Holographic metasurfaces for the new generation of biomedical ultrasound applications

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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

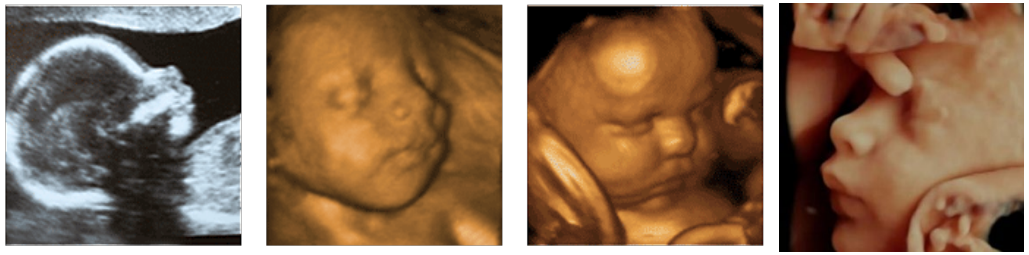
a) Thermal Effects

- Temperature rise
- Sonoluminescence

b) Mechanical Effects

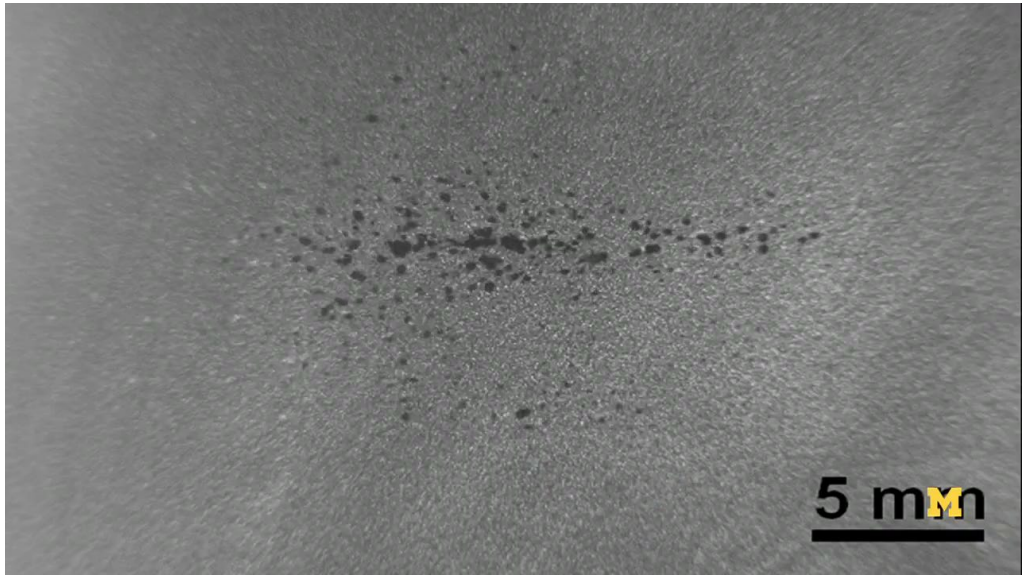
- Radiation force
- Flow (in fluids) and deformations (in solids)
- Cavitation (inertial and non-inertial)

