# Shaping therapeutical acoustic images using acoustic holograms

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Colloquium 610 Emerging Topics In Acoustic And Mechanical Metamaterials 25 April – 27 April 2022, Castellón de la Plana, Spain

# 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

## Effects of ultrasound on matter

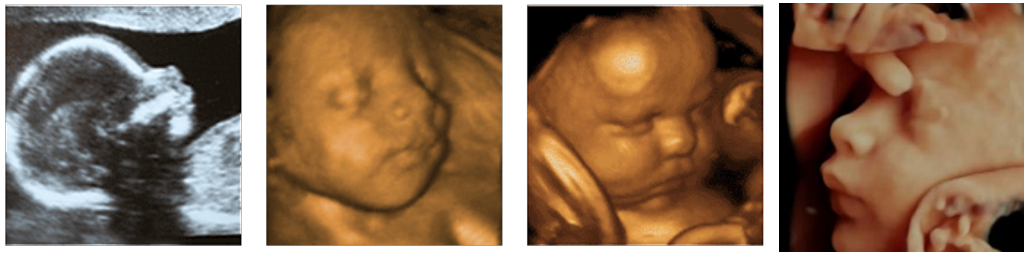
a) Thermal Effects

- Temperature rise
- Sonoluminescence

b) Mechanical Effects

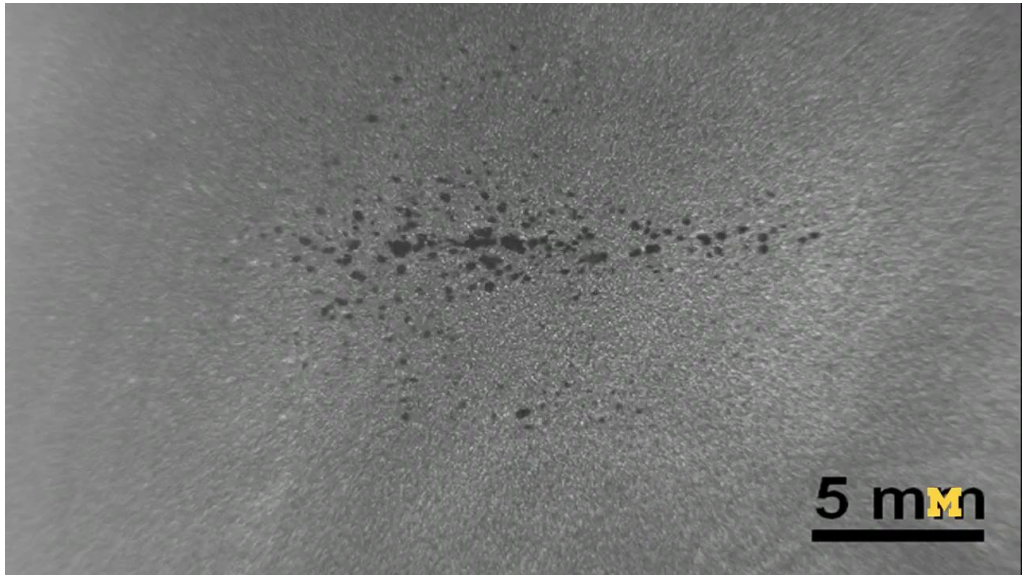
- Radiation force
- Flow (in fluids) and deformations (in solids)
- Cavitation (inertial and non-inertial)

Low amplitude ultrasound



GE Healthcare (2019)

High amplitude ultrasound




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

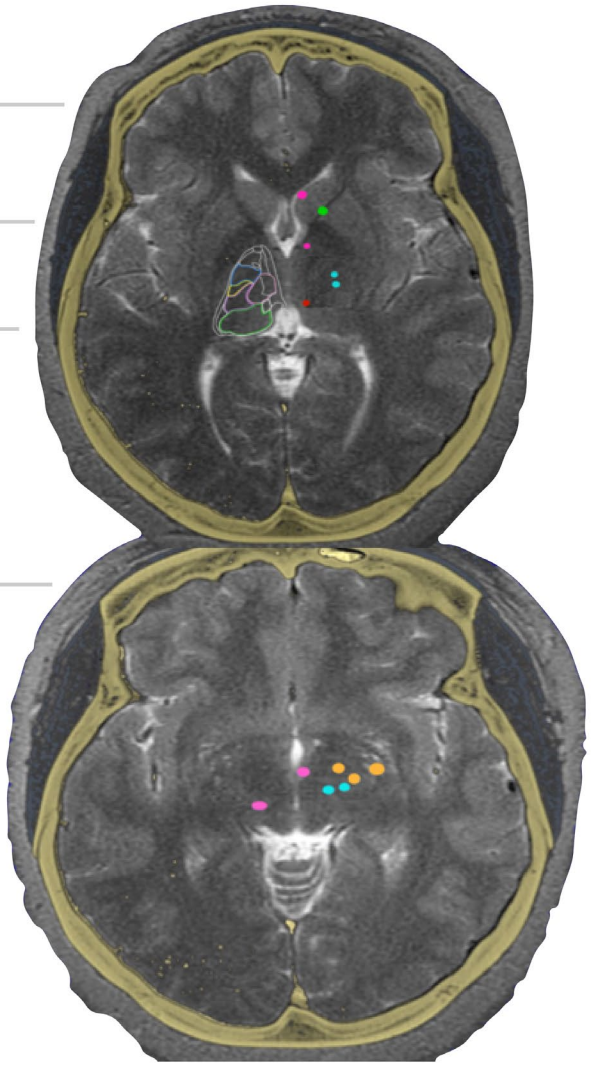
## Other derived effects

- 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
- Particle / tissue trapping
- Many other specific effects …

**Some examples for neurological diseases…**

# Thermal tissue ablation

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

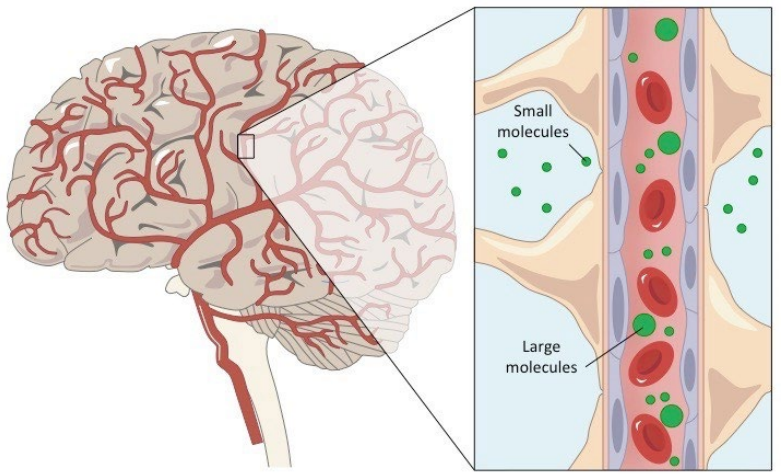
https://www.fusfoundation.org/diseases-and-conditions/neurological

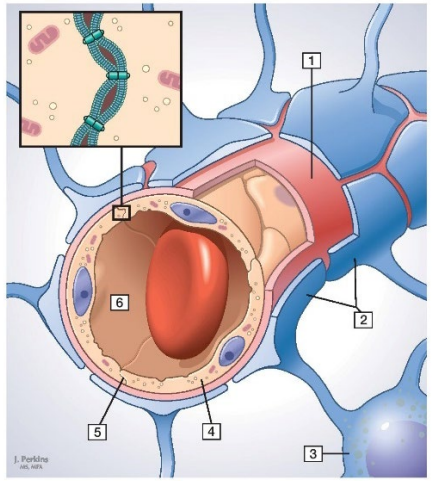
# Localized drugs and gene delivery

## 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



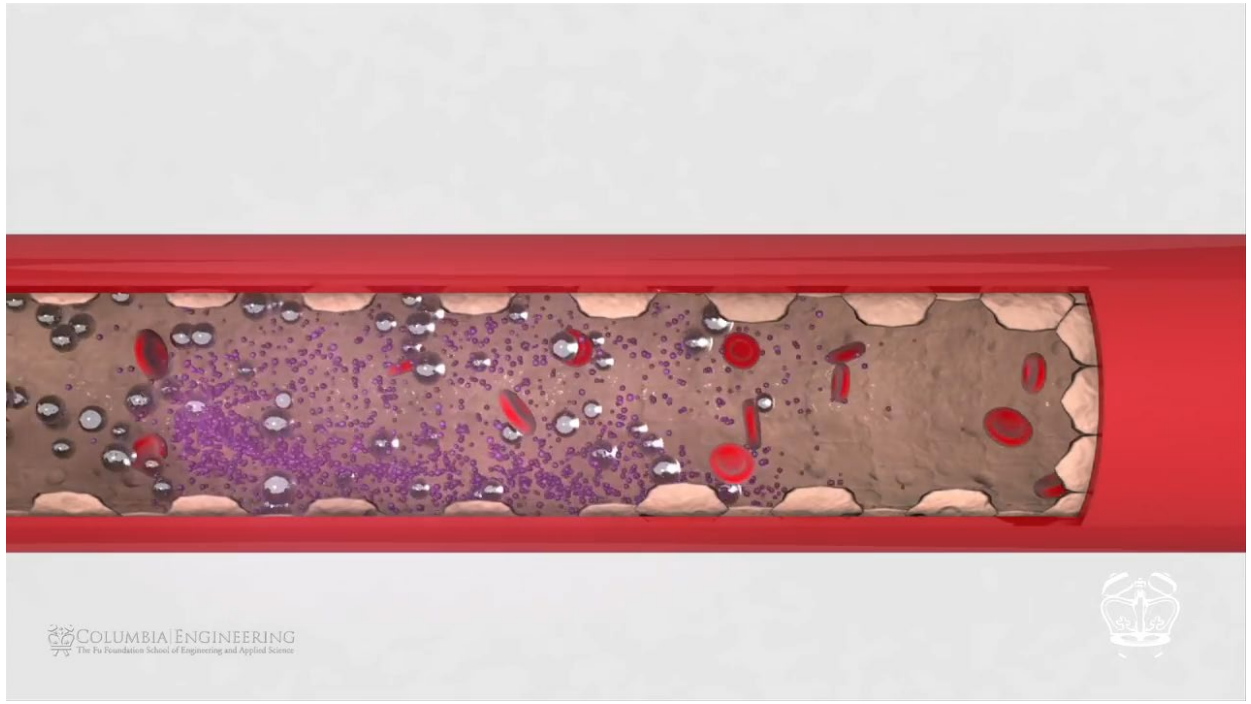




### Treatment

- 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....



