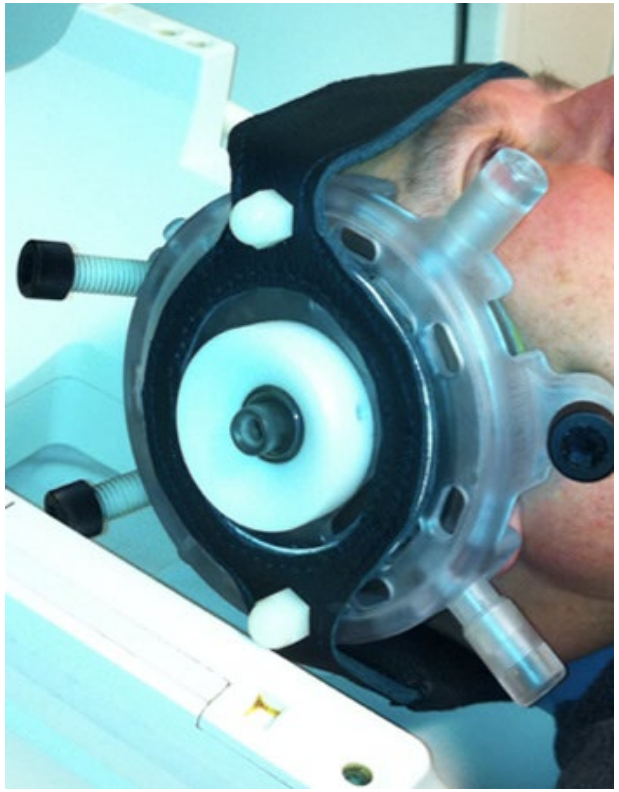


Transcraneal ultrasound systems

Single element transducer

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





BRAINSONIX CORPORATION



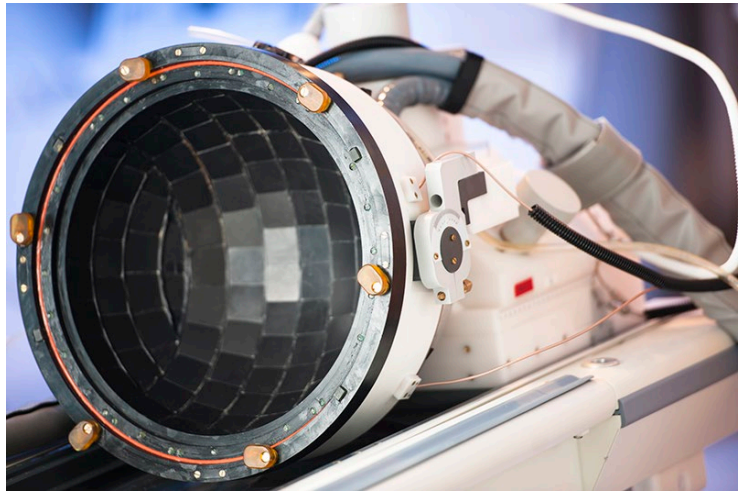
Transcraneal ultrasound systems

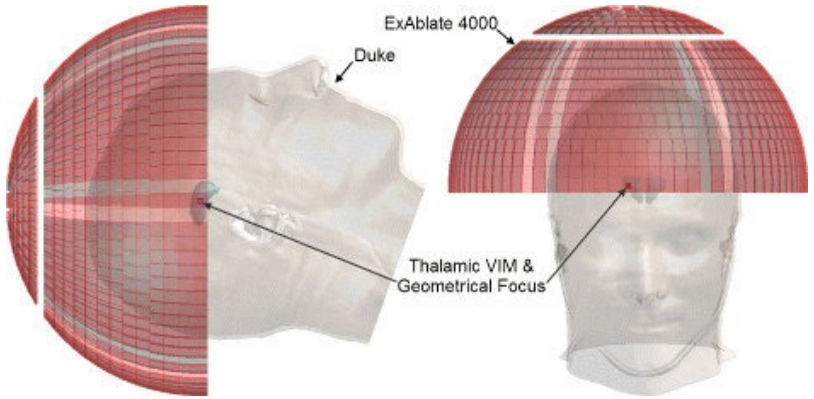
Magnetic resonance-guided focused ultrasound (MRgFUS)

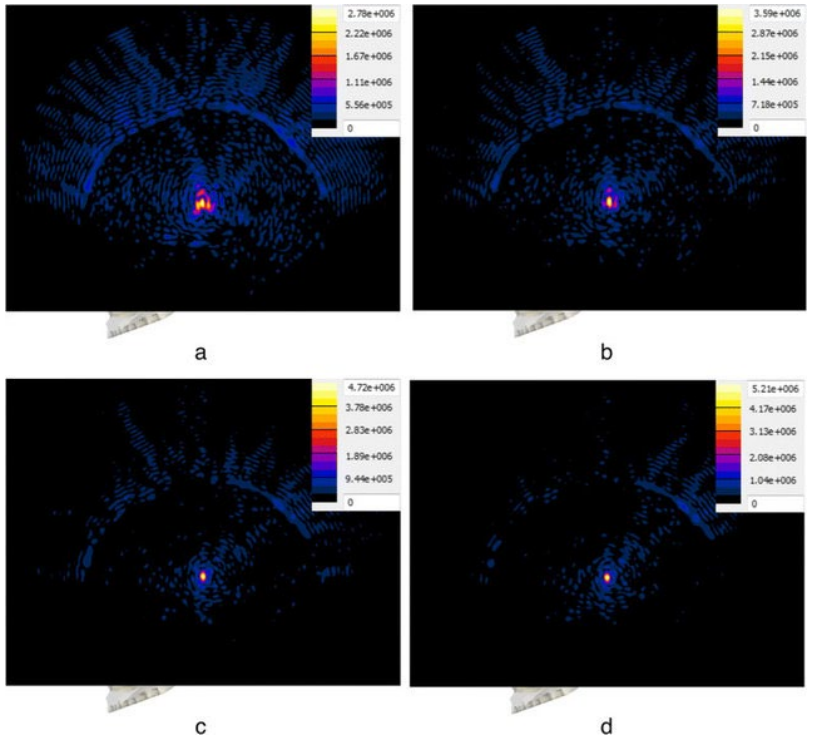
- Phased array
  - Skull aberrations can be mitigated
  - Focal steering
  - MRI guided
- Thermal ablation (650 kHz)
- BBB Opening (220 kHz)
- Expensive

INSIGHTEC









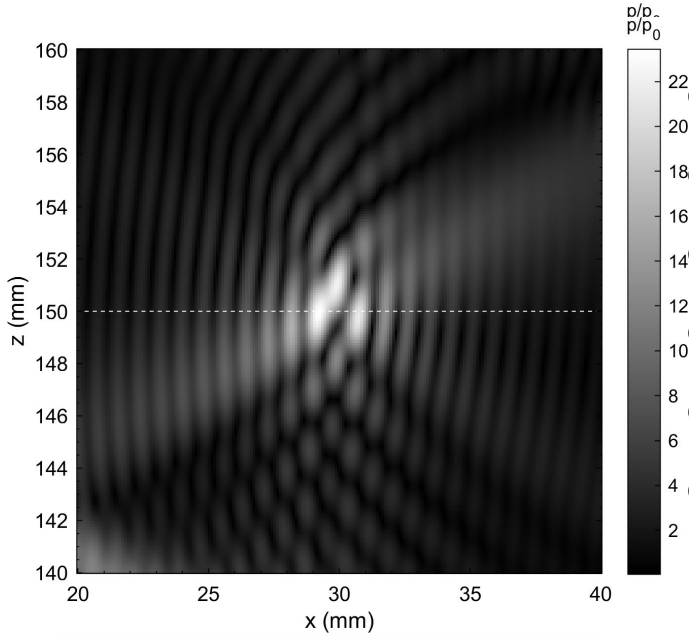
Focusing challenges

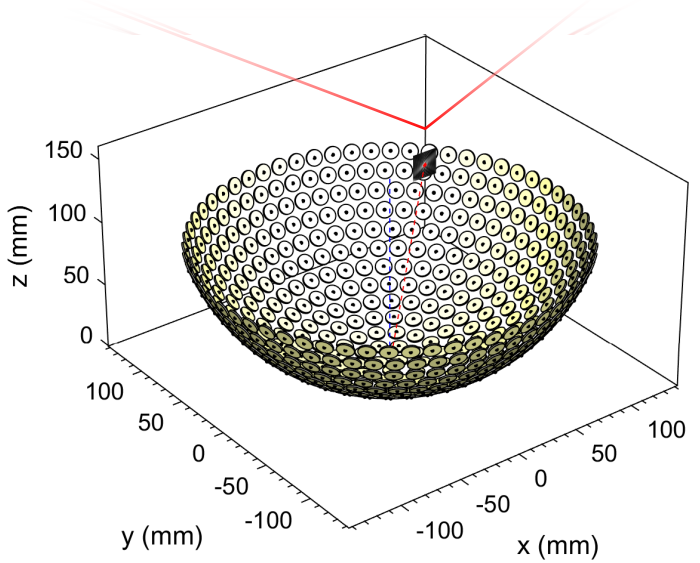
Focusing

- 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



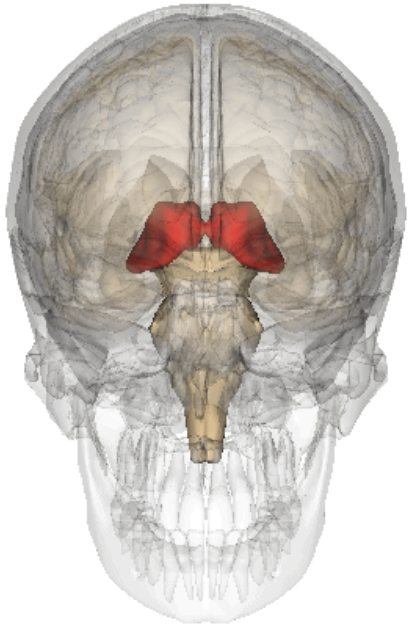


Focusing challenges

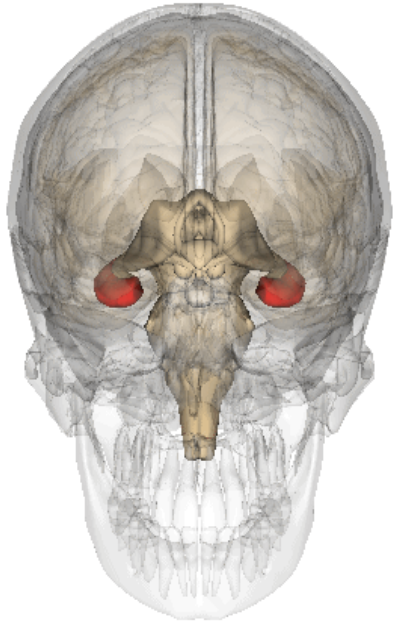
Complex target morphology

- Can we adapt the beam to the therapeutical target?