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

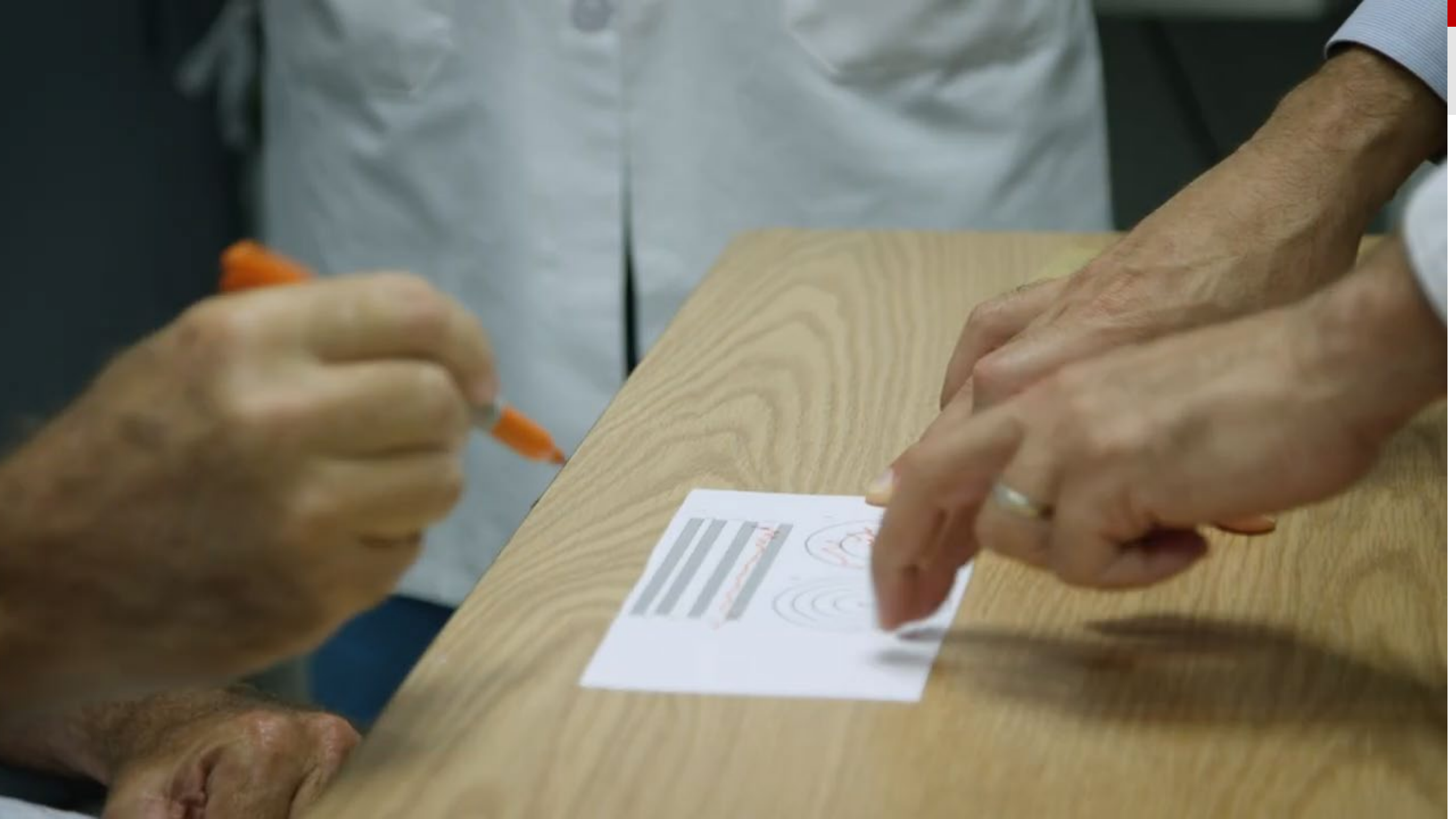
Drug delivery

- 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

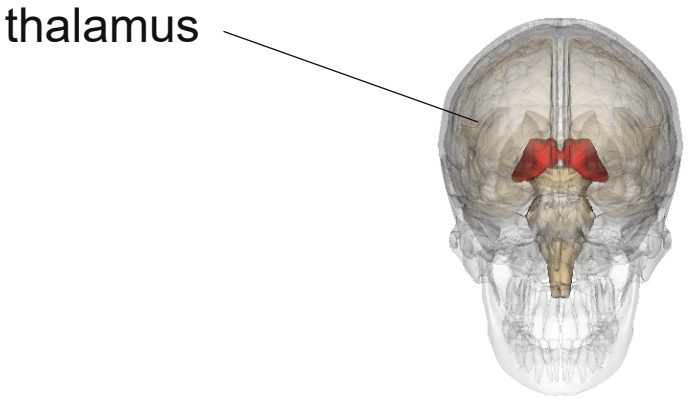
Thalamotomy for essential tremor

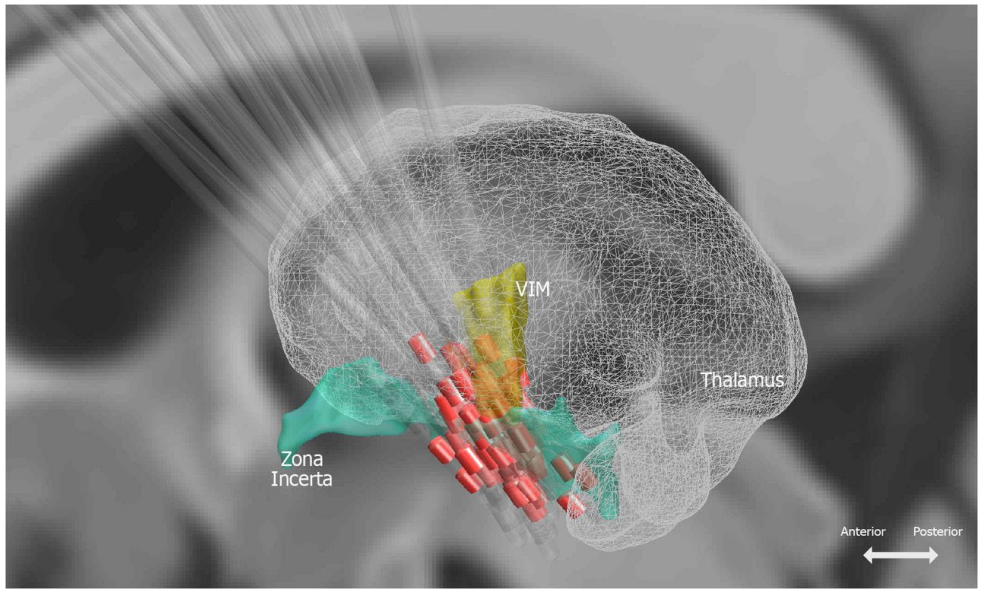
Problem

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

Treatment

- Ablation of deep-brain thalamic subnucleus (VIM, ventralis intermedius)
- Classical treatment: Ablation using electrodes





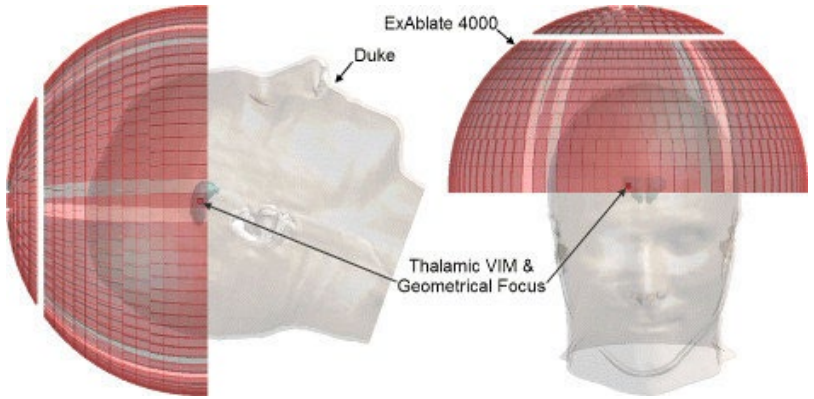
Brain 142(10):3086-3098 (2019)