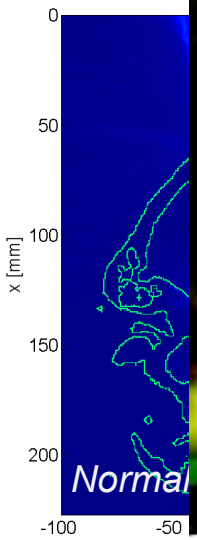

Courtesy of Columbia University


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

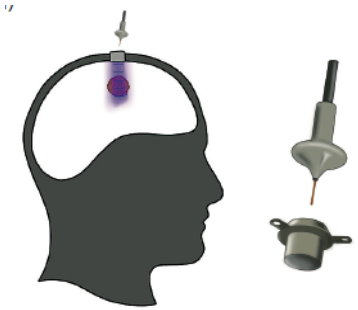
# Focus

**Transc**

- Refrac
- Absorp
- Reflec
- Scatte



# Transcraneal ultrasound therapy systems



**Intracranial implants**

- Implanted in a burr hole (diagnostic biopsy or post tumor resection glioblastoma)
- Invasive
- Poor focusing
- Fixed focus



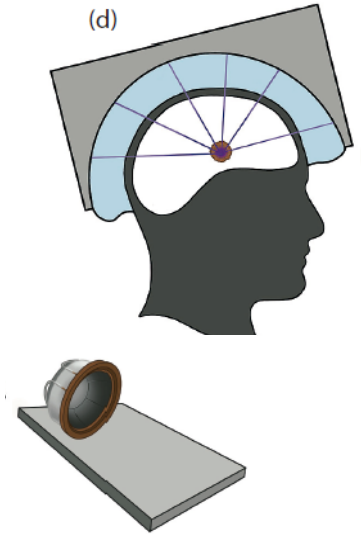
**Single element transducer**

- Simple, cheap
- No aberration correction
- Uncontrolled focusing
- Focus change on steering



**Phased array**

- Skull aberrations mitigated
- Focal steering
- Limited steering : diffraction lobes
- Moderately expensive




- **Magnetic resonance-guided focused ultrasound (MRgFUS)**
- Skull aberrations mitigated
- Focal steering
- MRI guided: thermometry
- Limited steering: diffraction lobes
- Expensive

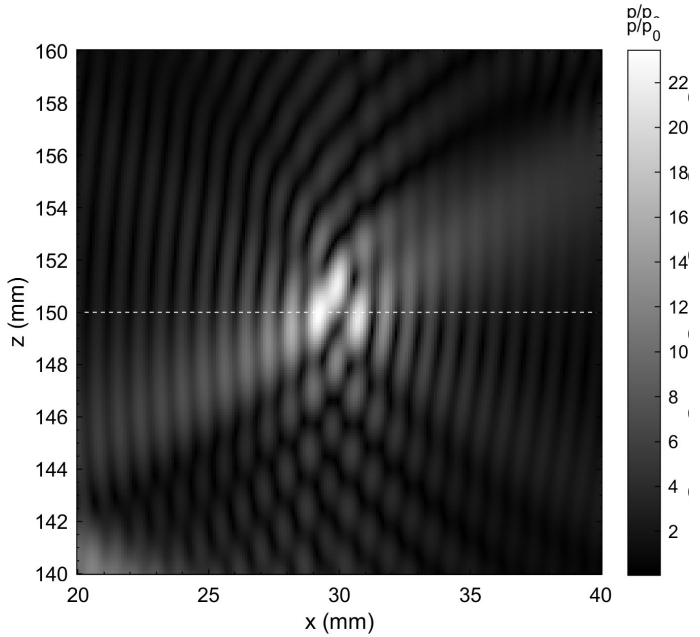
# Focusing challenges

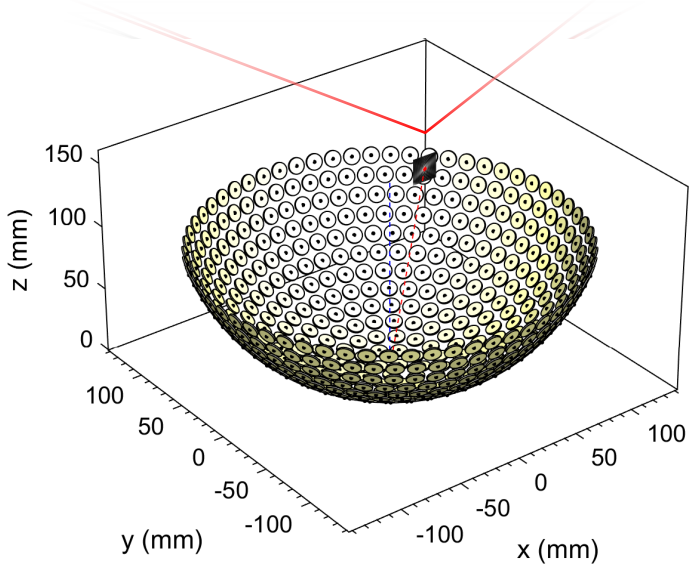
## Focusing

- 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



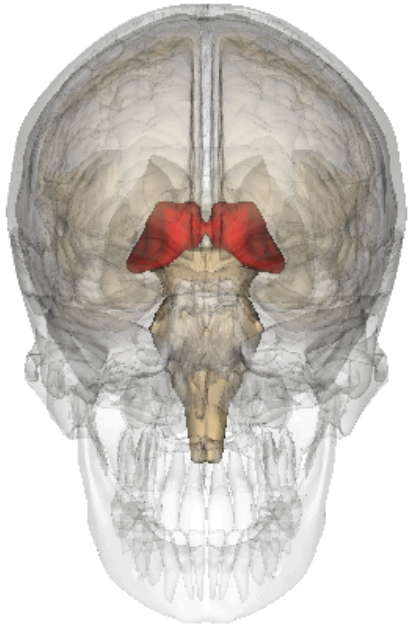



# Focusing challenges

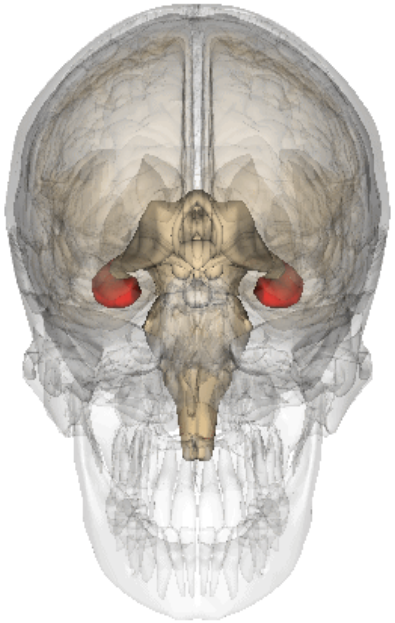
**Complex target morphology**

- Can we adapt the beam to the therapeutical target?

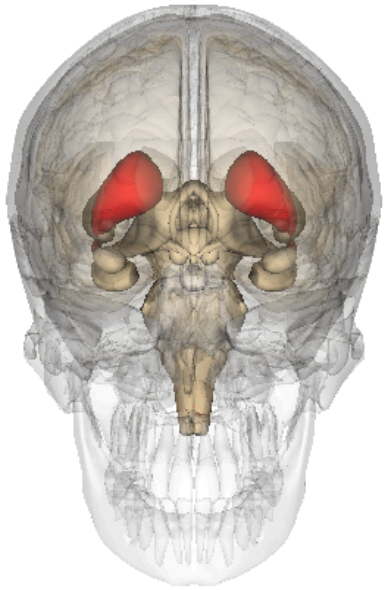
Thalamic nuclei



Hippocampus

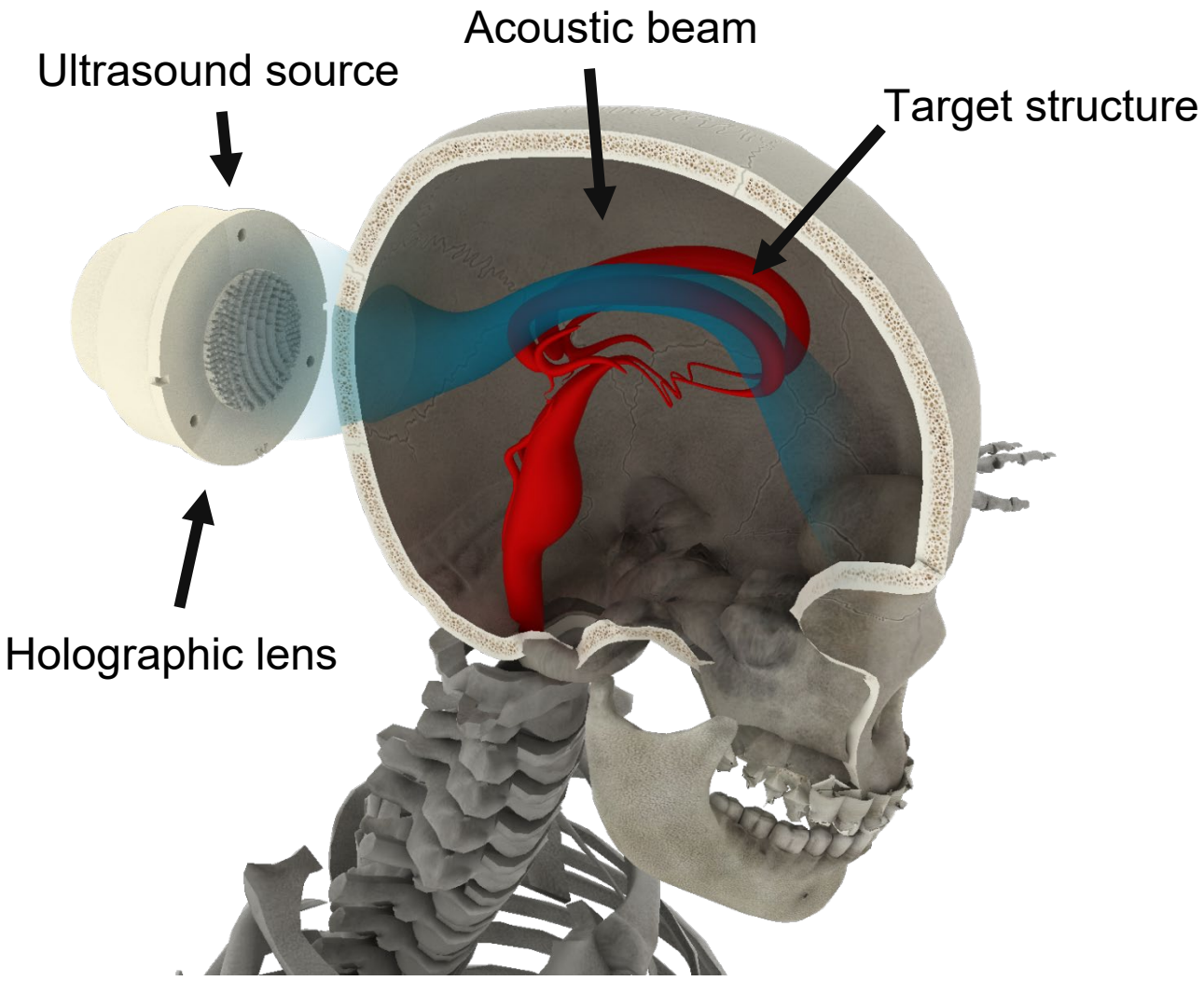


Caudate nucleus



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

# Acoustic holograms




**Acoustic hologram**

- Encode a time-reversed (phased-conjugated) wavefront in a 3D-printed holograms

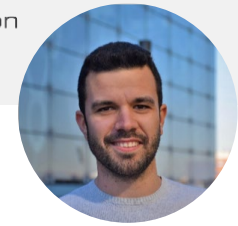
**Benefits**

- Correct skull aberrations
- Generate arbitrary acoustic images
- Low-cost system
- MRI compatible