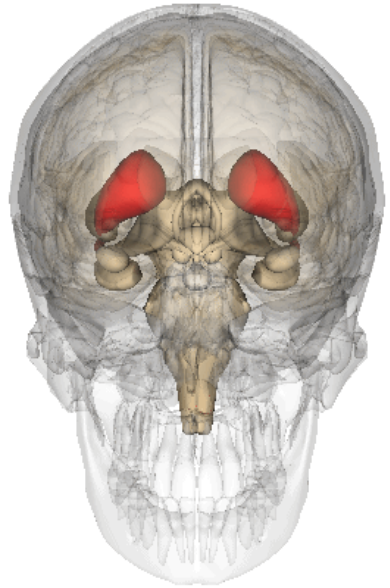
Thalamic nuclei



Hippocampus



Caudate nucleus

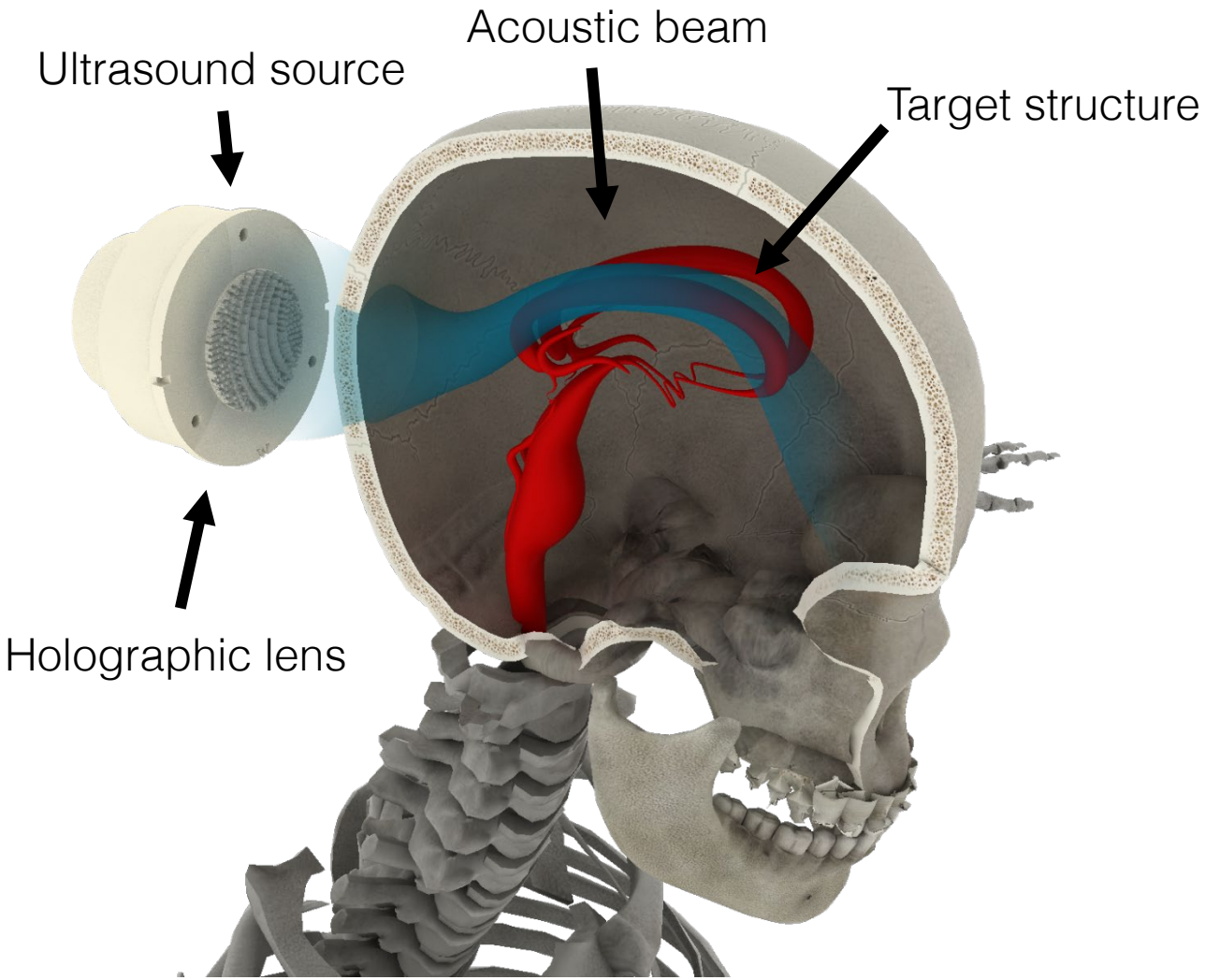


http://www.brainfacts.org/3D-Brain

Acoustic holograms

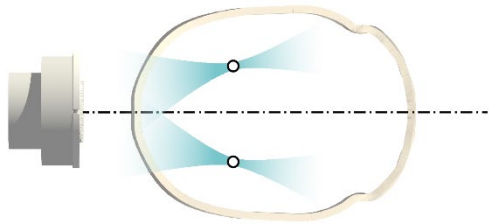
Instiuto de Instrumentación para Imagen Molecular (I3M)
Universitat Politècnica de València (UPV) – Spanish Research Council (CSIC)
València, Spain

Acoustic holograms

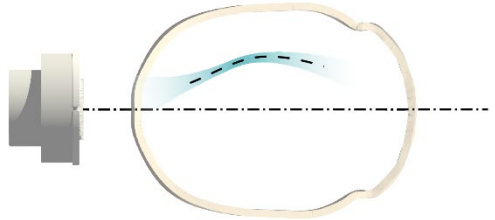


Configurations

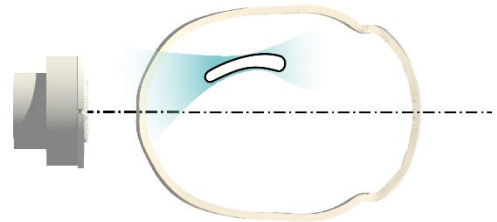
1) Multiple point



2) Self-bending beams



3) Volumetric treatments

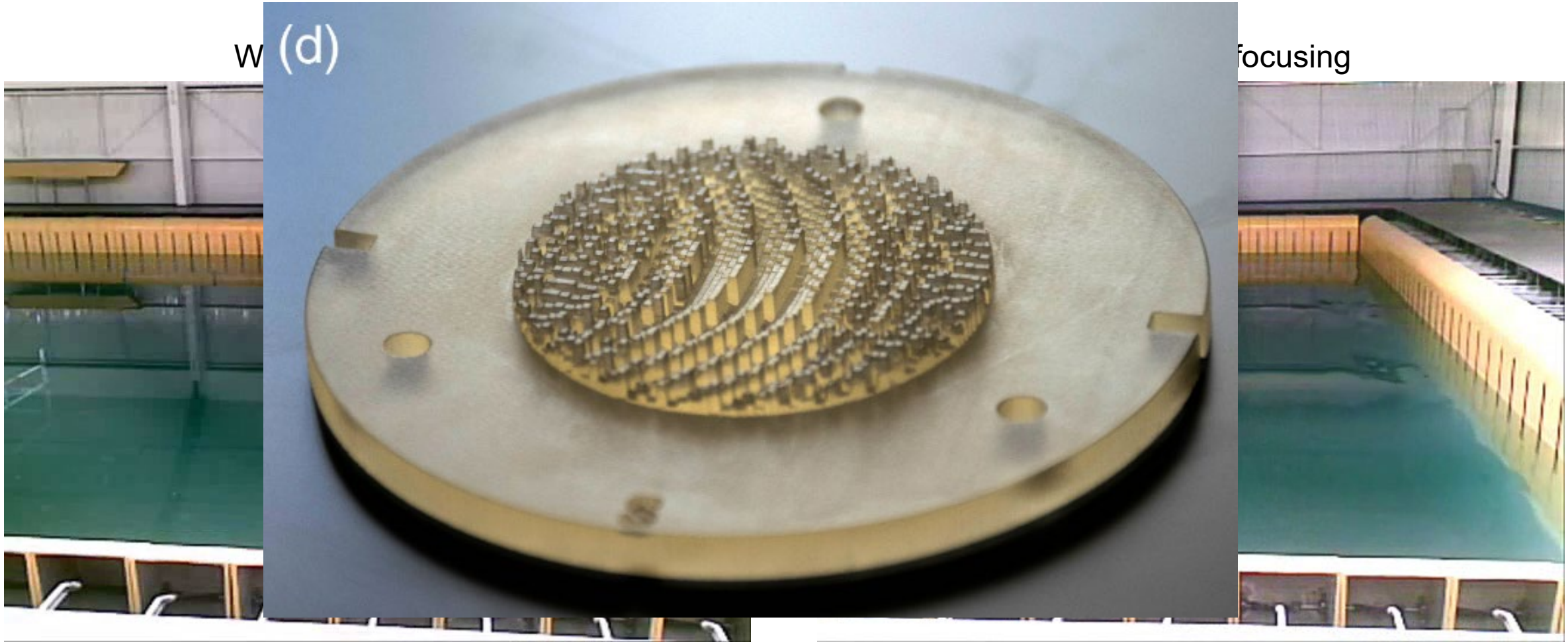


Jiménez-Gambín, et al. Phys Rev Appl 12 014016 (2019)

Acoustic holograms

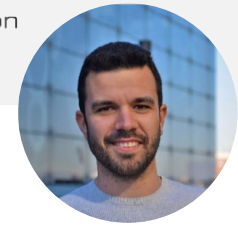
Time-reversal symmetry

- Acoustic wave equation show time-reversal symmetry



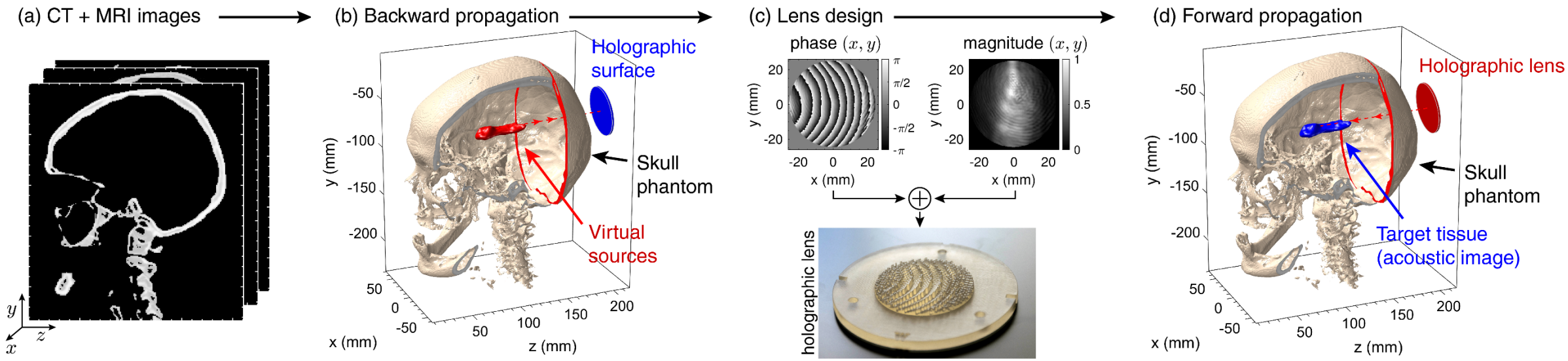
Acoustic holograms

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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 for the brain

Experimental setup

- Ultrasound measurements in water-tank
- 3D, 5 µm resolution steeped Axis

Flat ultrasound transducer

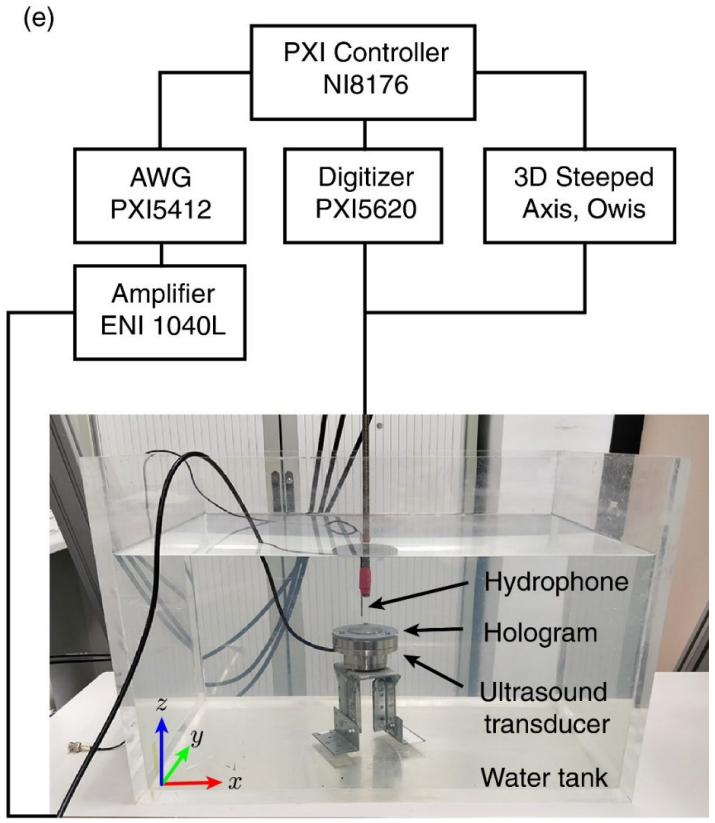
- Frequency: 1.1 MHz (1.4 mm wavelength)
- Aperture: 50 mm (36 wavelengths)