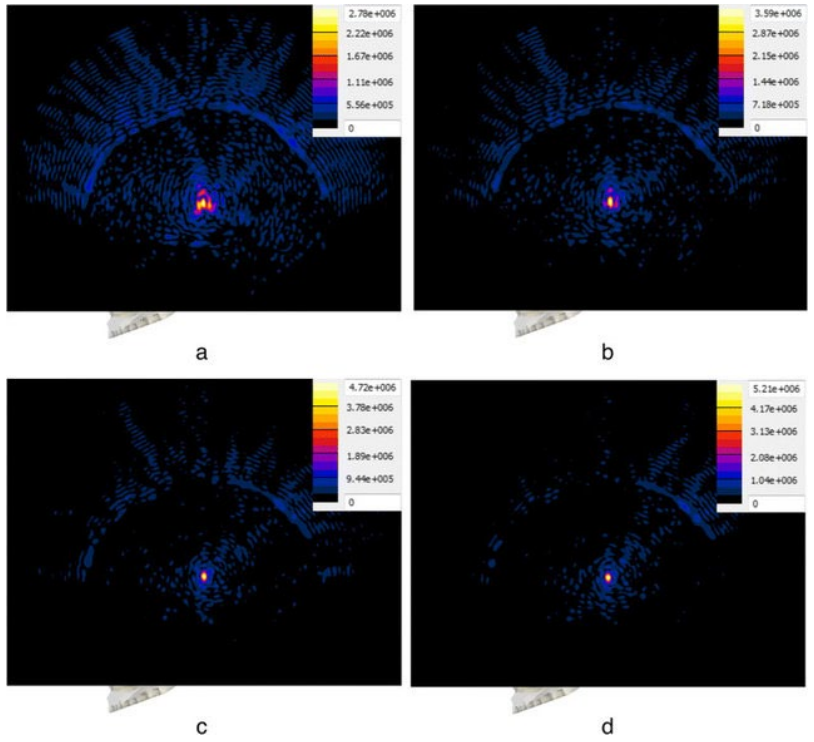
Thermal tissue ablation

Magnetic resonance-guided focused ultrasound (MRgFUS)

- **US thalamotomy:** 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)