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

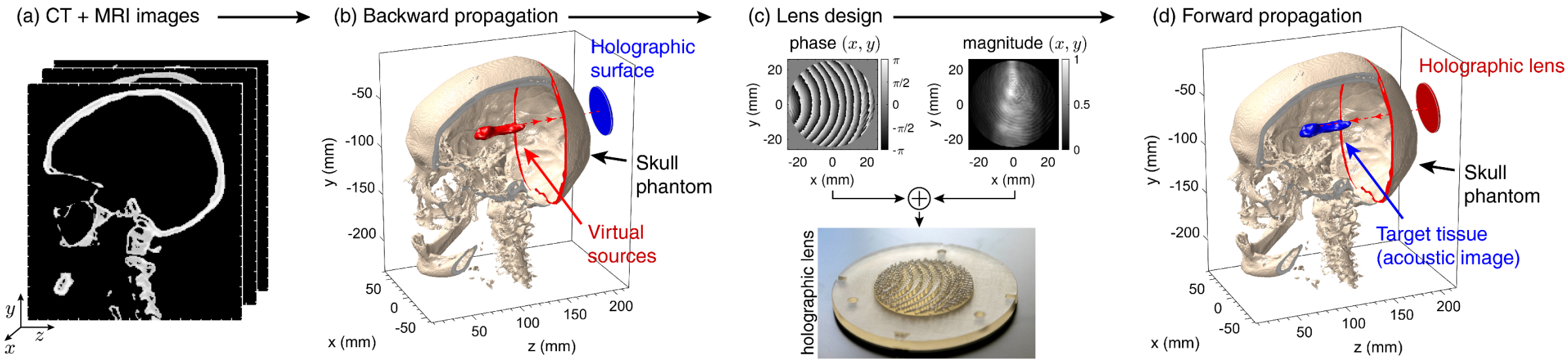
# Acoustic holograms

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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)

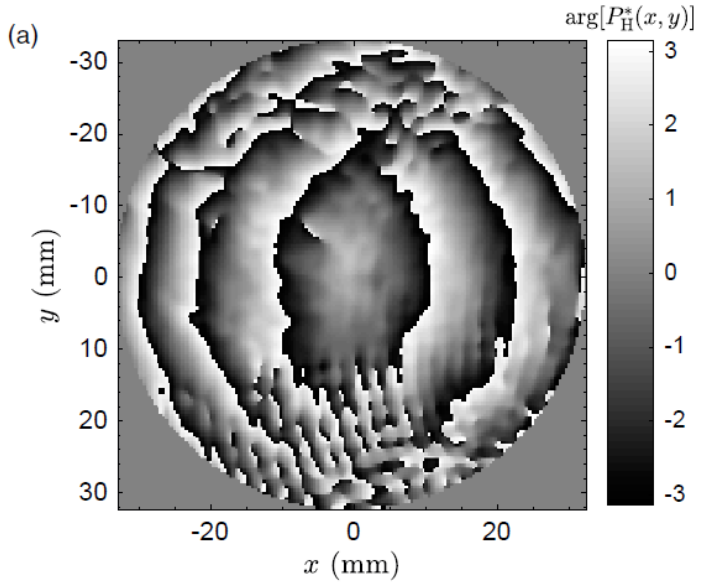
$$T(x, y) = \frac{2Ze^{-ik_0(d-h(x,y))}}{2Z\cos(k_L h(x, y)) + i(Z^2 + 1)\sin(k_L h(x, y))},$$

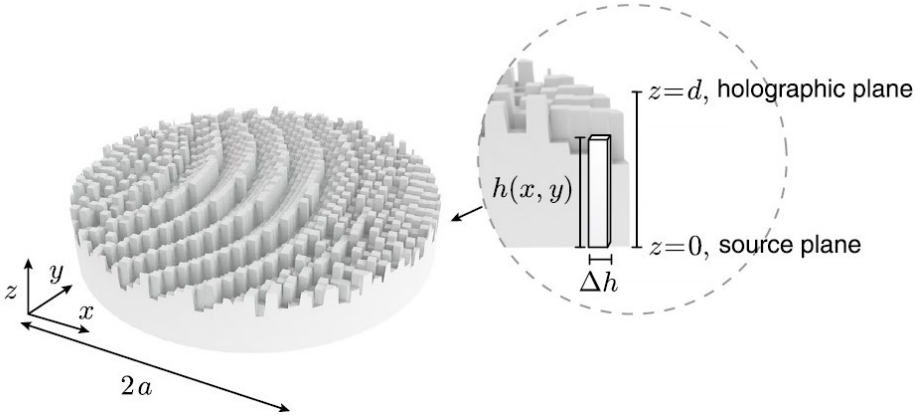
- Find the heigh function $h(x, y)$, producing

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

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)

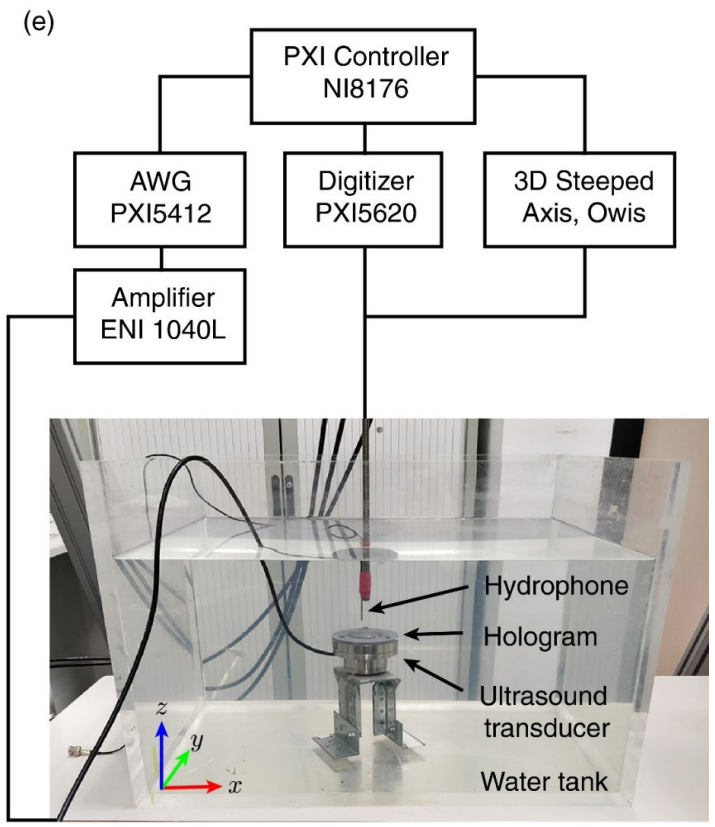
# Acoustic holograms for the brain

## Experimental setup

- Ultrasound measurements in water-tank
- 3D, 5 µm resolution steeped Axis
- Several transducers
- Frequency: 1.1 MHz (1.4 mm) to 0,5 MHz
- Aperture: 50 mm (36 wavelengths)
- Flat and 100 mm focused.

## Phantom / exvivo / invivo

- 3D-printed skull using PLA
- Real skulls
- In-vivo experiments (mice)









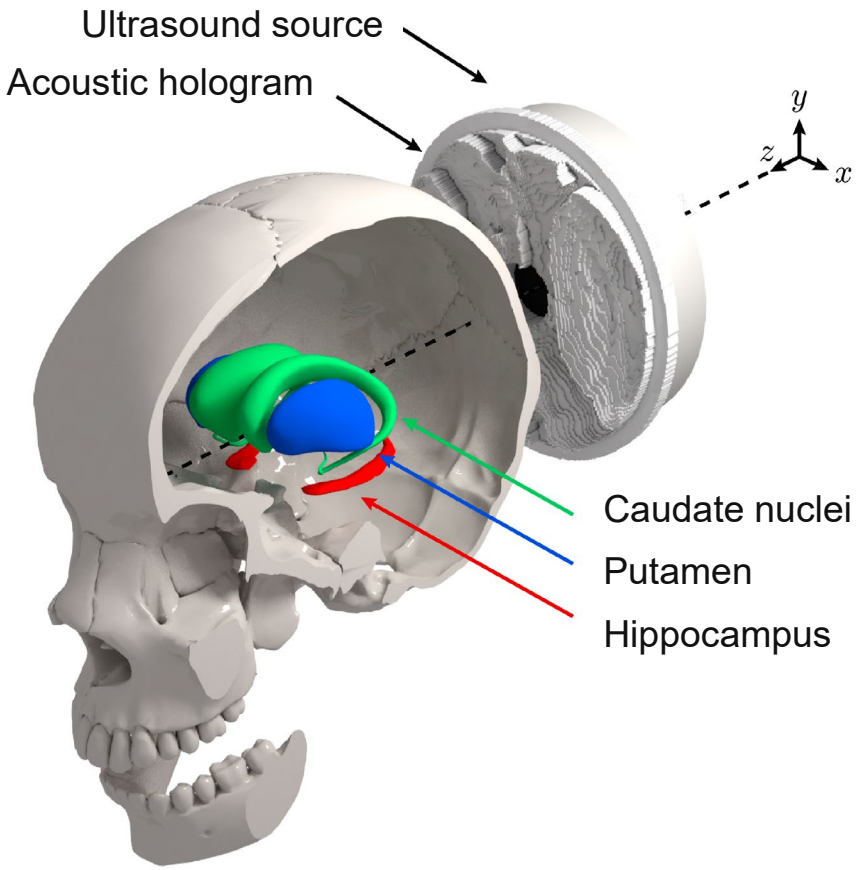

# Acoustic holograms

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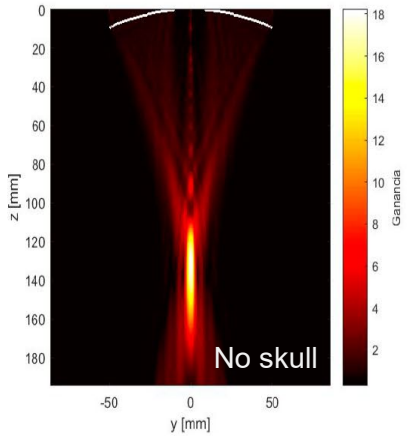