Skull phantom

- 3D-printed skull using polylactic acid
- Simulations including PLA properties

Verification

- Simulations including skull properties





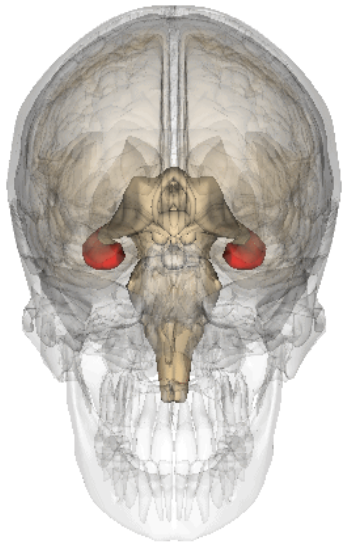


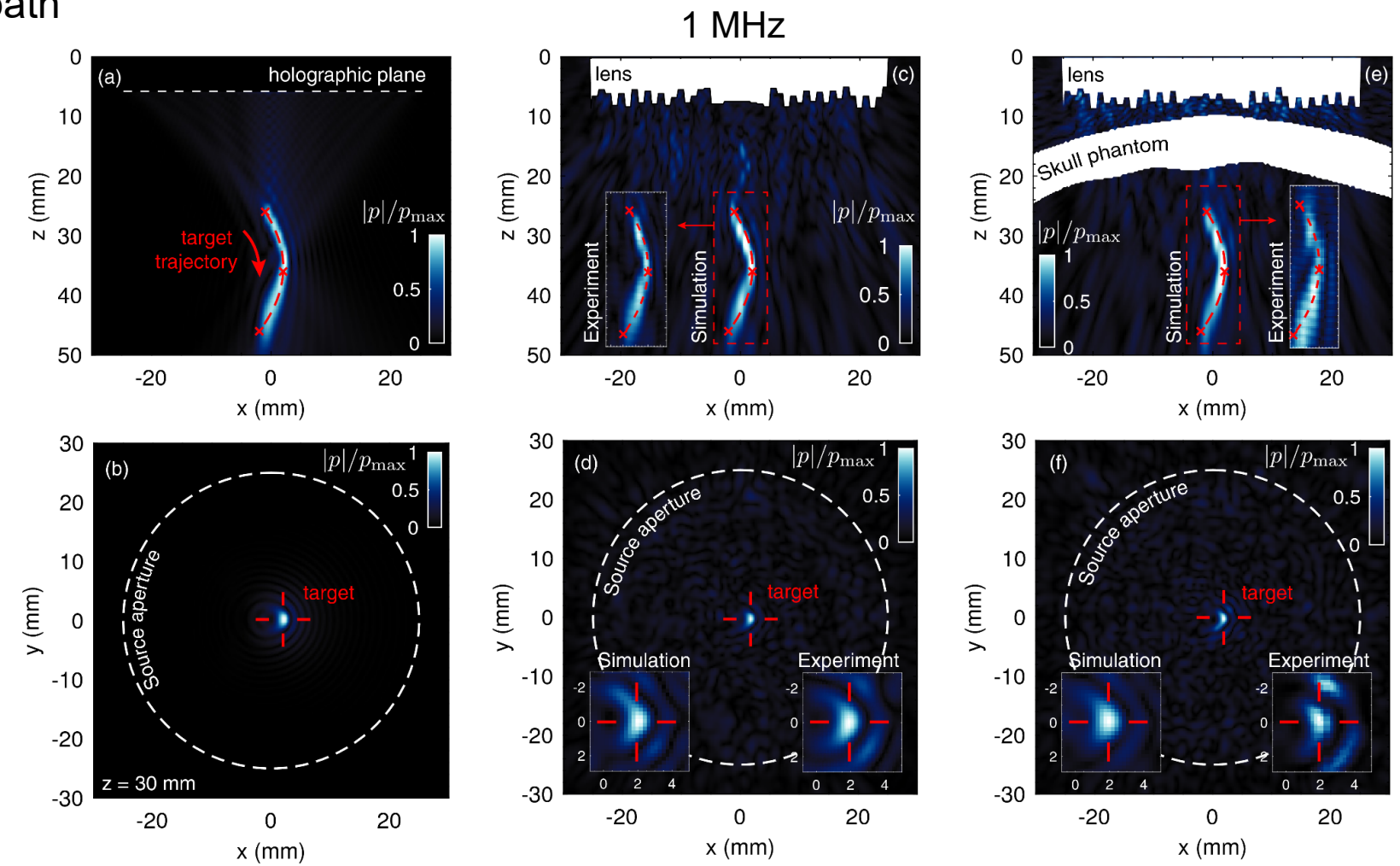


Acoustic holograms

Self-bending beams

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

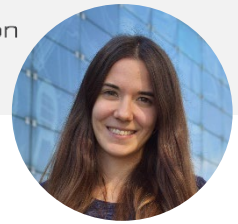




Jiménez-Gambín, et al. Phys Rev Appl 12 014016 (2019)

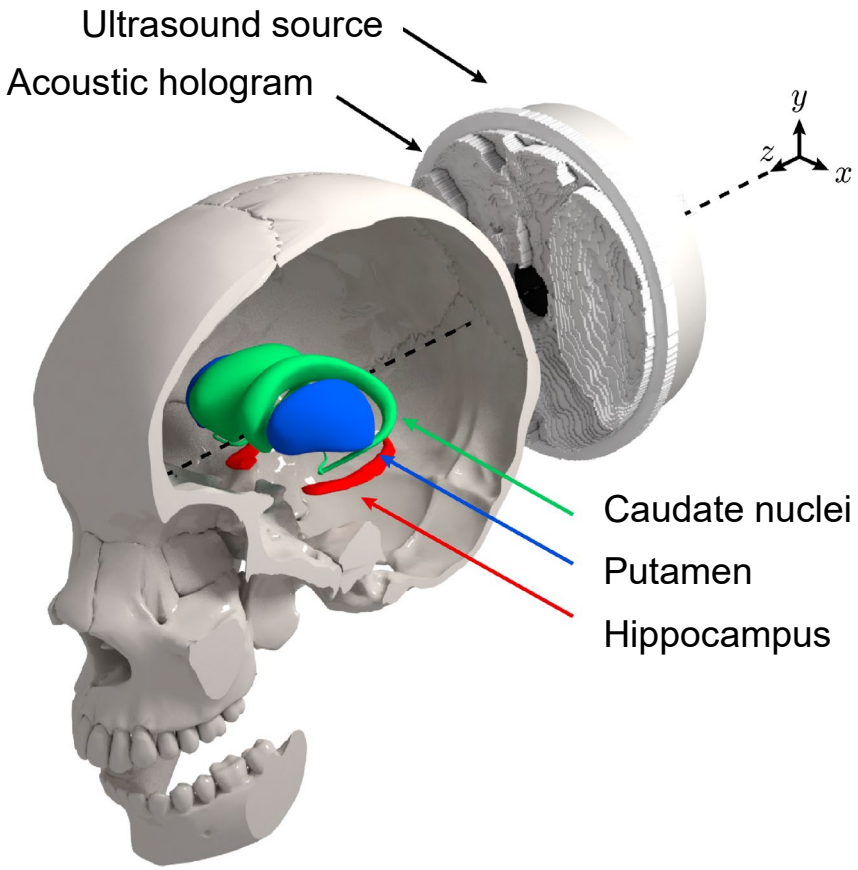
Acoustic holograms

i3M Instituto de Instrumentación para Imagen Molecular

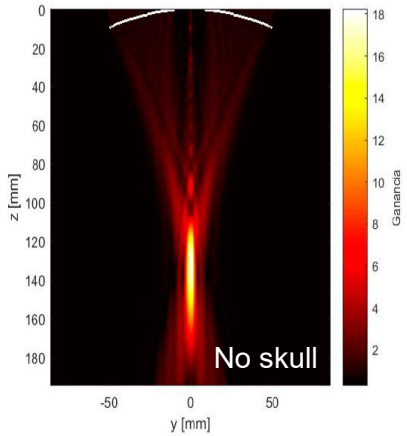


Bilateral focusing

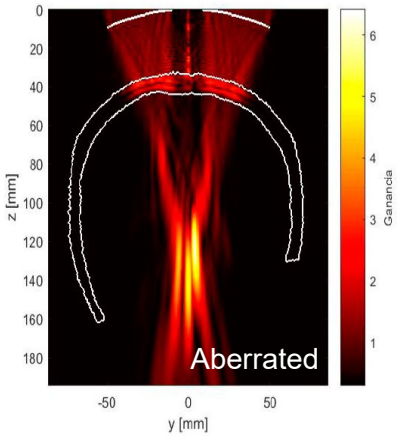
- Targeting at complex bilateral shapes



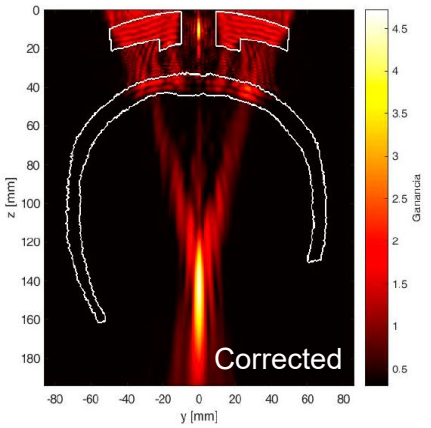
FUS transducer (500 kHz)



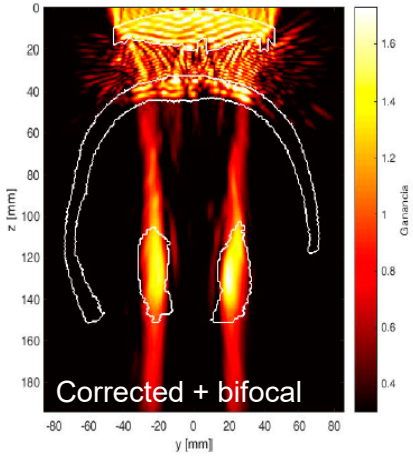
FUS transducer + skull



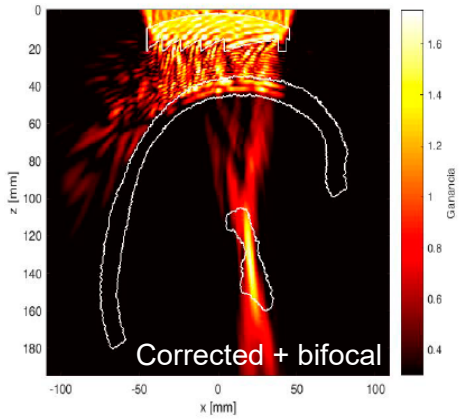
Hologram + skull



Bilateral focusing at hippocampus (coronal)



Bilateral focusing at hippocampus (sagittal)



Acoustic holograms

Using the temporal window

- Low thermal dose and deep-brain focusing



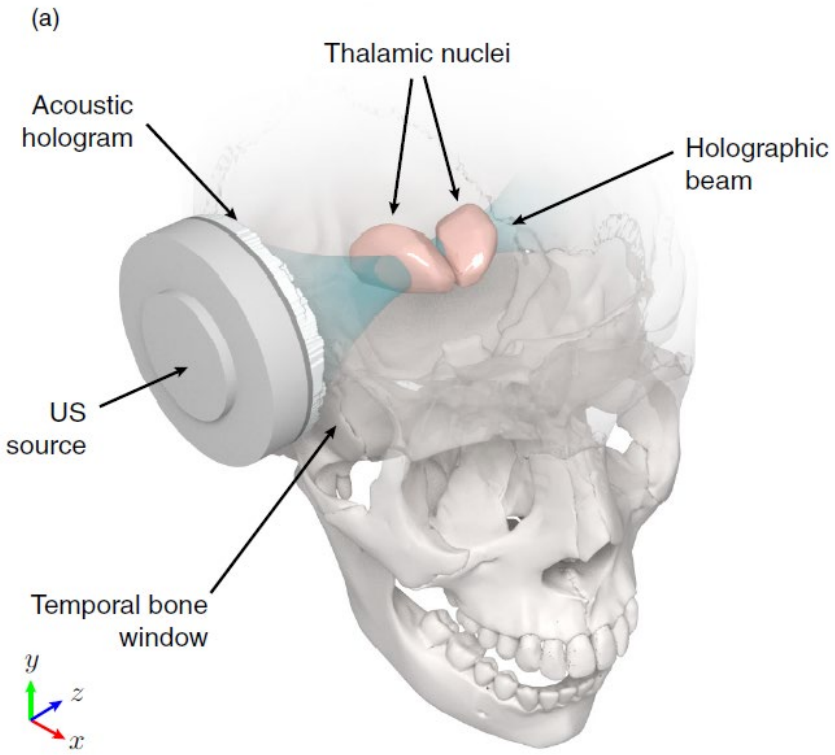
Acoustic holograms

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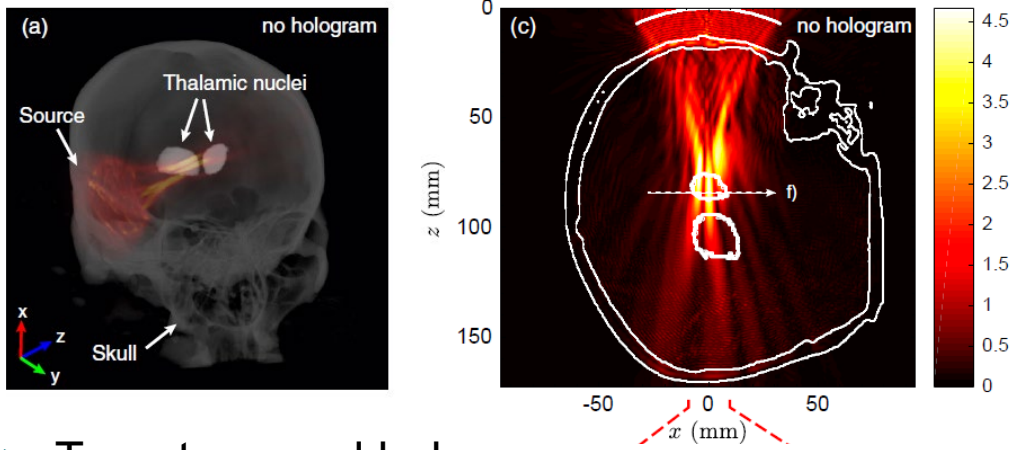


Using the temporal window

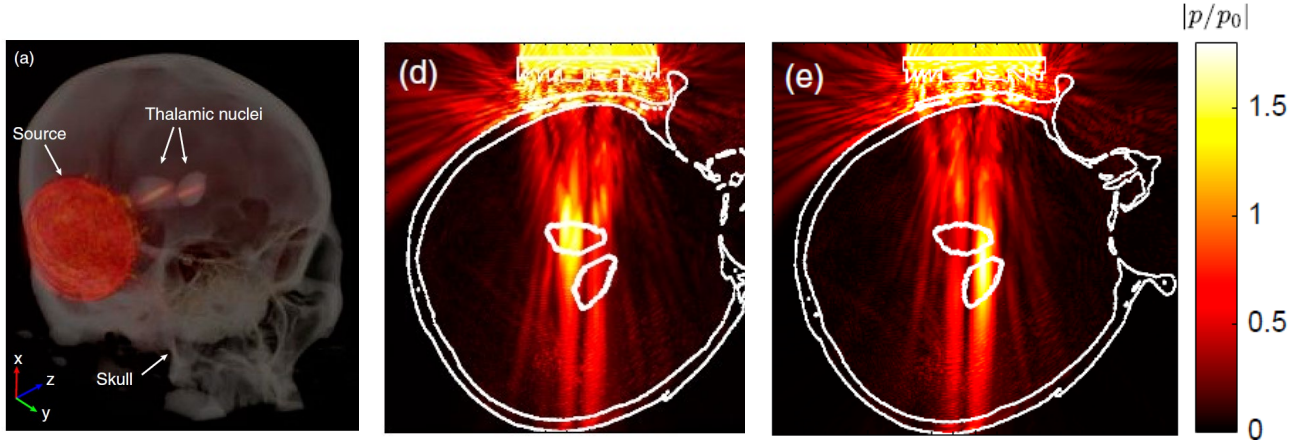
- Low thermal dose and deep-brain focusing