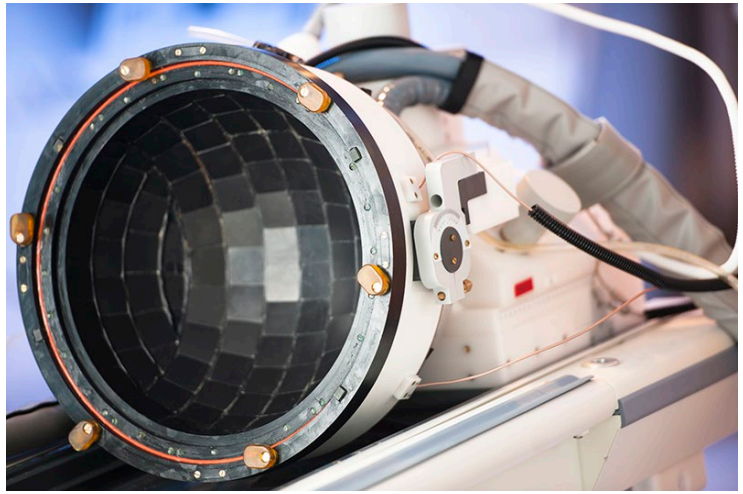
- **System:** MRgFUS phased array





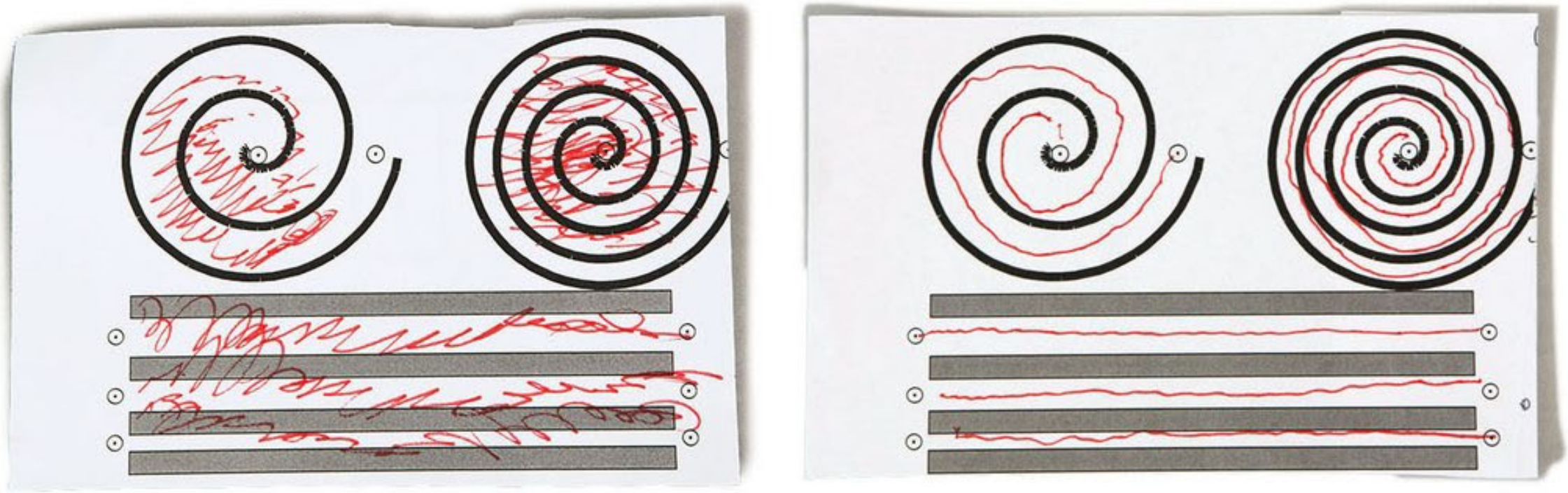
INSIGHTEC





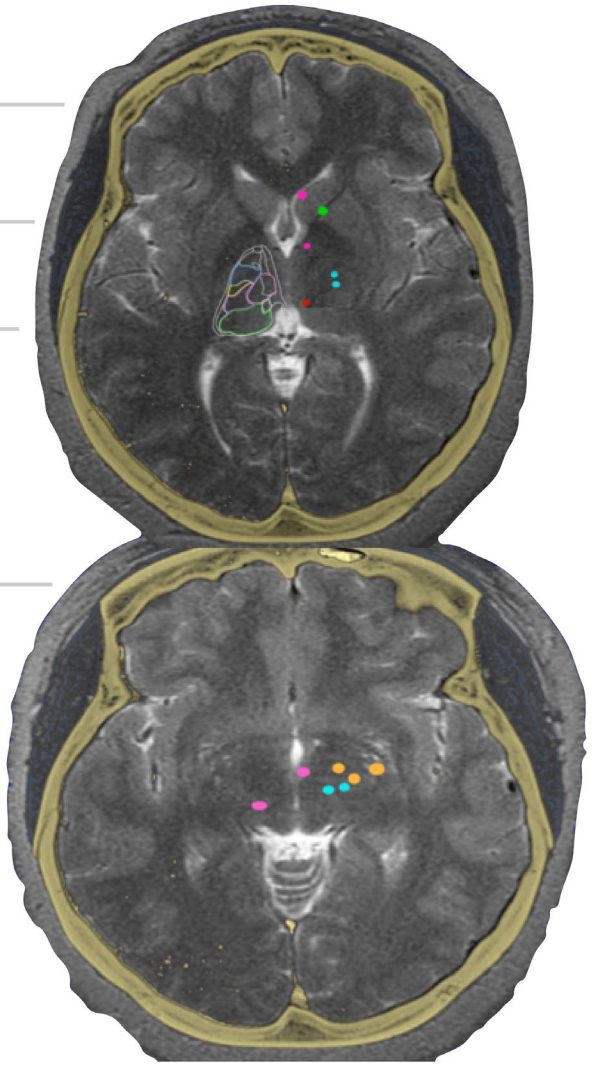
Thermal tissue ablation

Thalamotomy for essential tremor



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 effects of ultrasound in biological tissues

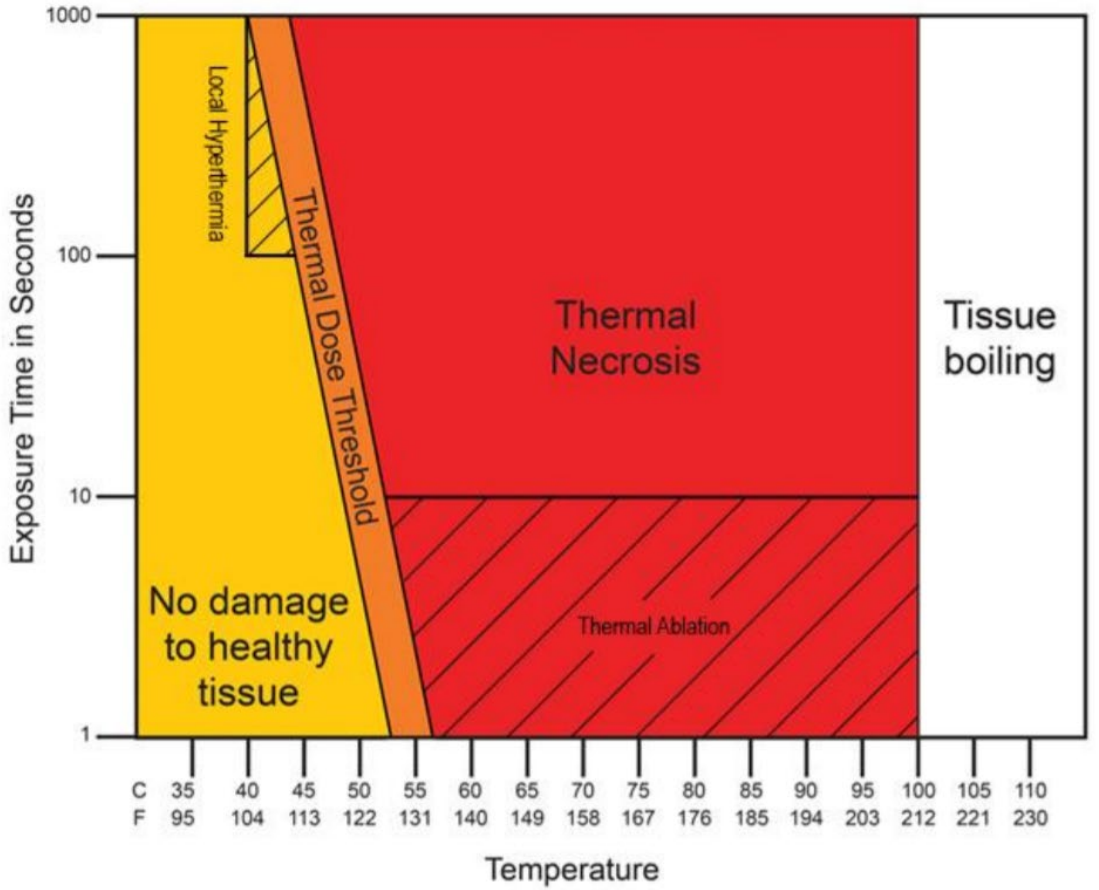
Thermal ablation

- **Mechanism**: Increases rapidly and destroys tissue by denaturing proteins.
- **Effect:** Tissue destruction

Local hyperthermia

- **Mechanism:** Moderate and slow temperature rise
- **Effect:** Immunomodulation, Increased sensitivity to chemotherapy or radiotherapy …

Thermal effects in human soft tissue



Localized drug and gene delivery

Blood-brain barrier opening

Problem

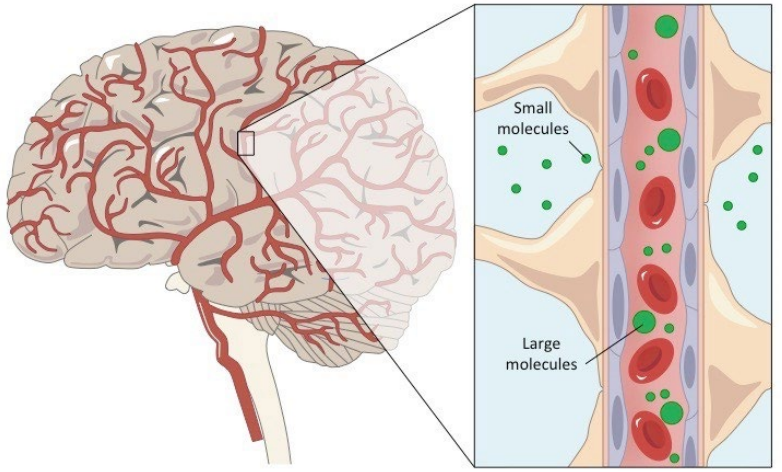
- Tight junctions in the endothelium prevent the passage of heavy molecules into the CNS
- Protection against infections, viruses
- Blocks drug delivery