## Bilateral focusing

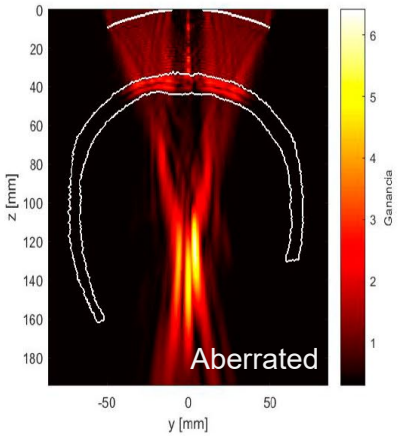
- Targeting at complex bilateral shapes



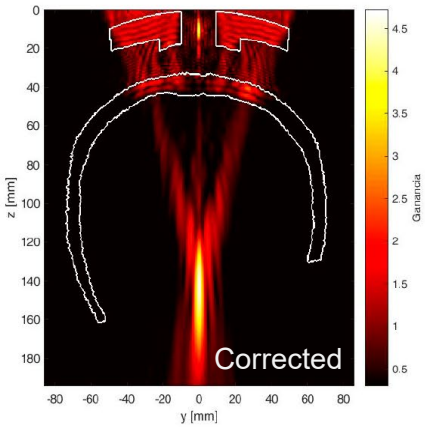

FUS transducer (500 kHz)



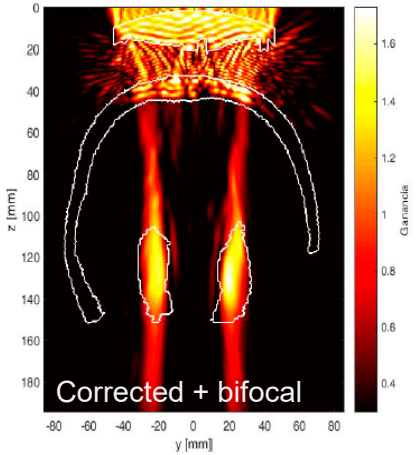

FUS transducer + skull



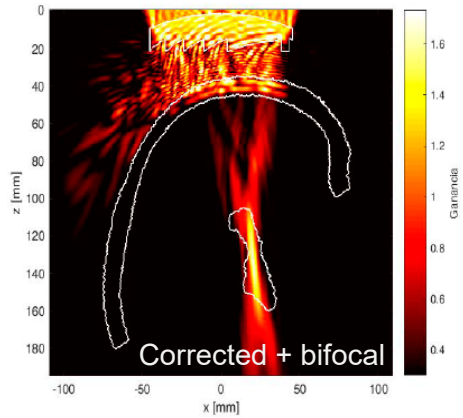

Hologram + skull




Bilateral focusing at hippocampus (coronal)



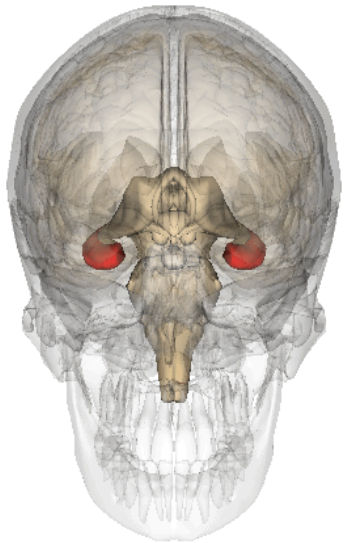

Bilateral focusing at hippocampus (sagittal)

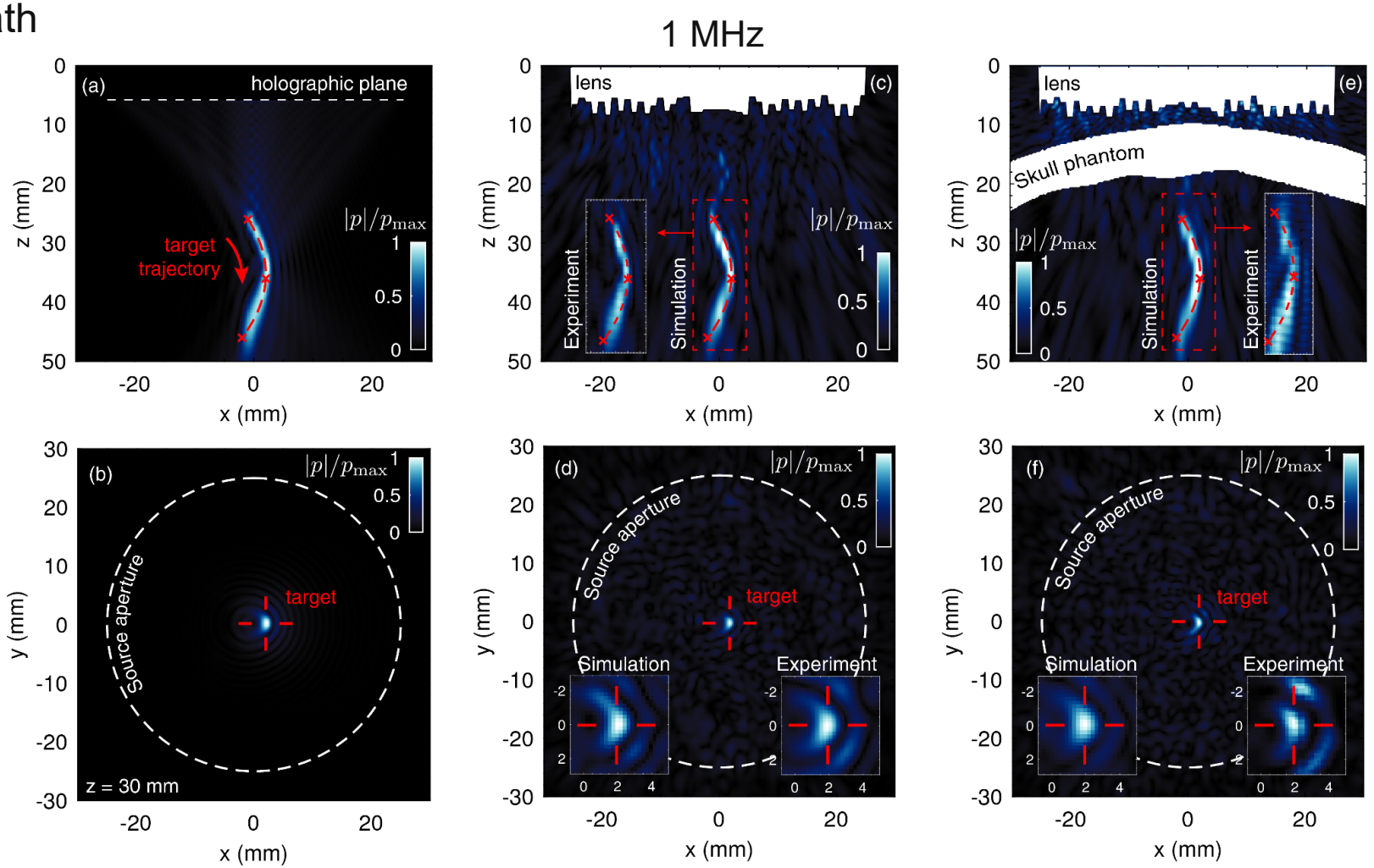


# Acoustic holograms

## 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

## Using the temporal window

- Low thermal dose and deep-brain focusing



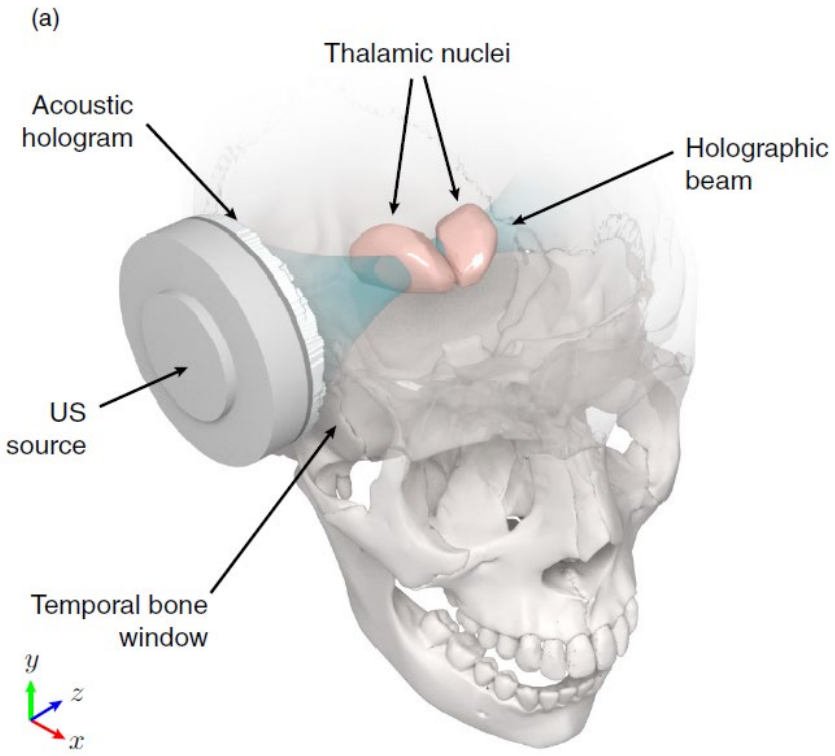
# Acoustic holograms

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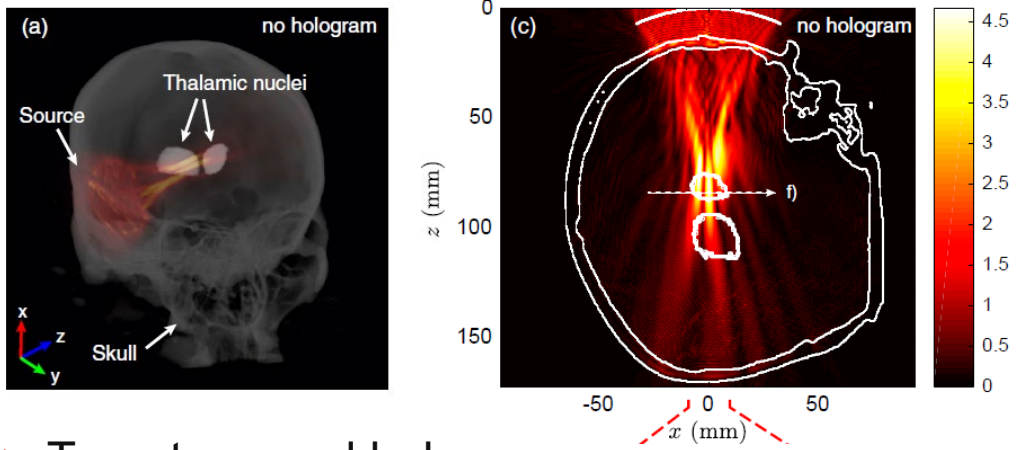