- Standard focused transducer (650 kHz)



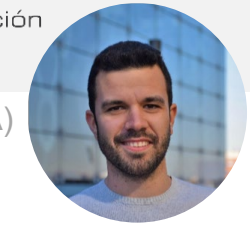
- Transtemporal hologram



Diana Andres, et al. *Ultrasound in Medicine and Biology*, (2022)

In-vivo validation

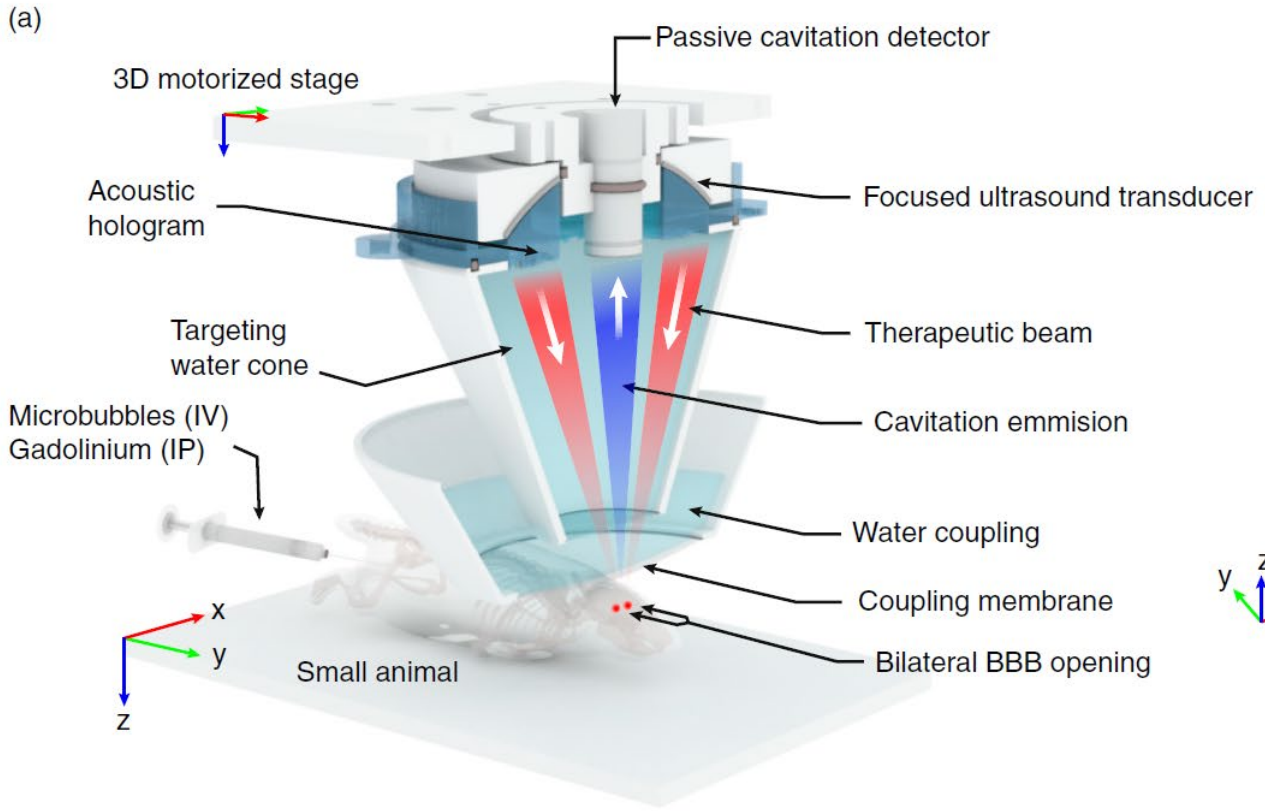
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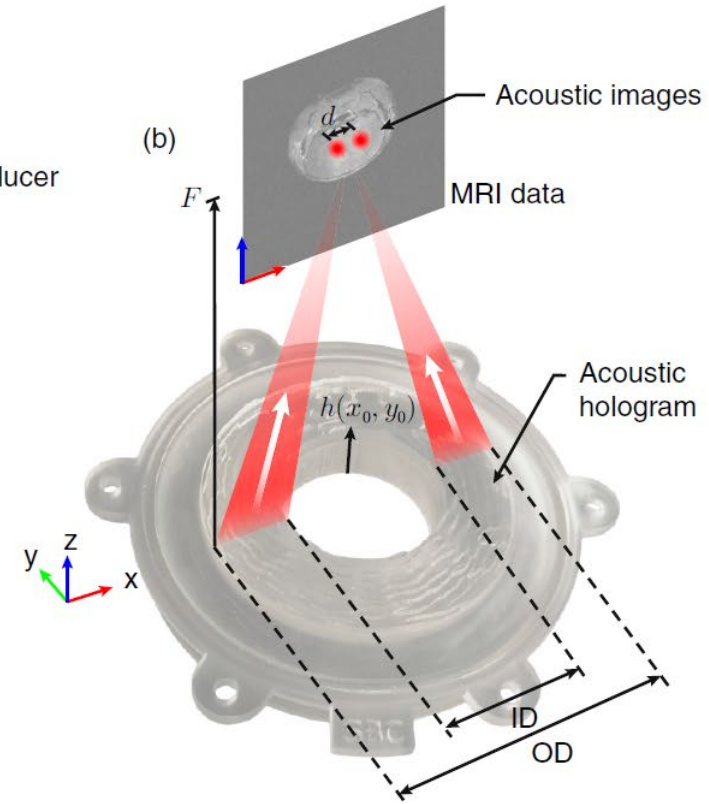


In collaboration with E.E. Konofagou, Columbia University (NYC, USA)

Bilateral blood-brain barrier opening

- First in-vivo application of acoustic holograms

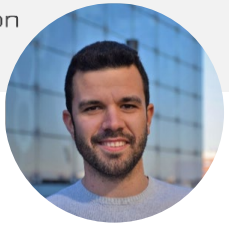




Sergio Jiménez-Gambín, et al., IEEE Transactions on Biomedical Engineering, 69 (4), pp. 1359 – 1368, (2022)

In-vivo validation

Instituto de Instrumentación para Imagen Molecular

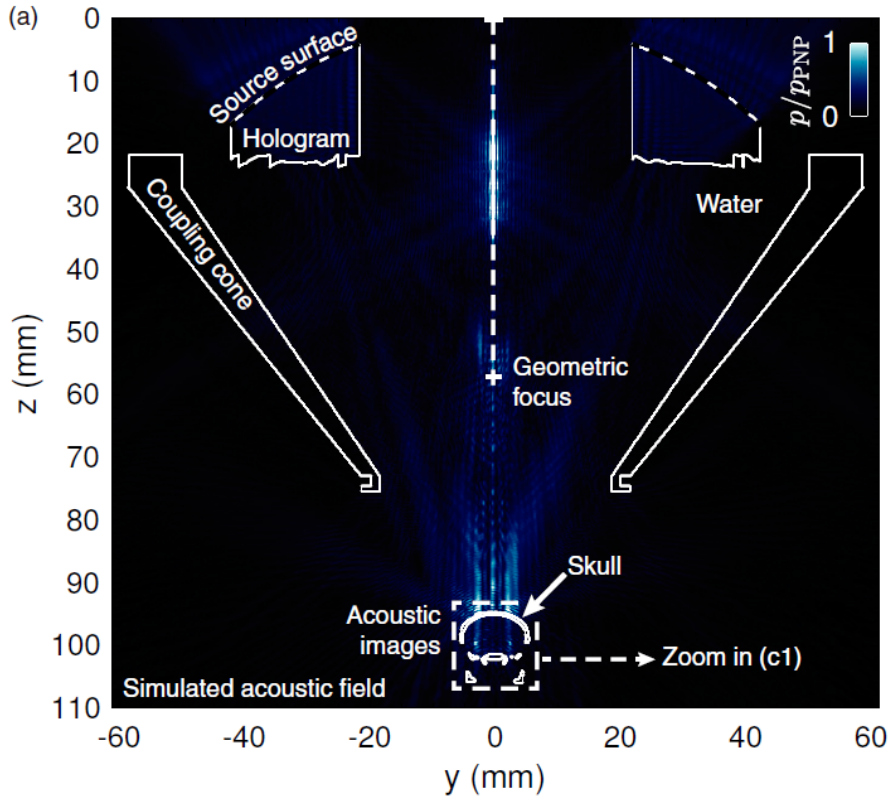


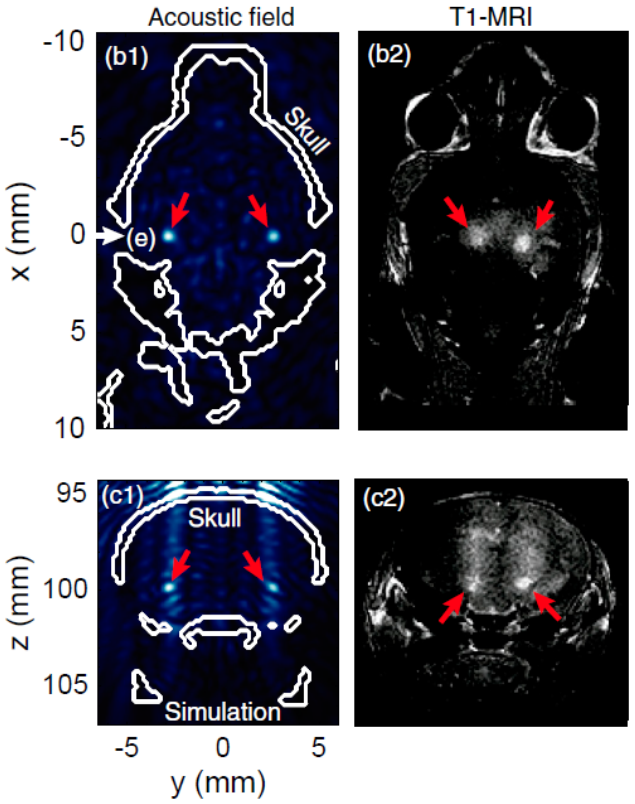
In collaboration with E.E. Konofagou, Columbia University (NYC, USA)