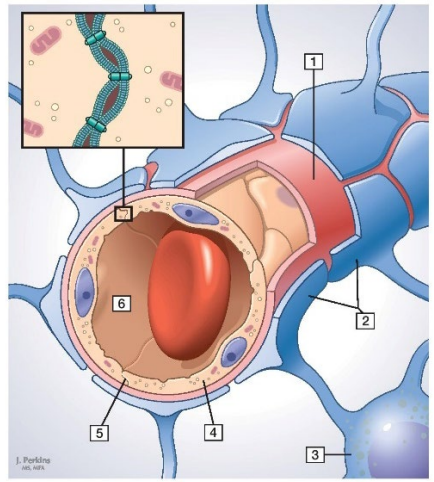
Treatment

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

Application

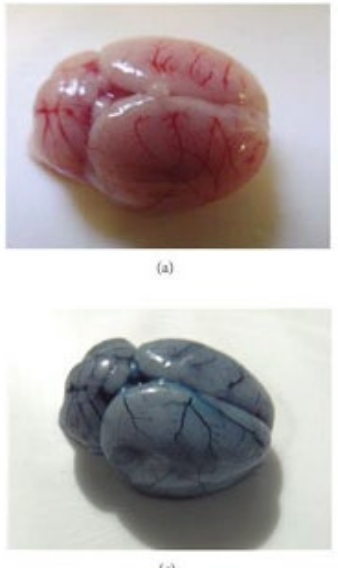
- Localized chemotherapy
- Therapies for Alzheimer's, Parkinson's, etc....







(A) Mid gestation guinea pig embryo injected with trypan blue (Wislocki, 1920)



Phoneutria nigriventer spider venom causes blood-brain barrier breakdown (BBBb).

Localized drug and gene delivery

Blood-brain barrier opening

Problem

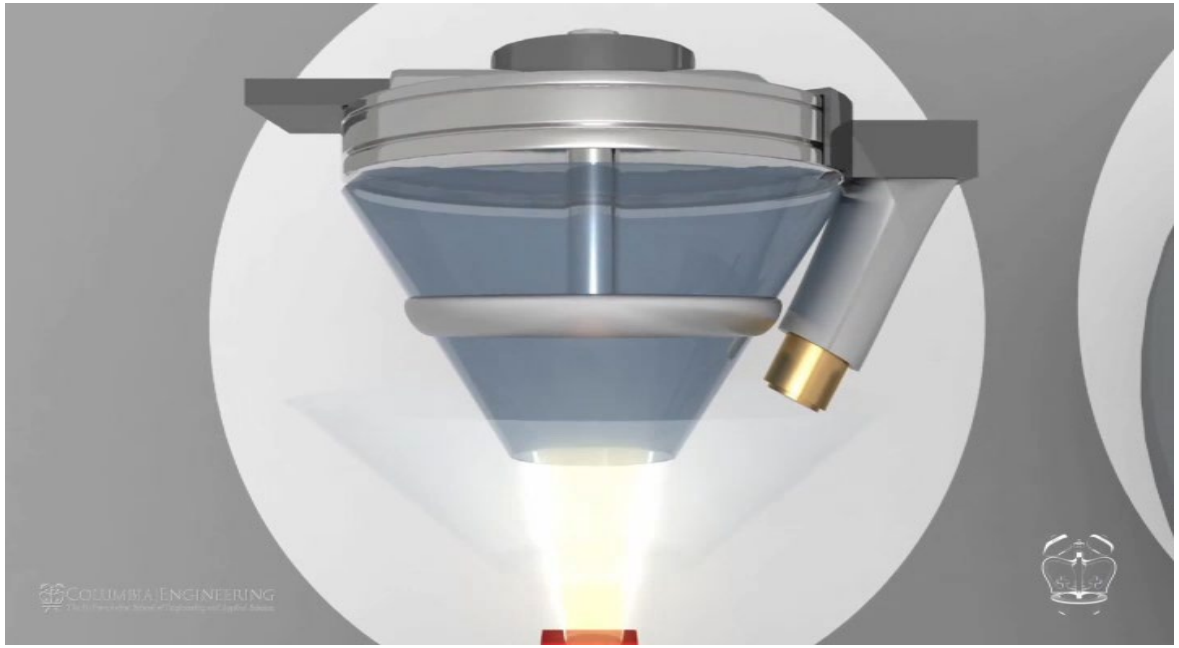
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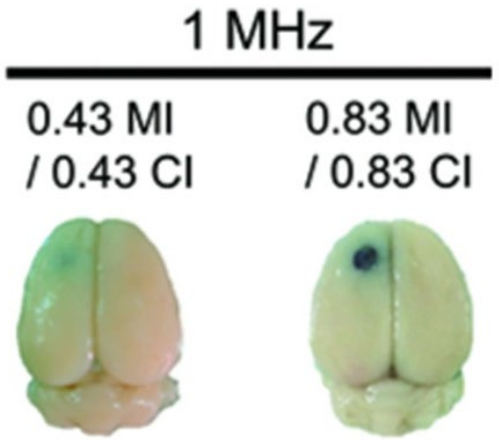
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Application

- Localized chemotherapy
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Nat Commun **9,** 2336 (2018).