## Using the temporal window

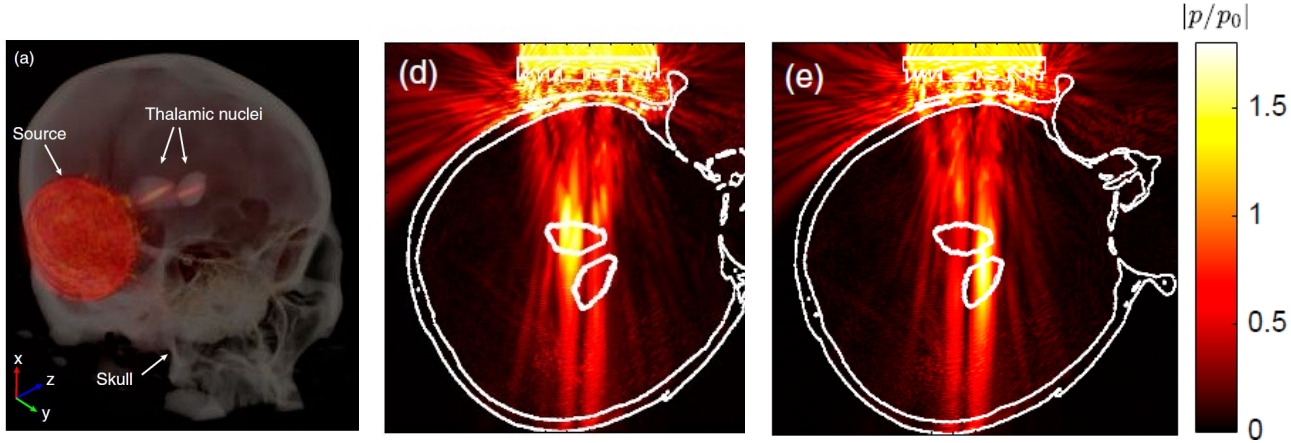
- Low thermal dose and deep-brain focusing




- Standard focused transducer (650 kHz)

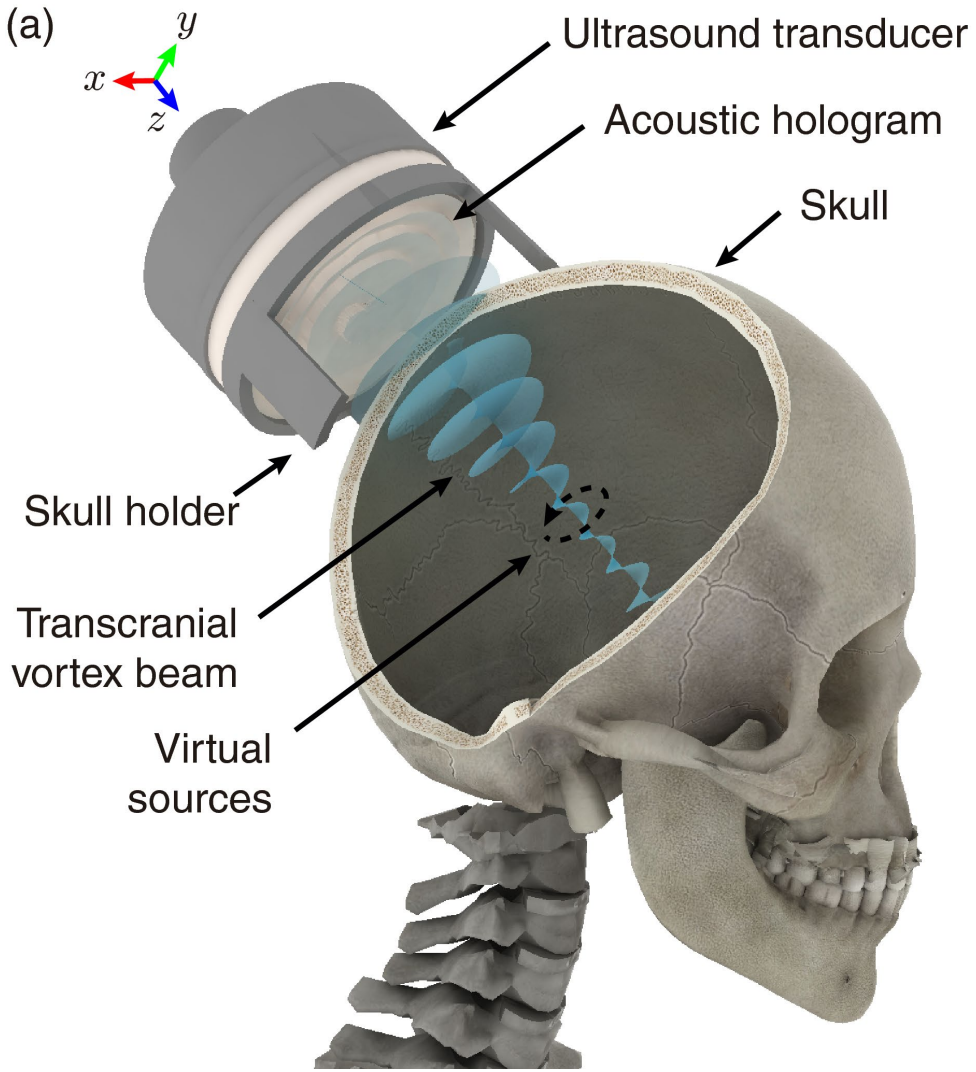


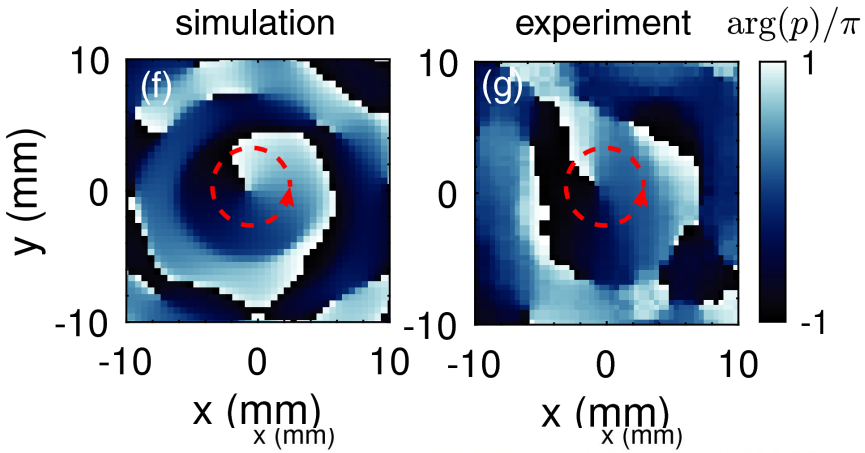

- Transtemporal hologram

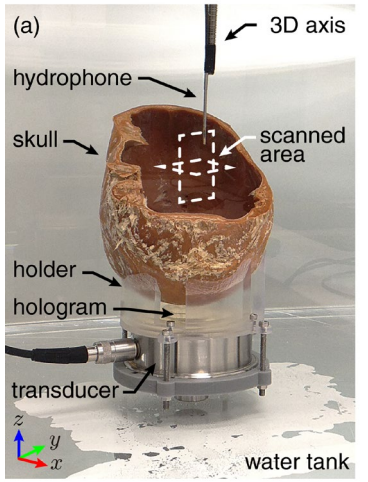



Diana Andrés, et al. *Ultrasound in Medicine & Biology* 48 (5) 872-886 (2022)

# Focusing acoustic vortices through the skull





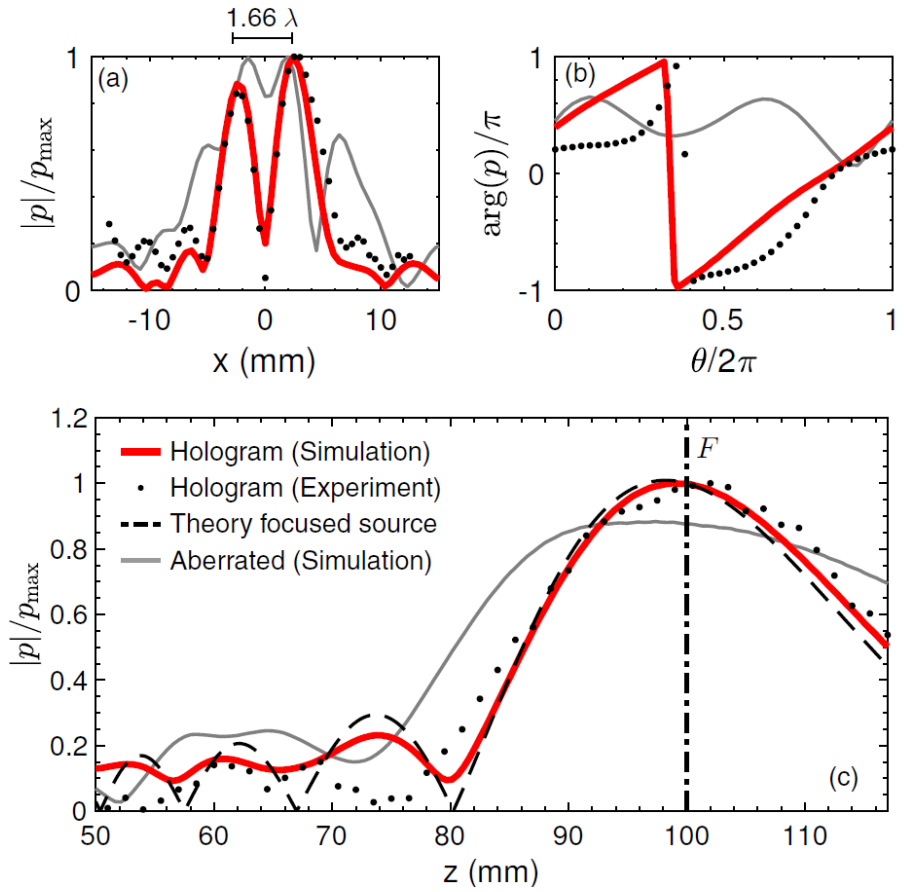


Jiménez-Gambín, et al. *Phys Rev Appl* 12 014016 (2019)