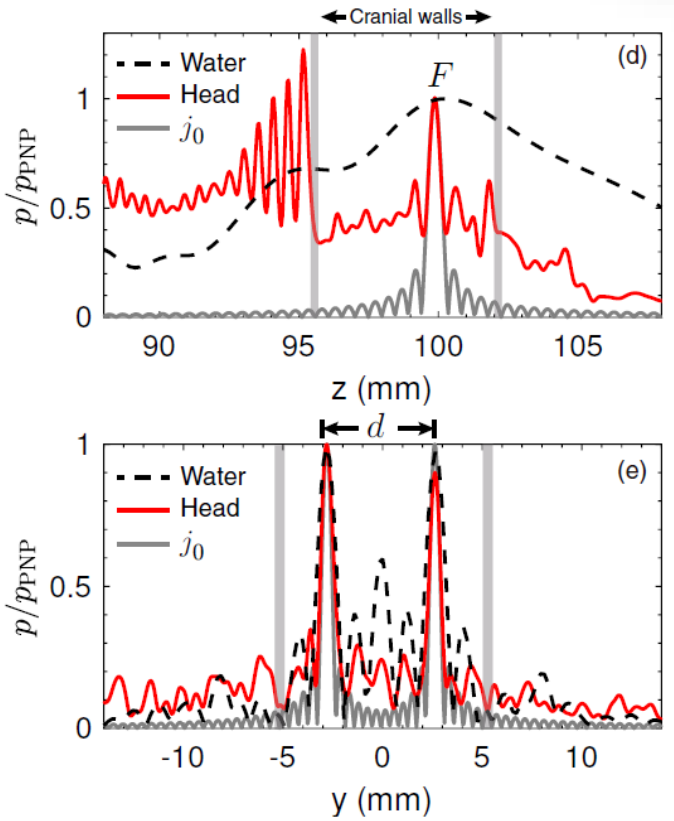
Bilateral blood-brain barrier opening

- First in-vivo application of acoustic holograms

1.6 MHz

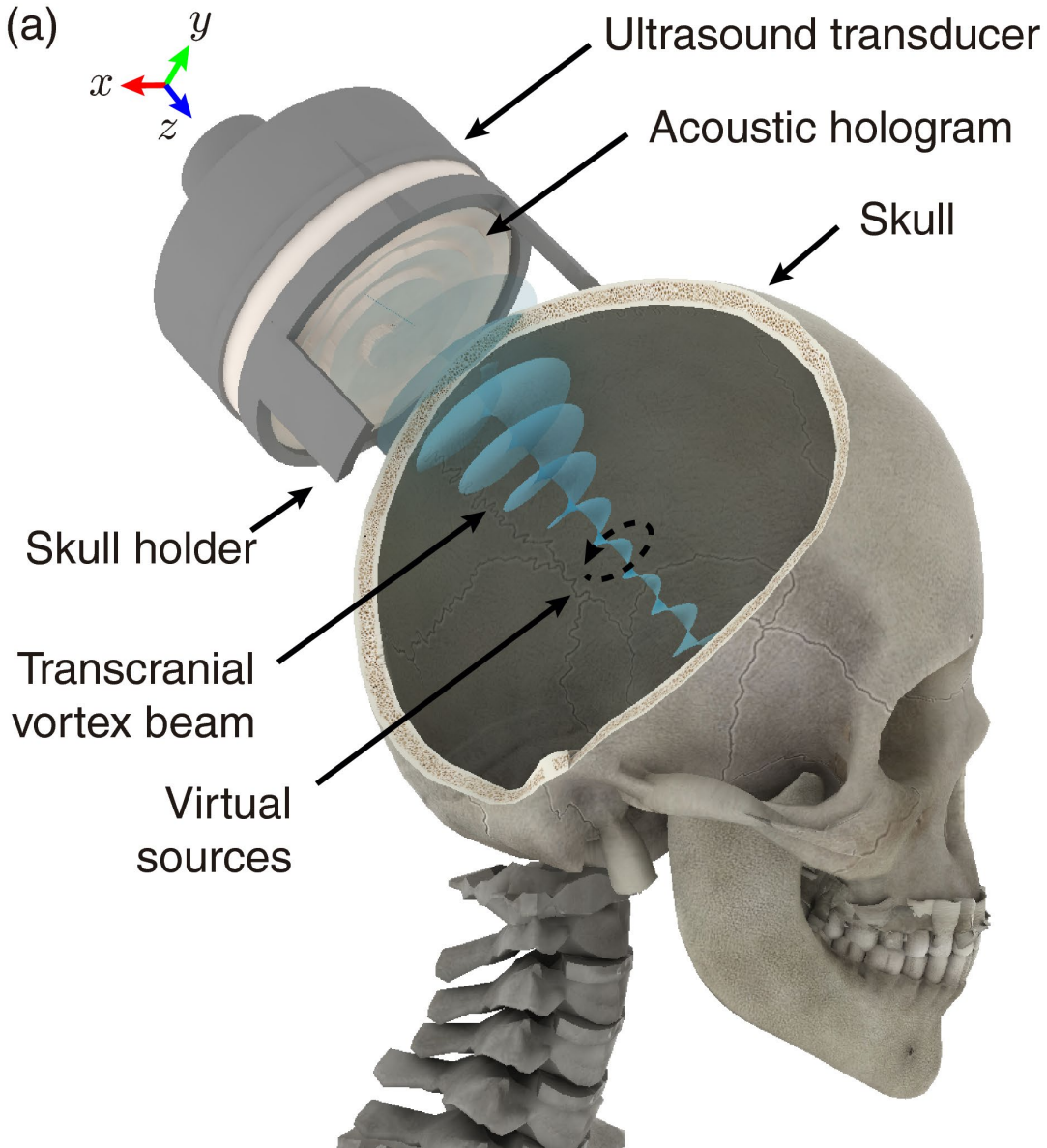


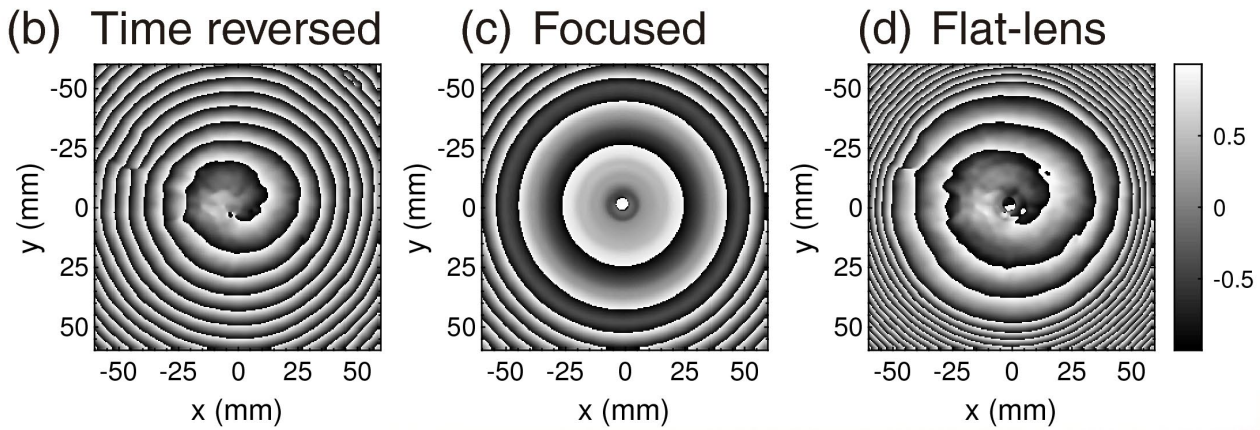


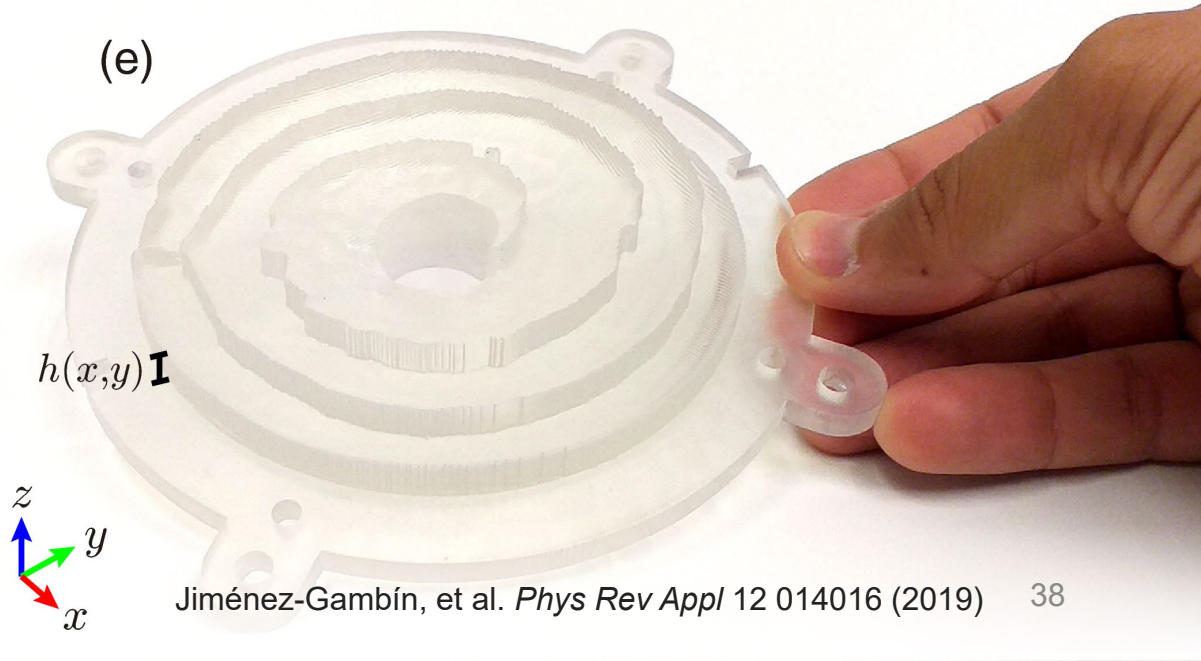


Sergio Jiménez-Gambín, et al., IEEE Transactions on Biomedical Engineering, 69 (4), pp. 1359 – 1368, (2022)

Acoustic vortices in the brain





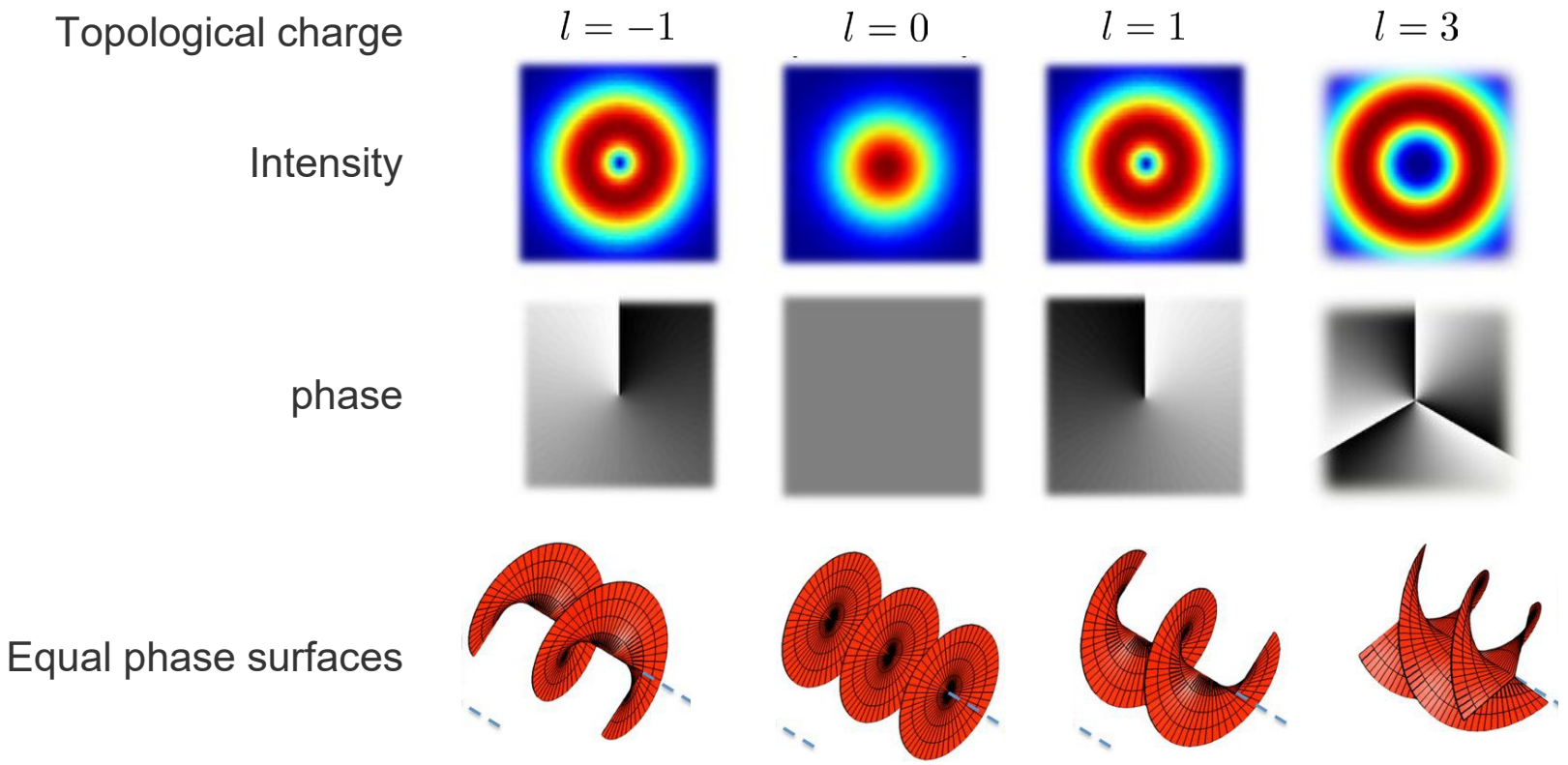


Jiménez-Gambín, et al. *Phys Rev Appl* 12 014016 (2019)