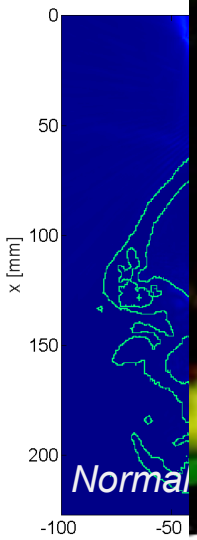
Sci Rep **6,** 33264 (2016).


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

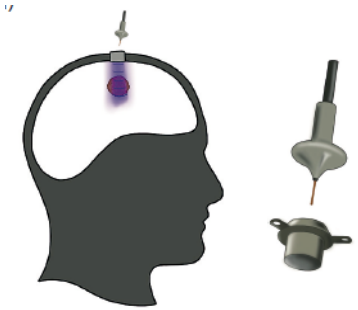
Focus

Transc

- Refrac
- Absor
- 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



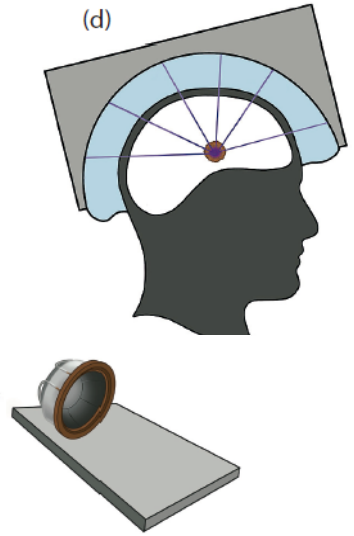
Single element transducer

- 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

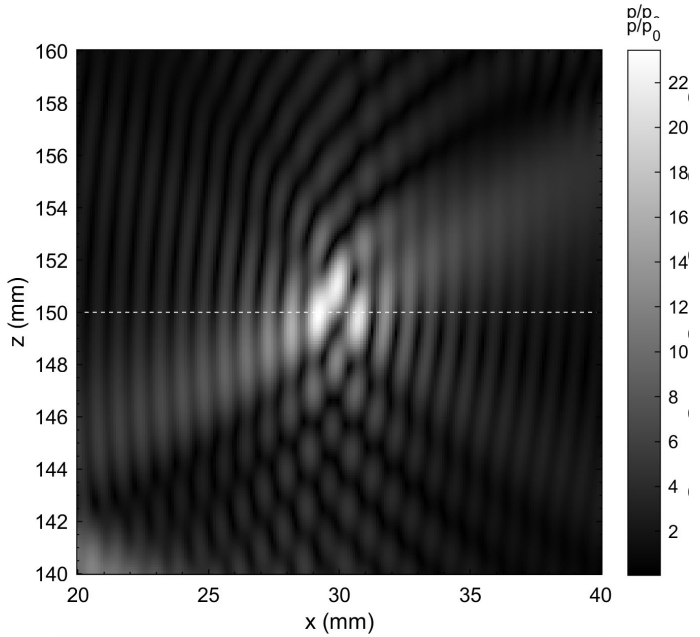
Focusing challenges

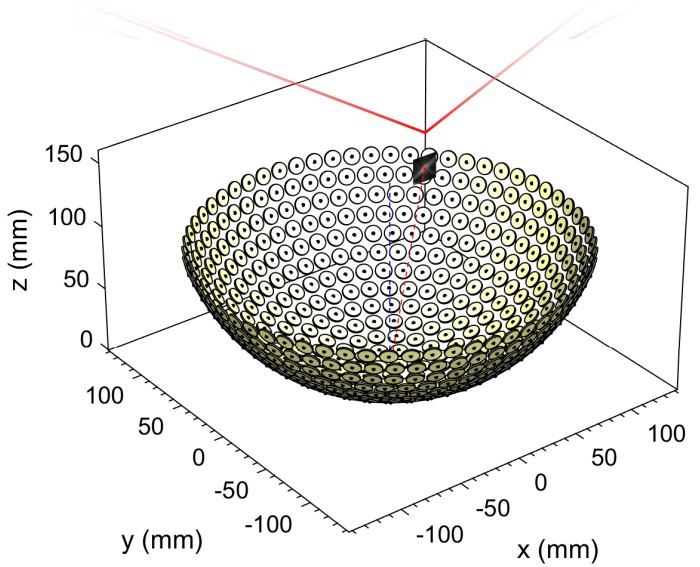
Focusing

- 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



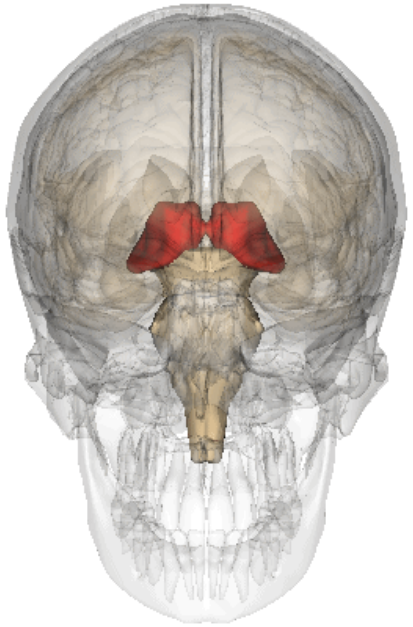


Focusing challenges

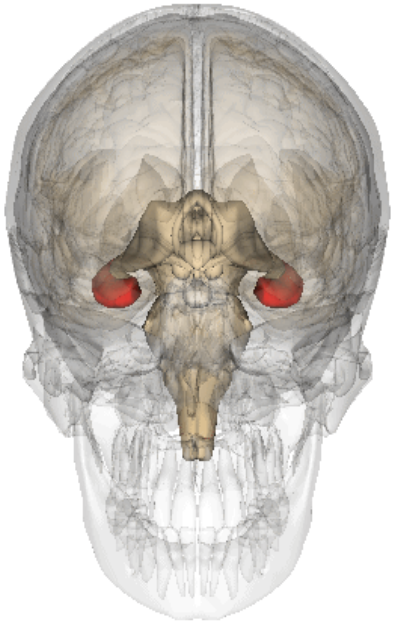
Complex target morphology

- Can we adapt the beam to the therapeutical target?