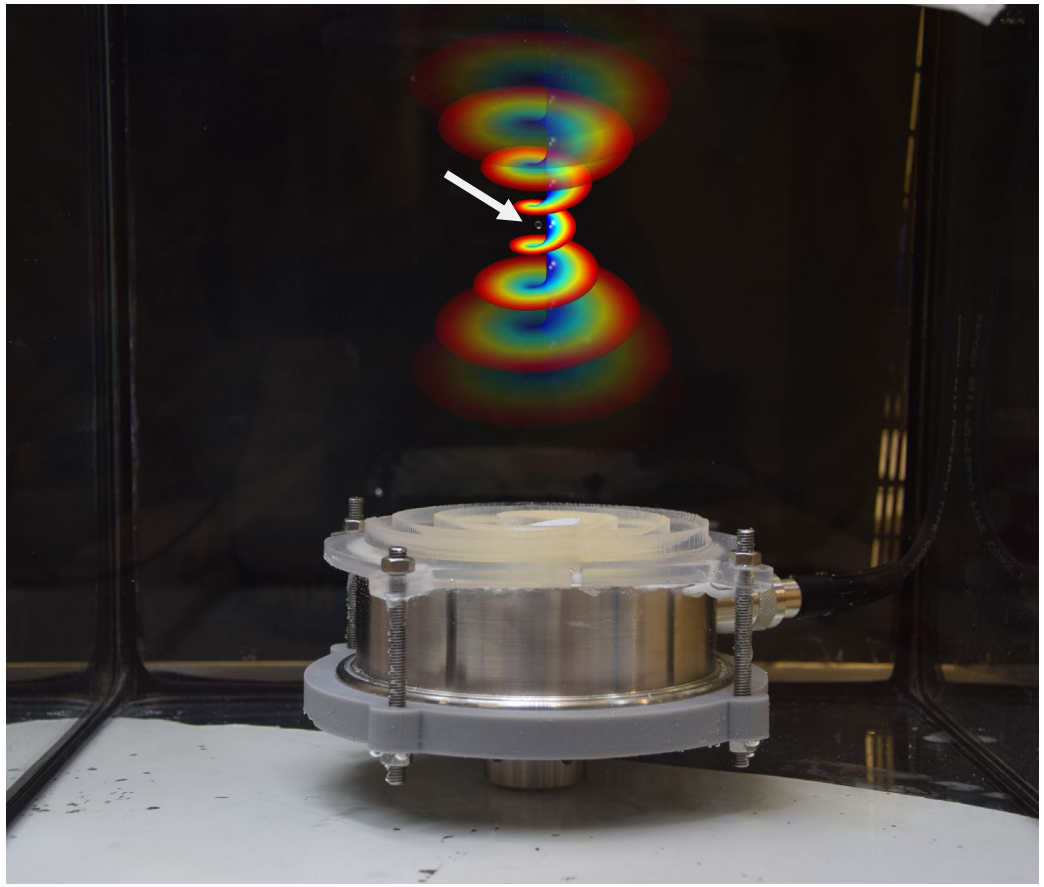
# Focusing acoustic vortices through the skull

## Topological charge can be tuned

- Aberration correction




- Particle trapping: potential for clot manipulation



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

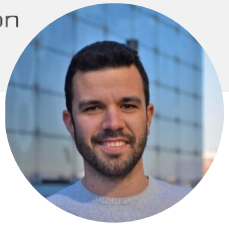
# Focusing acoustic vortices through the skull

## Vortex focusing by holograms

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

# In-vivo validation for BBBO

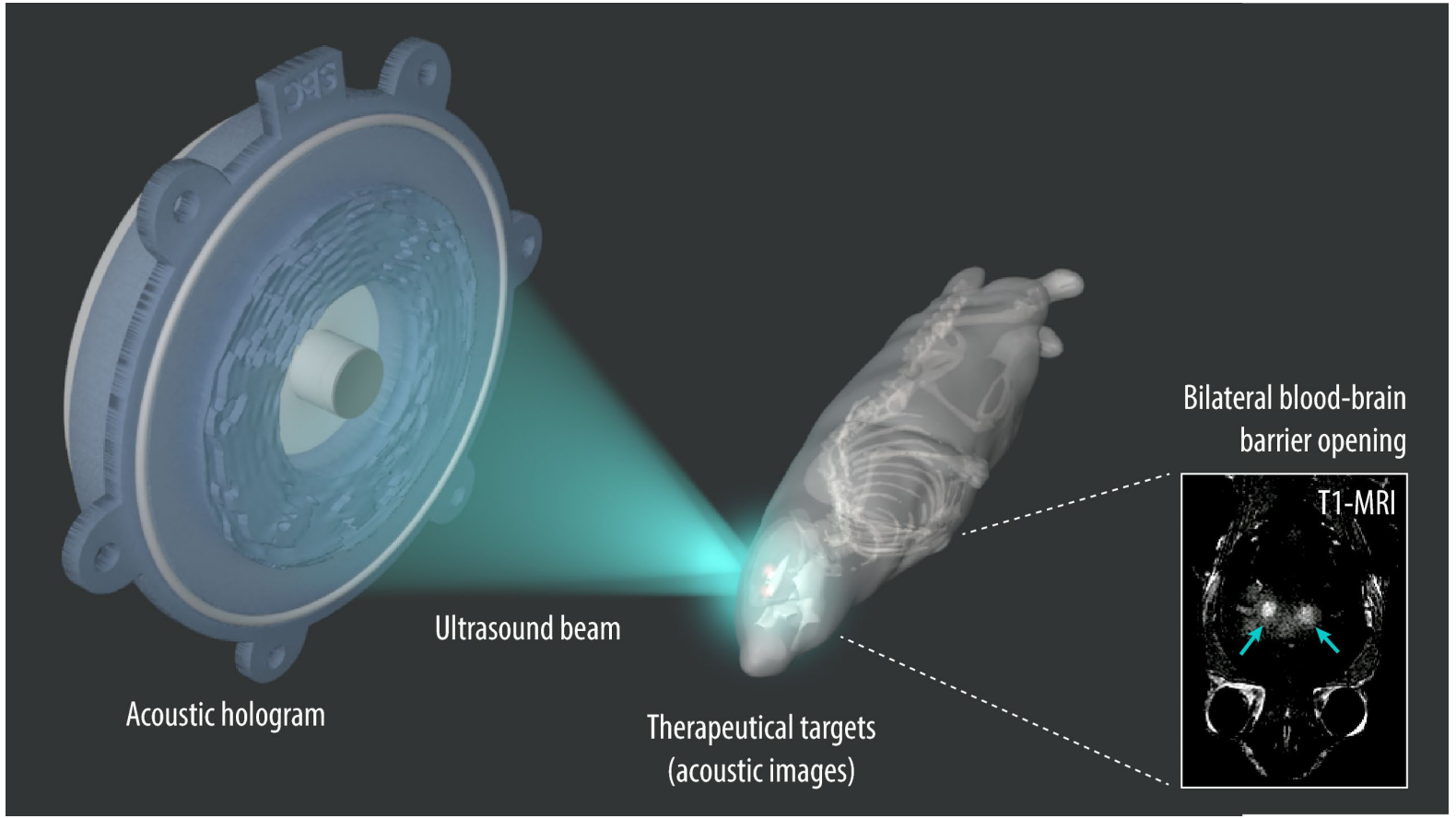
i3M Instituto de Instrumentación para Imagen Molecular



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

## Bilateral blood-brain barrier opening

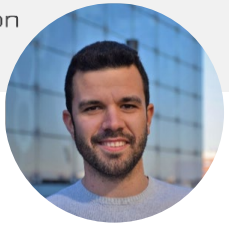
- First in-vivo application of acoustic holograms




Jiménez-Gambín, et al. IEEE Transactions on Biomedical Engineering 69 (4) 2022
(featured at the cover May 2022)

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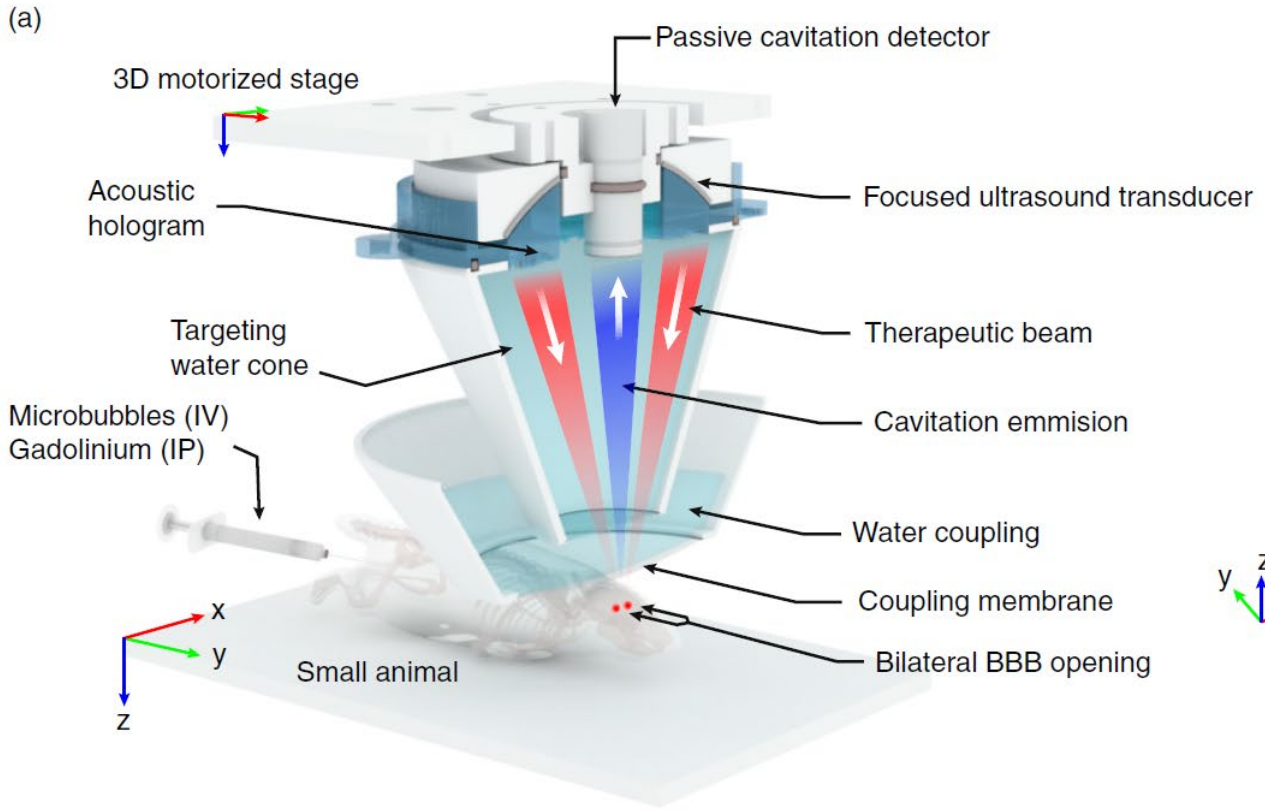
Instituto de Instrumentación para Imagen Molecular