Acoustic vortices in the brain

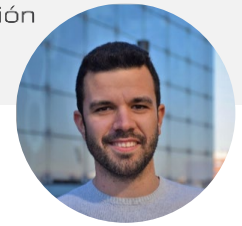
Acoustic vortex beams

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



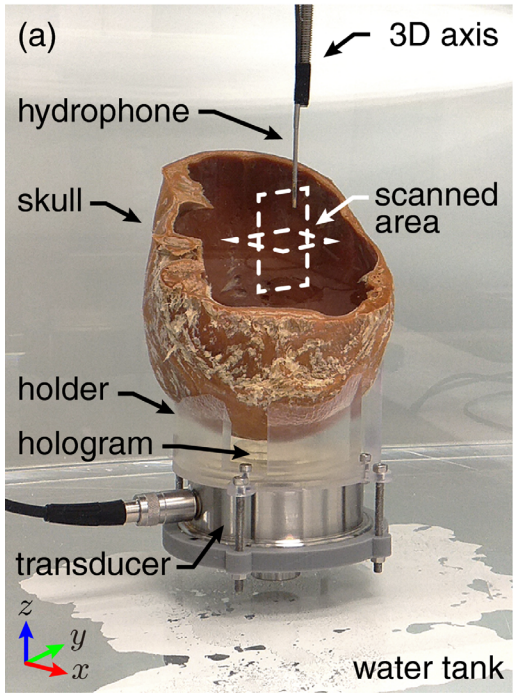
Acoustic vortices in the brain

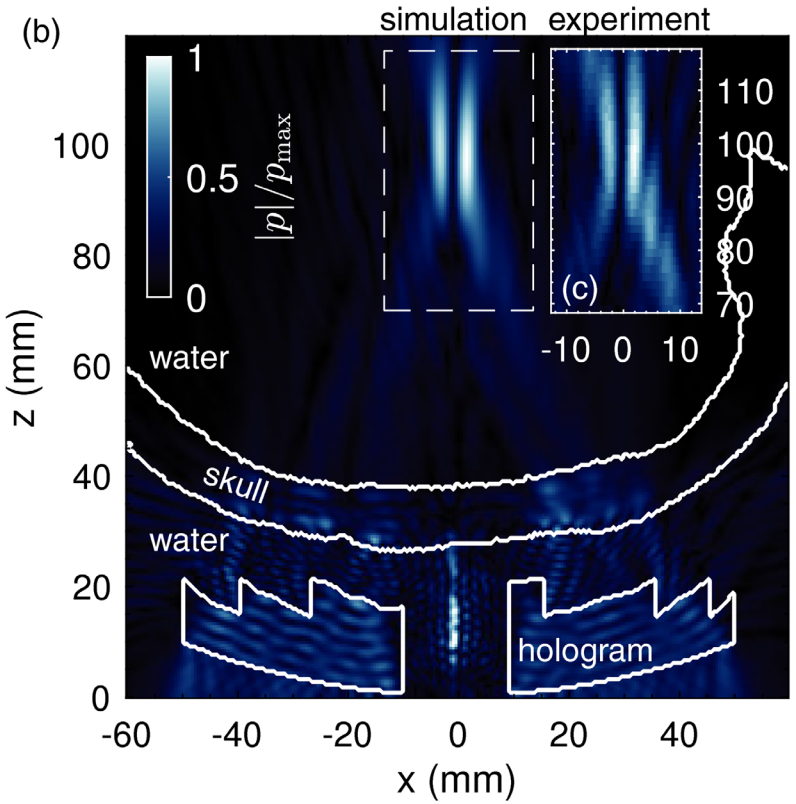
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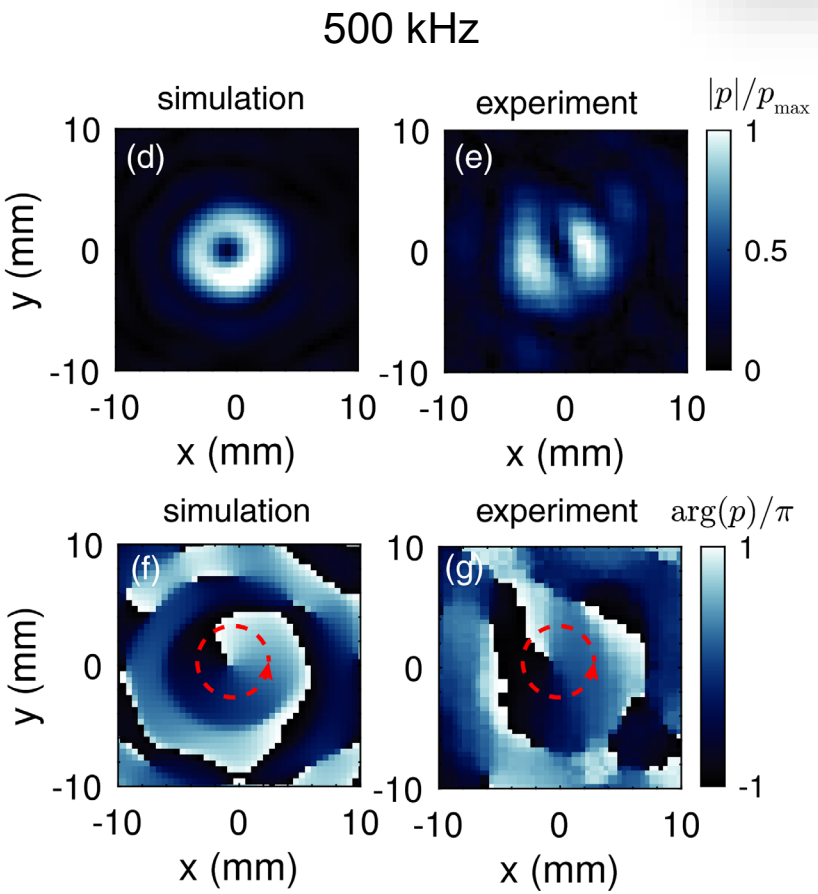


Aberration correction ex-vivo

- A phase dislocation is restored using a focused vortex beam





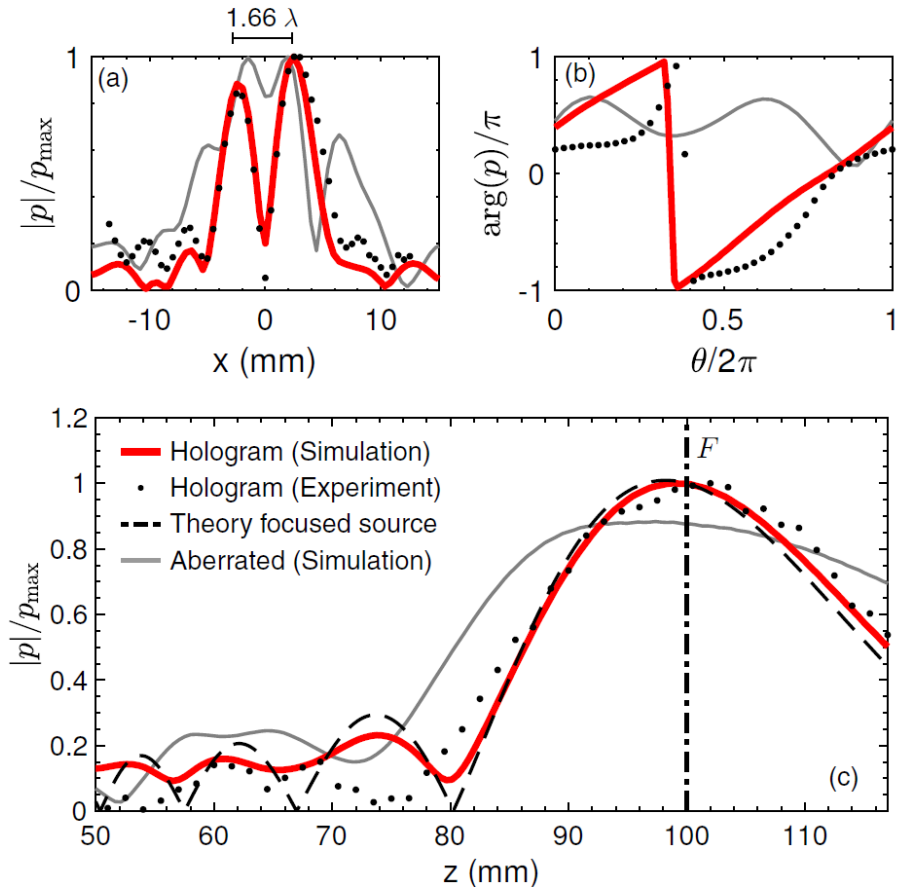


Jiménez-Gambín, et al. *Phys Rev Appl* 12 014016 (2019)

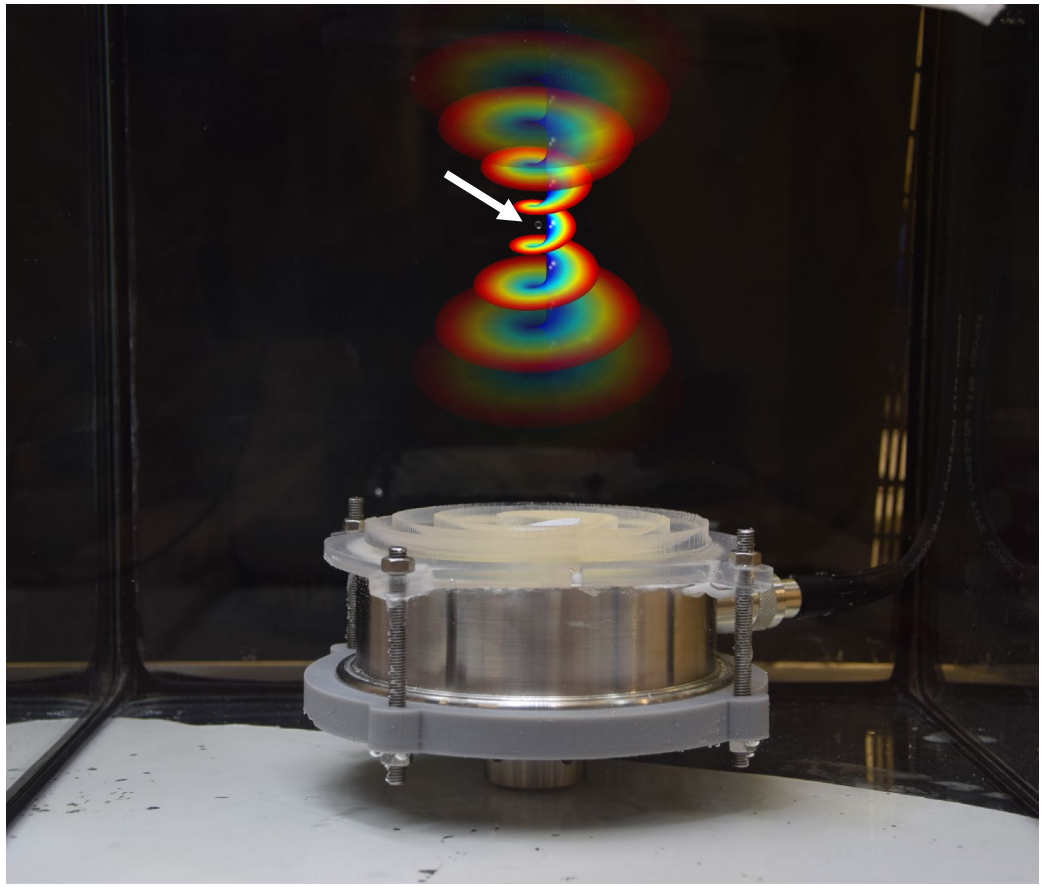
Acoustic vortices in the brain

Aberration correction

- Topological charge can be tuned



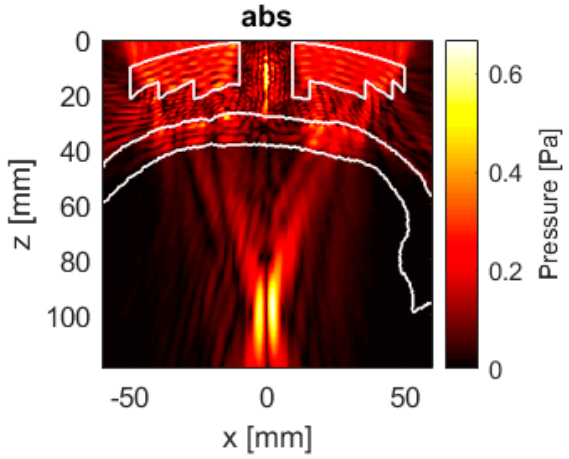
- Particle trapping: potential for clot manipulation

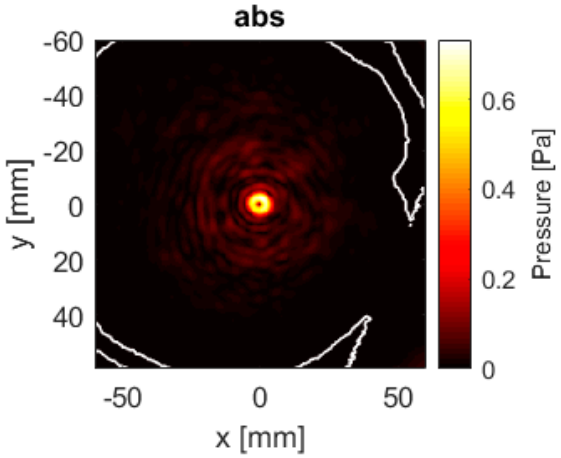


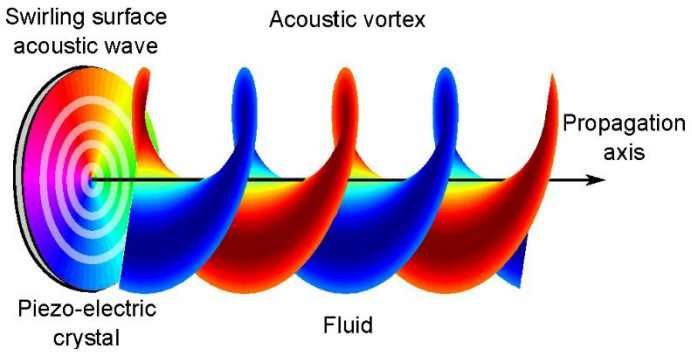
Jiménez-Gambín, et al. *Phys Rev Appl* 12 014016 (2019)

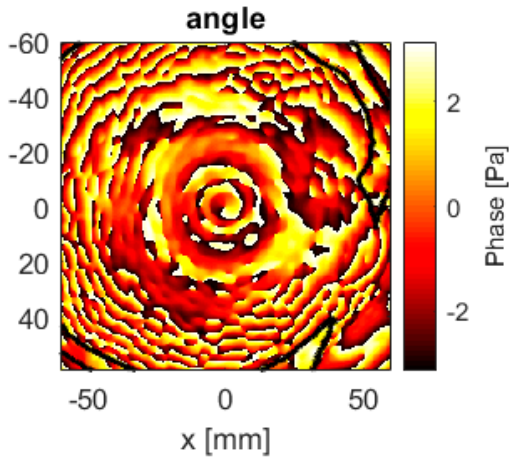
Vortex beams

Vortex focusing by holograms









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

Thermal holograms

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In collaboration with Jonathan Vappou, CNRS (France)