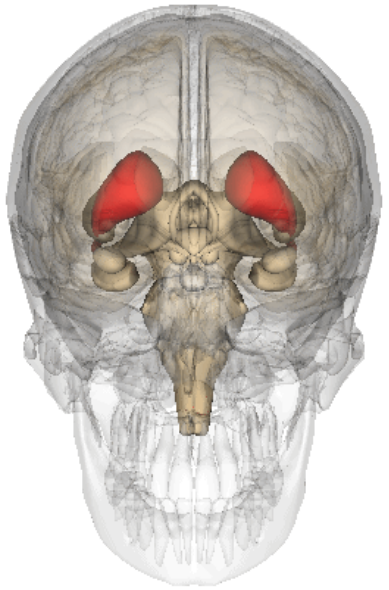
Thalamic nuclei



Hippocampus

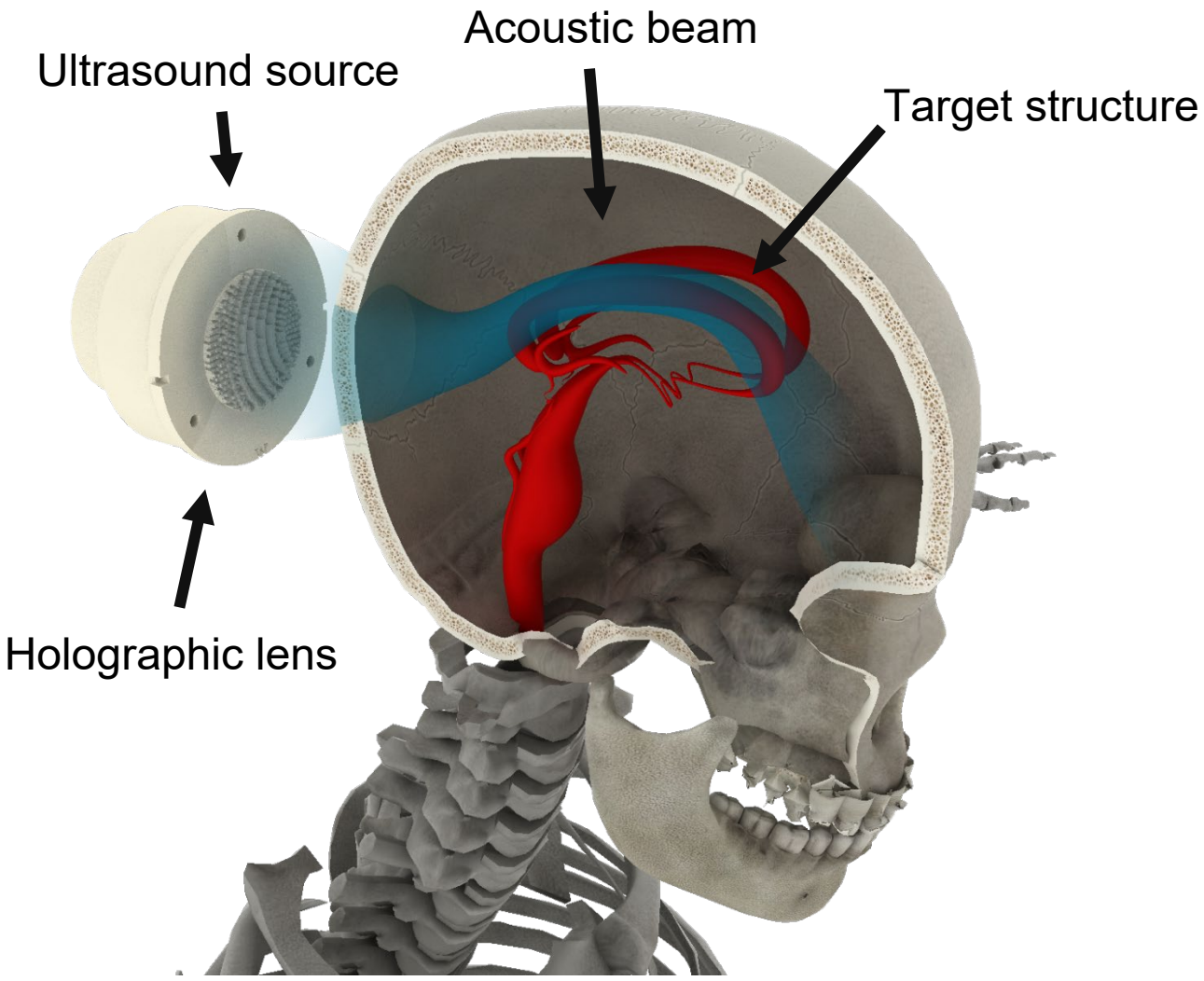


Caudate nucleus



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)

Why holograms?

High pixel density:

- Frecuency: 1 MHz → λ = 1.5 mm

No grating lobes.

- Separation < $\lambda/2$

Wide angular spectrum:

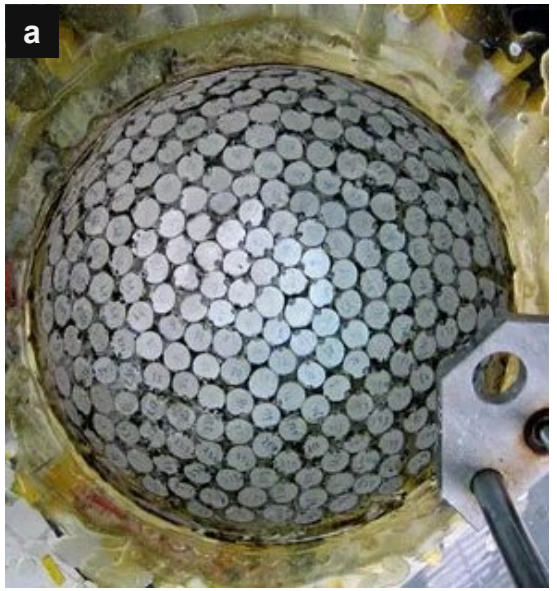
- Encode multiple scattering,
- Reflections,
- Reverberation.