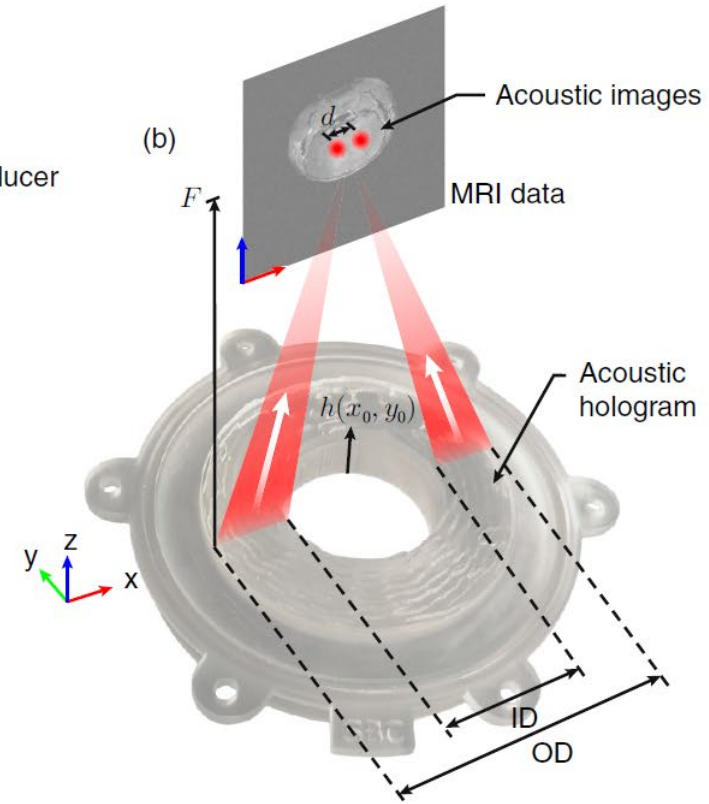


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## Bilateral blood-brain barrier opening

- First in-vivo application of acoustic holograms

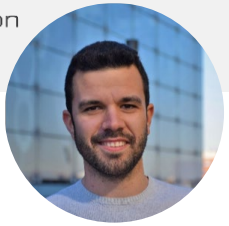



Jiménez-Gambín, et al. IEEE Transactions on Biomedical Engineering 69 (4) 2022

# In-vivo validation for BBBO

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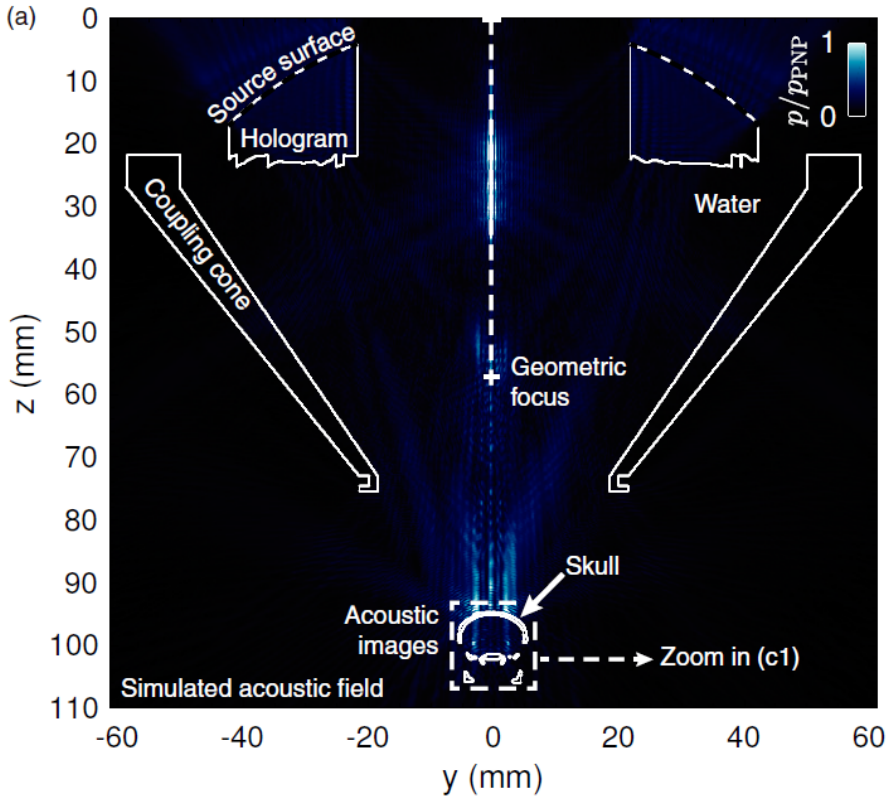


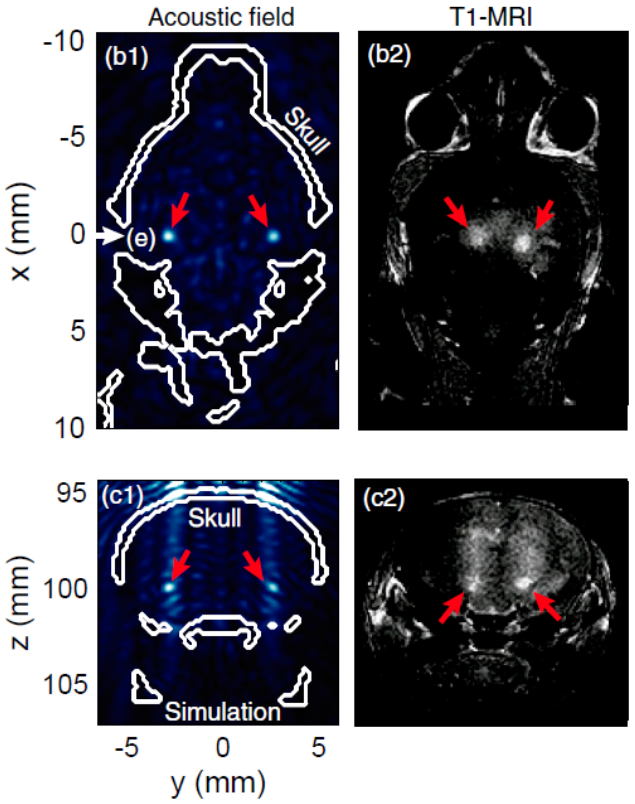
In collaboration with E.E. Konofagou, Columbia University (NYC, USA)

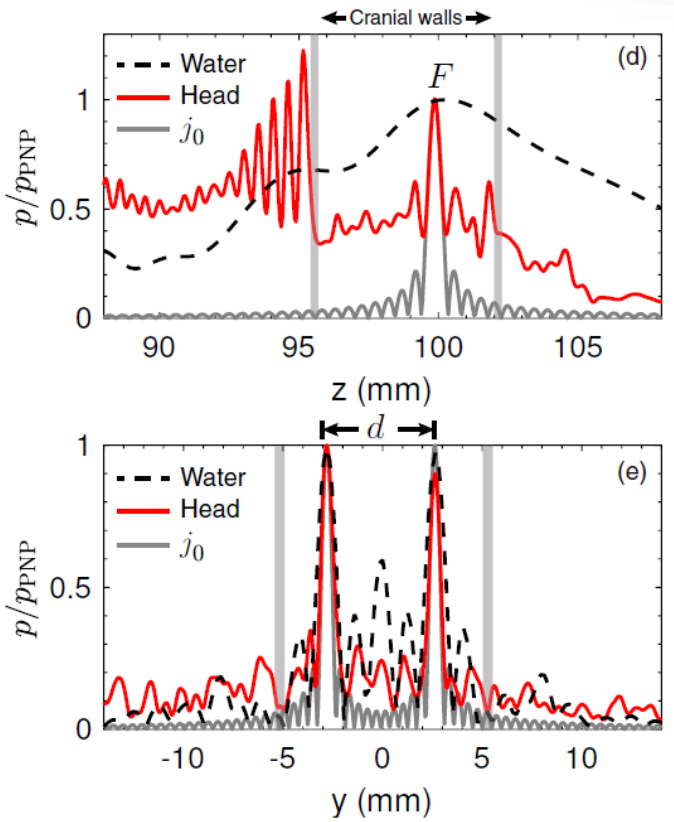
## Bilateral blood-brain barrier opening

- First in-vivo application of acoustic holograms

1.6 MHz




Jiménez-Gambín, et al. IEEE Transactions on Biomedical Engineering 69 (4) 2022

# Thermal holograms

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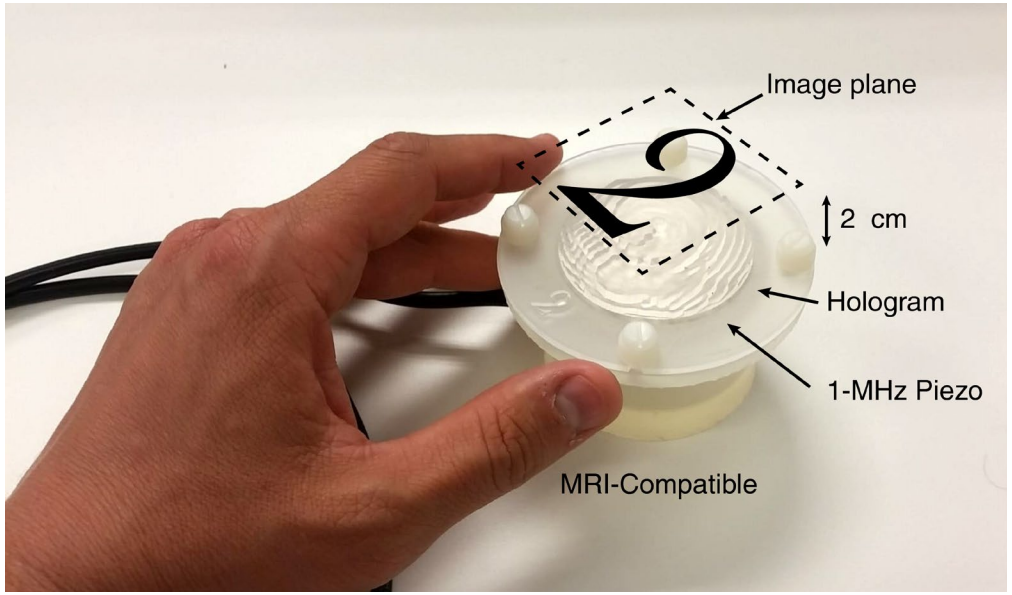