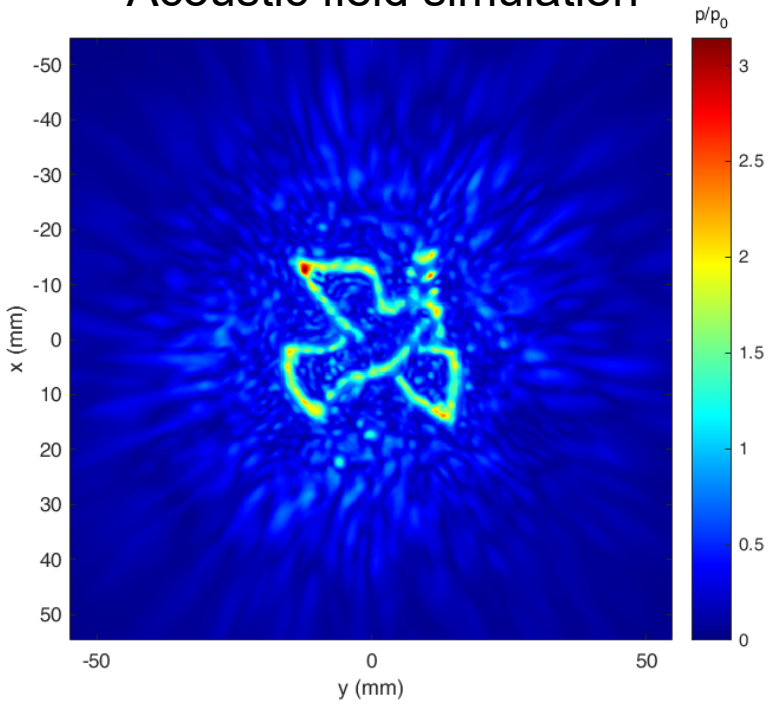
Thermal patterns for ultrasound hyperthermia

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

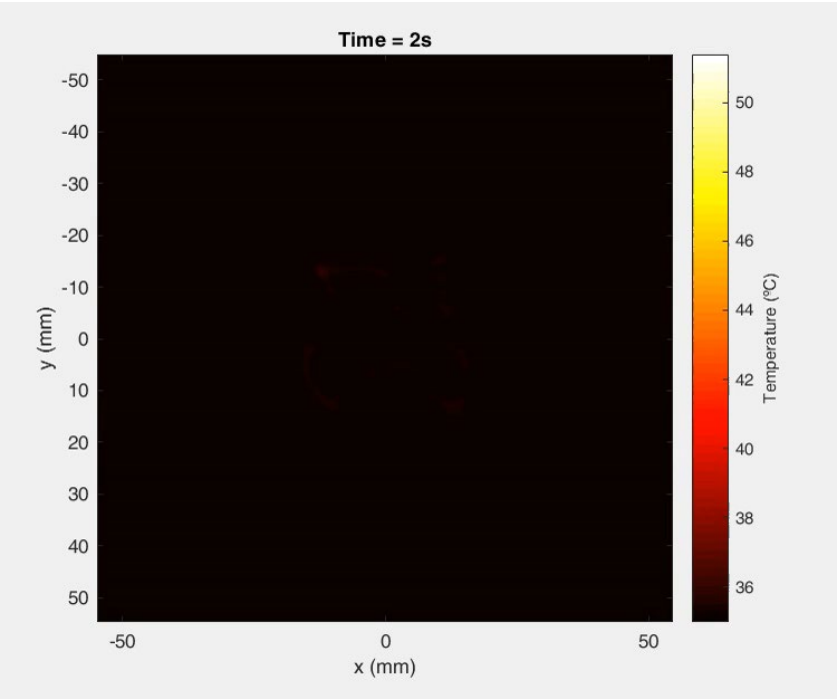
Image



Acoustic field simulation



Thermal simulation



D Andrés, at al. Applied Physics Letters, 120 (8), pp. 084102, (2022)

Thermal holograms

Instituto de Instrumentación para Imagen Molecular

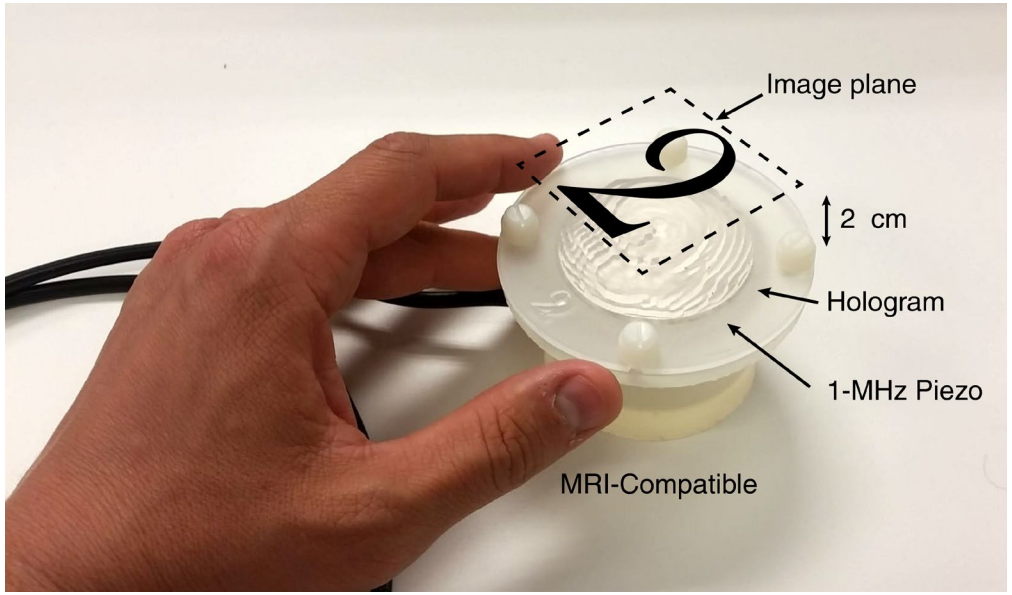


In collaboration with Jonathan Vappou, CNRS (France)

Thermal patterns for ultrasound hyperthermia

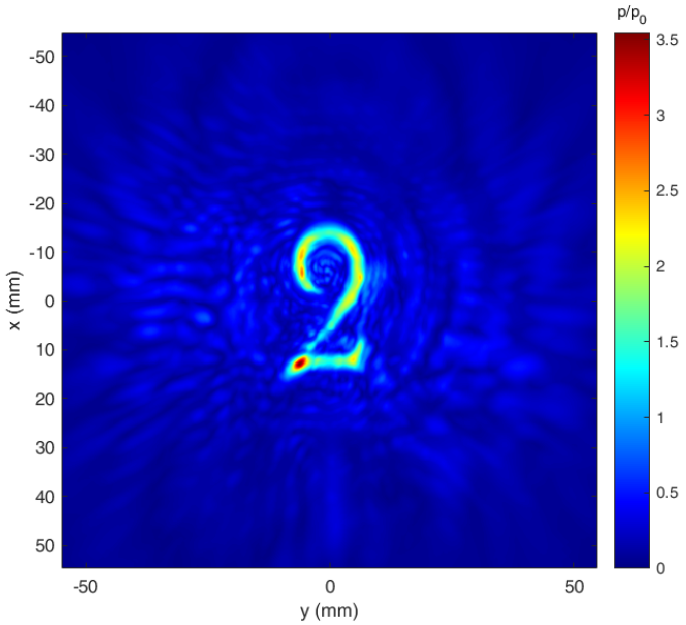
- Mild and local rise temperature
- Activate immune system
- Enhance drug administration
- Enhance chemotherapy

Experimental setup

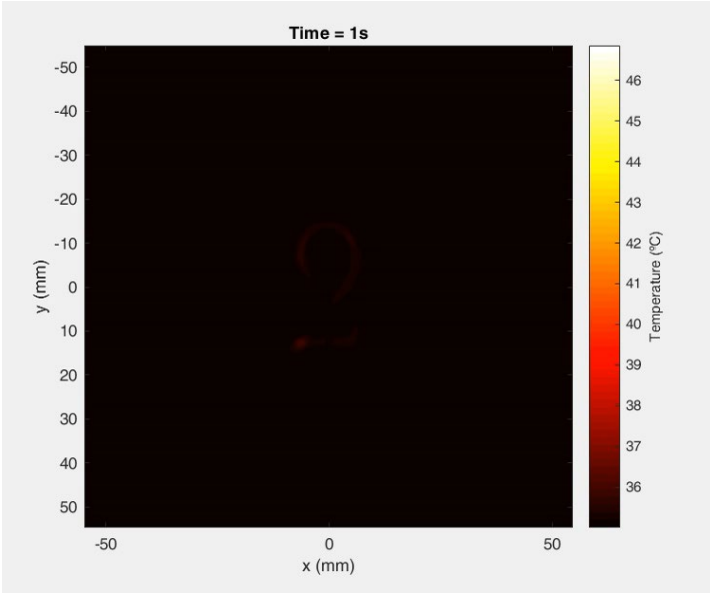


Thermal camera

Simulation (field)



Simulation (thermal)



D Andrés, at al. Applied Physics Letters, 120 (8), pp. 084102, (2022)

Thermal holograms

Instituto de Instrumentación para Imagen Molecular

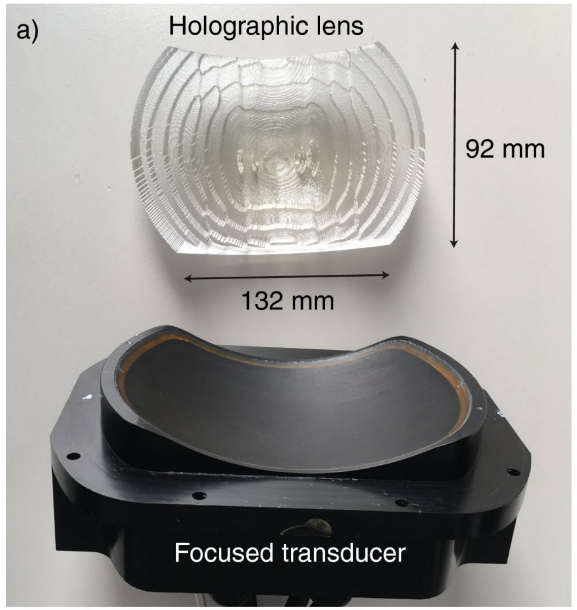
In collaboration with Jonathan Vappou, CNRS (France)



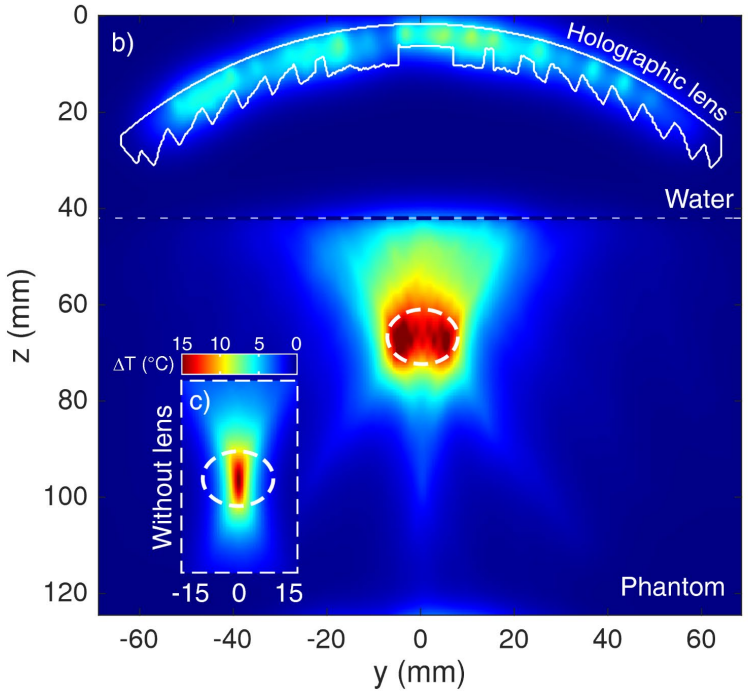
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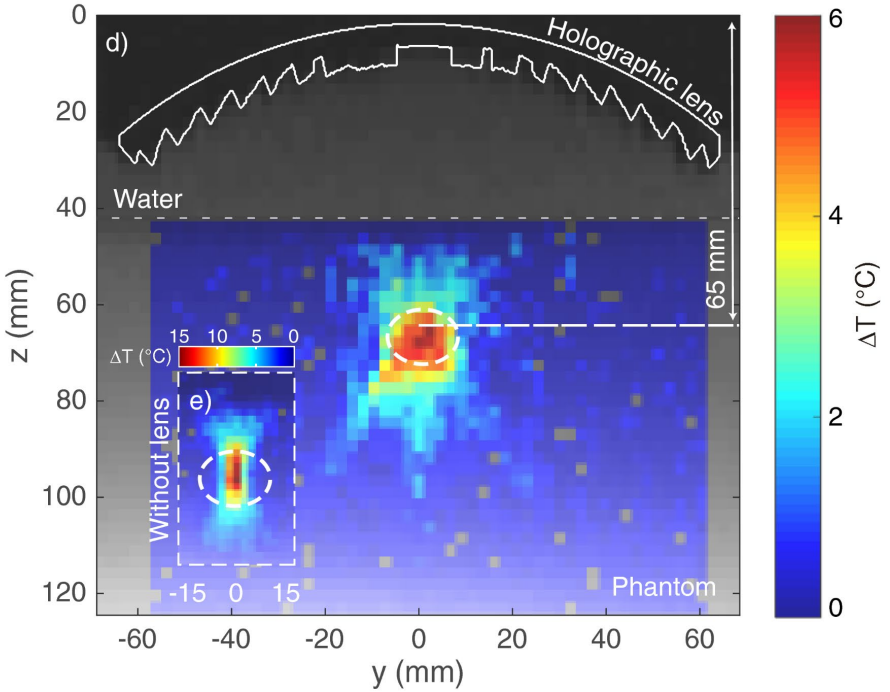
Experimental setup



Thermal simulation



1.5-Tesla MRI thermometry



D Andrés, at al. Applied Physics Letters, 120 (8), pp. 084102, (2022)