In collaboration with Jonathan Vappou, CNRS (France)

## Thermal patterns for ultrasound hyperthermia

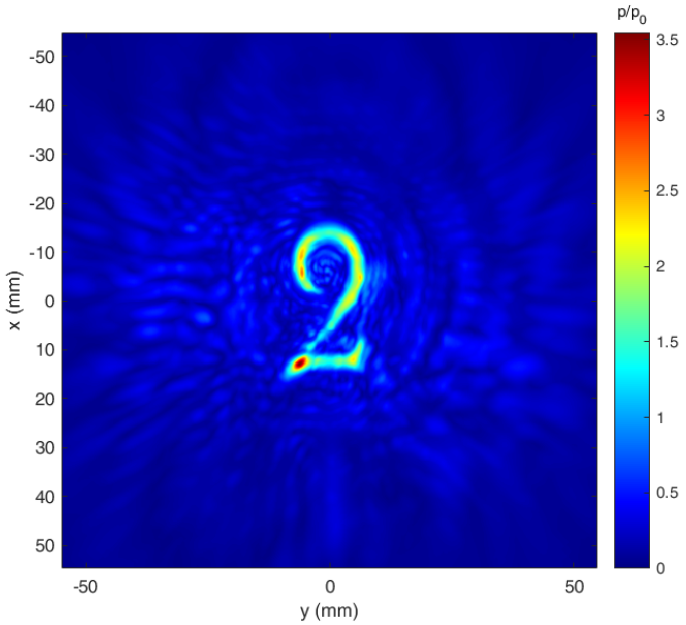
- Mild and local rise temperature
- Activate immune system
- Enhance drug administration
- Enhance chemotherapy

Experimental setup

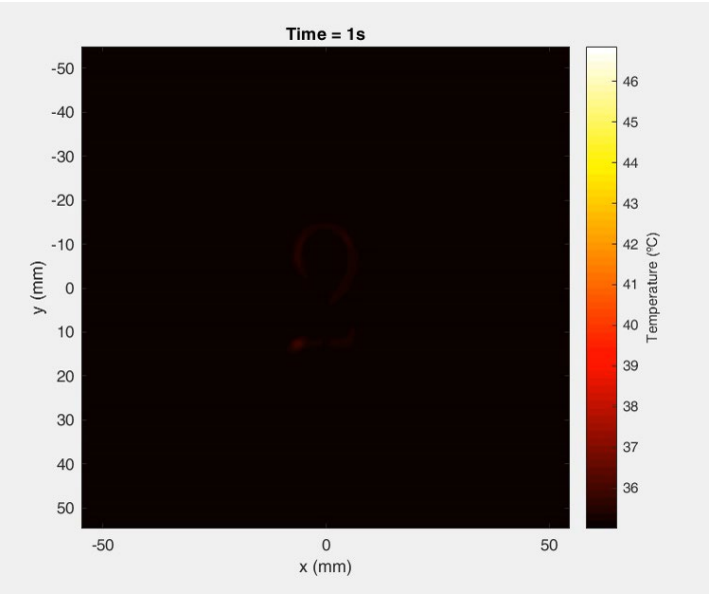



Thermal camera

Simulation (field)




Simulation (thermal)




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

# Thermal holograms

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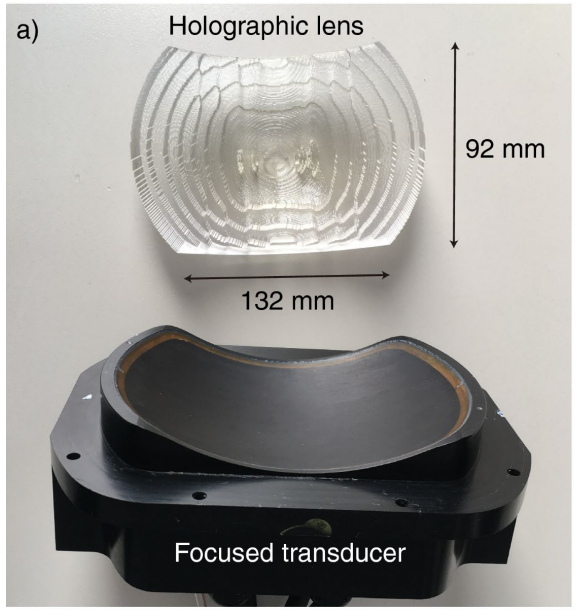
In collaboration with Jonathan Vappou, CNRS (France)



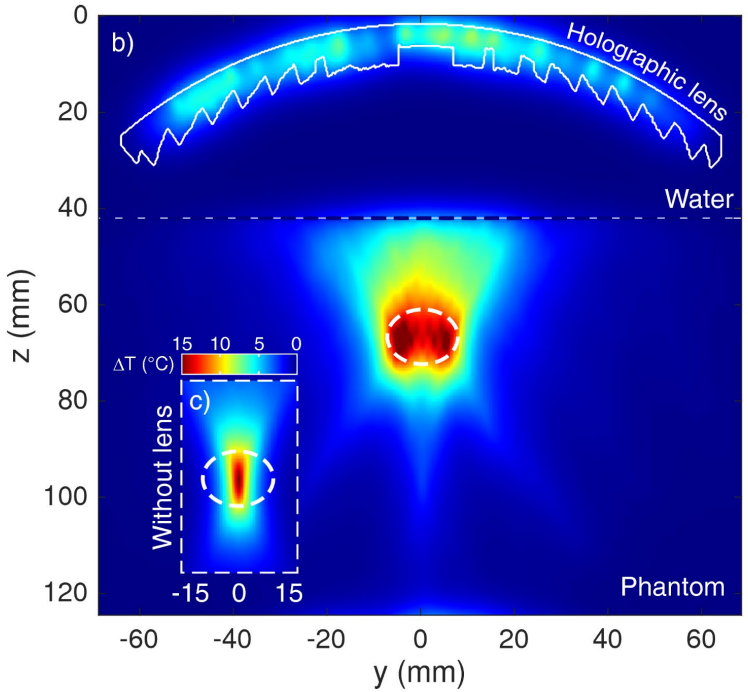
## Thermal patterns for ultrasound hyperthermia

- Mild and local rise temperature
- Activate immune system
- Enhance drug administration such as chemotherapy
- Enhance radiotherapy: invitro tested on human glioma spheroids (viability < %10)

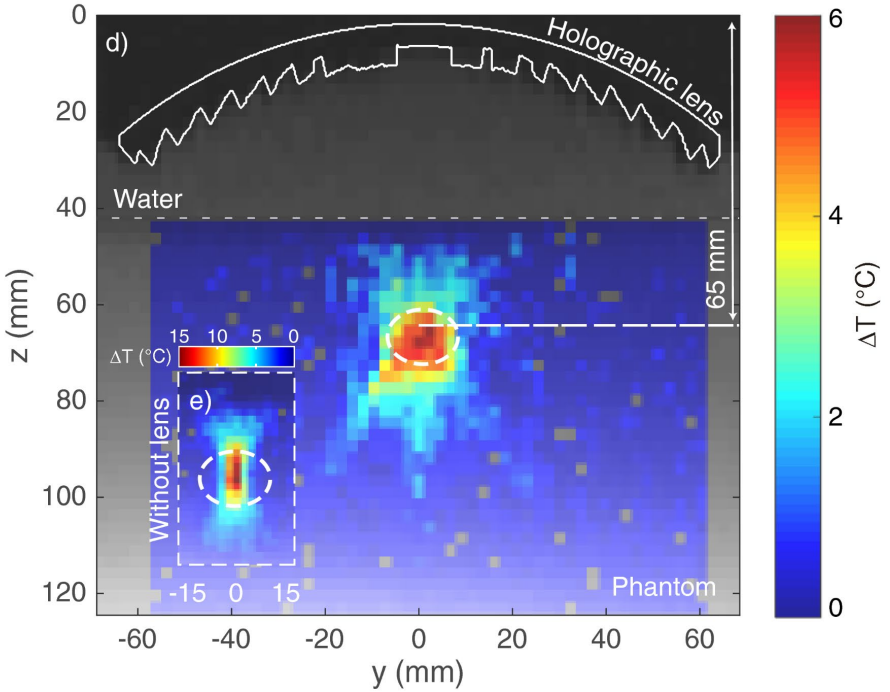
Experimental setup




Thermal simulation




1.5-Tesla MRI thermometry




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

# Conclusions

## Acoustic Holograms

- Aberrations due to stiff layers can be corrected
- Sharp acoustic images are restored
- Low-cost systems: (passive) phased-array
- Cheap MRI compatible
- Miniaturize

## Drawbacks

- Patient specific
- Narrow band: limitations on angular spectrum and type of signals
- 3D printed materials absorb US, can heat and deform on long pulses if not refrigerated
- Impedance matching with US transducer?

## Ongoing work

- Hologram design for specific applications: **non-human primates** and **human trials**
- Broadband / phase and amplitude holograms: **phononic crystals** and **metamaterials**
- Reconfigurable holograms: Towards active **spatial-sound modulators (for high-amplitude US)**

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

# Publications

**Papers**

- S. Jiménez-Gambín, et al. “Holograms to focus arbitrary ultrasonic fields through the skull.” Physical Review Applied, 12 (1), pp. 014016, (2019)
- S. Jiménez-Gambín, et al. “Transcranial focusing of ultrasonic vortices by acoustic holograms”. Physical Review Applied, 14(5), 054070 (2020)
- S. Jiménez-Gambín, et al. “Acoustic Holograms for Bilateral Blood-Brain Barrier Opening in a Mouse Model”. IEEE Transactions on Biomedical Engineering 69 (4) 1359 - 1368 (2022)
- D. Andrés, et al. “Thermal holographic patterns for ultrasound hyperthermia”. Applied Physics Letters, 120 (8), pp. 084102, (2022)
- D. Andrés, et al. “Numerical Study of Acoustic Holograms for Deep-Brain Targeting through the Temporal Bone Window” *Ultrasound in Medicine & Biology* 48 (5) 872-886 (2022)
- M. Ferri, et al. “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)

**Patent**

- US Patent App. 17287715 / WO2020084181A1 / PCT ES2019070713. N. Jiménez, S. Jiménez-Gambín, J.M. Benlloch, F. Camarena. Method for Producing a Lens and Ultrasound Device Comprising the Lens (2018)

# Acknowledgements


**Instituto de Instrumentación para Imagen Molecular**

- Sergio Jimenez-Gambín (PhD, now PostDoc at Columbia University)
- Diana Andrés (PhD Candidate)
- Nathalie Lamothe (PhD Candidate)
- Francisco Camarena (Prof. UPV)
- José María Benlloch (Prof. CSIC)





**Funding**

- Spanish Ministry of Science / AEI: 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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