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**

Single element transducers → Phased-arrays systems → 3D Printed Lenses → Volumetric Holograms → Reconfigurable metasurfaces

Acknowledgments

Instituto de Instrumentation para Imagen Molecular

- Sergio Jimenez-Gambín (PhD, now in Columbia NYC)
- 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)
- Jonathan 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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FONDO EUROPEO DE DESARROLLO REGIONAL

"Una manera de hacer Europa"

UNIVERSITAT POLITÈCNICA DE VALÈNCIA

"Hear for Tomorrow". Hearing Conservation Association / Institute of Acoustics. Royal Academy of Engineering. 30th March 2022

Brain therapy using acoustic holograms

Noé Jiménez, PhD

JdC-I Postdoc, Instituto de Instrumentación para Imagen Molecular,
Universitat Politècnica de València / Consejo Superior de Investigaciones Científicas
(València, Spain)

Acoustic holograms for the brain

Semi-analytical methods: propagation in free media (water)

- Rayleigh-Sommerfeld integral:

$$p(\mathbf{r},\omega) = \frac{i\omega\rho_0}{2\pi}\int_S \frac{v_0(\mathbf{r}_0)\exp\left(-ik_0\left|\mathbf{r}-\mathbf{r}_0\right|\right)}{\left|\mathbf{r}-\mathbf{r}_0\right|}dS,$$

Simulation methods: propagation including the skull

- Pseudo-spectral time-domain simulation with *k*-space corrector (Treeby's *k*-wave package)

$$\begin{aligned}\frac{\partial\rho}{\partial t} &= -\rho_0\nabla\cdot\mathbf{u} - \mathbf{u}\cdot\nabla\rho_0,\\ \frac{\partial\mathbf{u}}{\partial t} &= -\frac{1}{\rho_0}\nabla p,\\ p &= c_0^2\left(\rho + \mathbf{d}\cdot\nabla\rho_0 - \mathrm{L}\rho\right),\end{aligned}$$

- Low numerical dispersion, explicit solver
- Soft-tissue absorption in the form: $\alpha(\omega) = \alpha_0\omega^\gamma$,
- Frequency power-law attenuation using the fractional Laplacian: $\mathrm{L} = \tau\frac{\partial}{\partial t}\left(-\nabla^2\right)^{\frac{\gamma}{2}-1} + \eta\left(-\nabla^2\right)^{\frac{\gamma+1}{2}-1}$,

Acoustic holograms

Hologram design

- Record field at the holographic surface

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

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

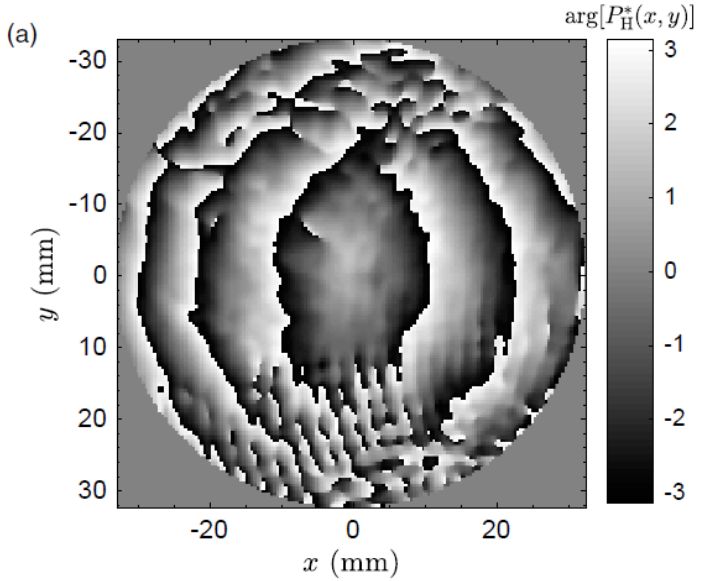
$$T(x, y) = \frac{2Ze^{-ik_0(d-h(x,y))}}{2Z\cos(k_L h(x, y)) + i(Z^2 + 1)\sin(k_L h(x, y))},$$

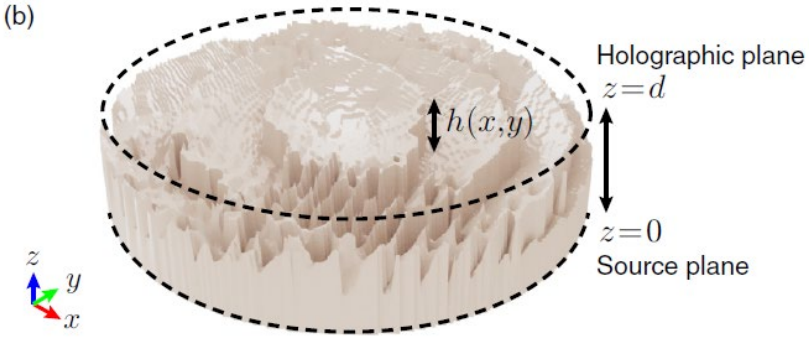
- Find the heigh function $h(x, y)$, producing

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

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

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



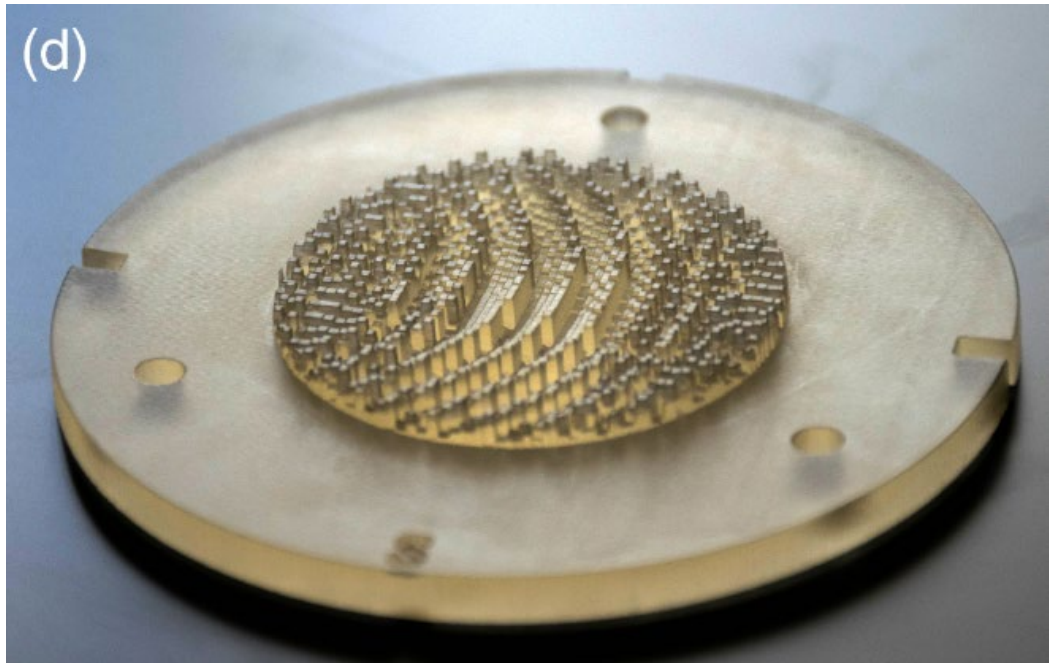


Jiménez-Gambín, et al. Phys Rev Appl 12 014016 (2019)

Acoustic holograms for the brain

Lens manufacturing

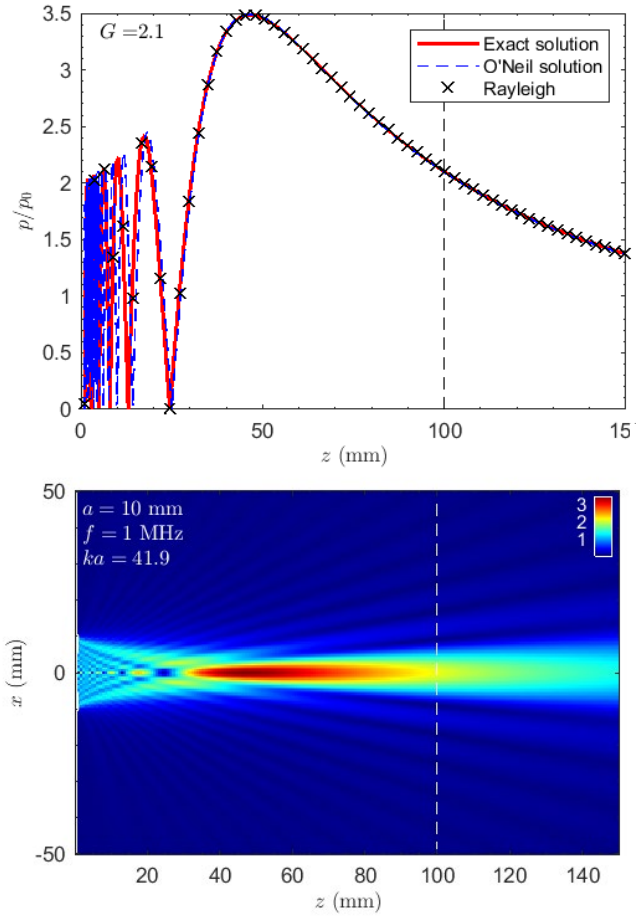
- Printing by stereo-lithography
- Objet30 (Stratasys), up to 10 µm
- Form3 (Formlabs), up to 25 µm



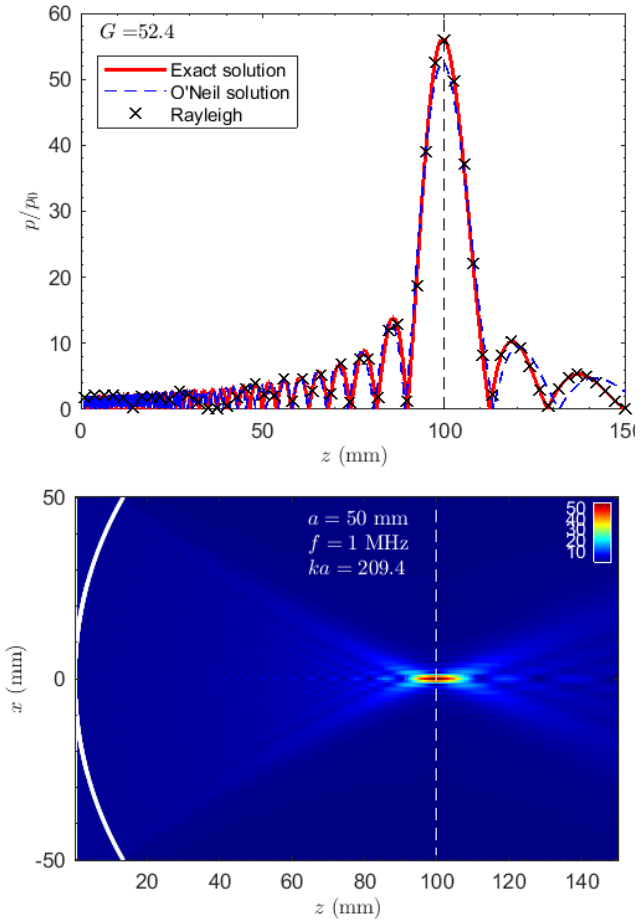
Focused ultrasound

Focused ultrasound allows to increase and localize mechanical energy

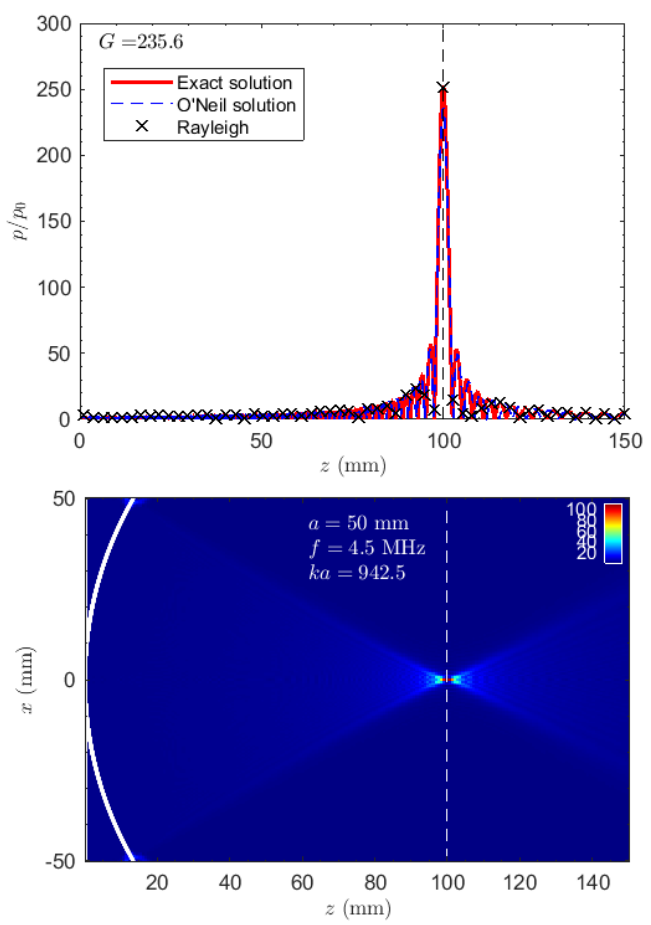
Gain = 2



Gain = 50



Gain = 200



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

- Thermal thalamotomy: ablation of the thalamus (VIM, ventralis intermedius)
- **Invasive**: Radiofrequency through a surgically inserted electrode in the thalamus.
- **Noninvasive,** using HIFU: 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)