Patient specific:

- Compensate refraction aberrations.

Treatment specific:

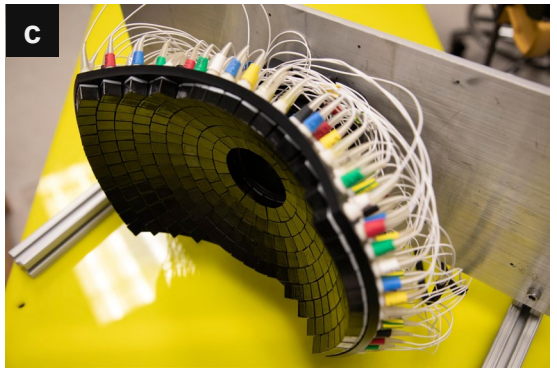
- Simultaneous focus on therapeutic target.



NaviFus: 1024 elements



Insightec Exablate: 2048 elements



Histosonics: 1024 elements

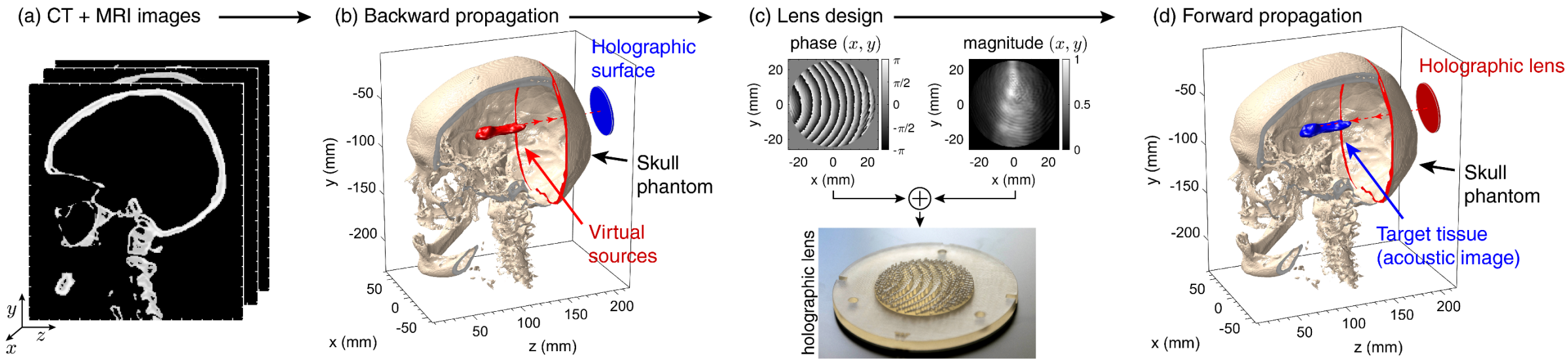


Holograms: > 100.000 elements

Acoustic holograms

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)

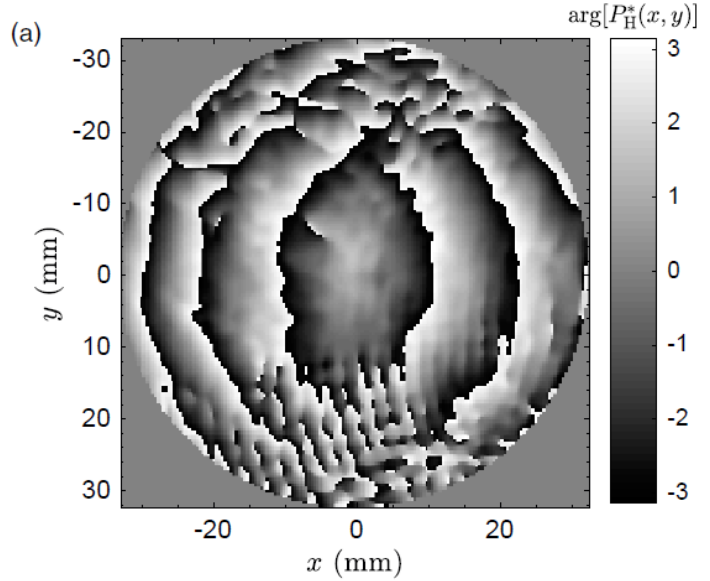
$$T(x, y) = \frac{2Ze^{-ik_0(d-h(x,y))}}{2Z\cos(k_L h(x, y)) + i(Z^2 + 1)\sin(k_L h(x, y))},$$

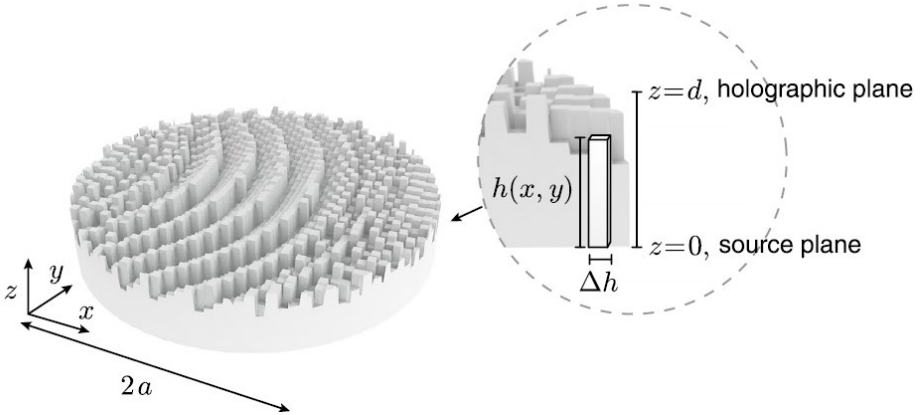
- Find the heigh function $h(x, y)$, producing

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

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)



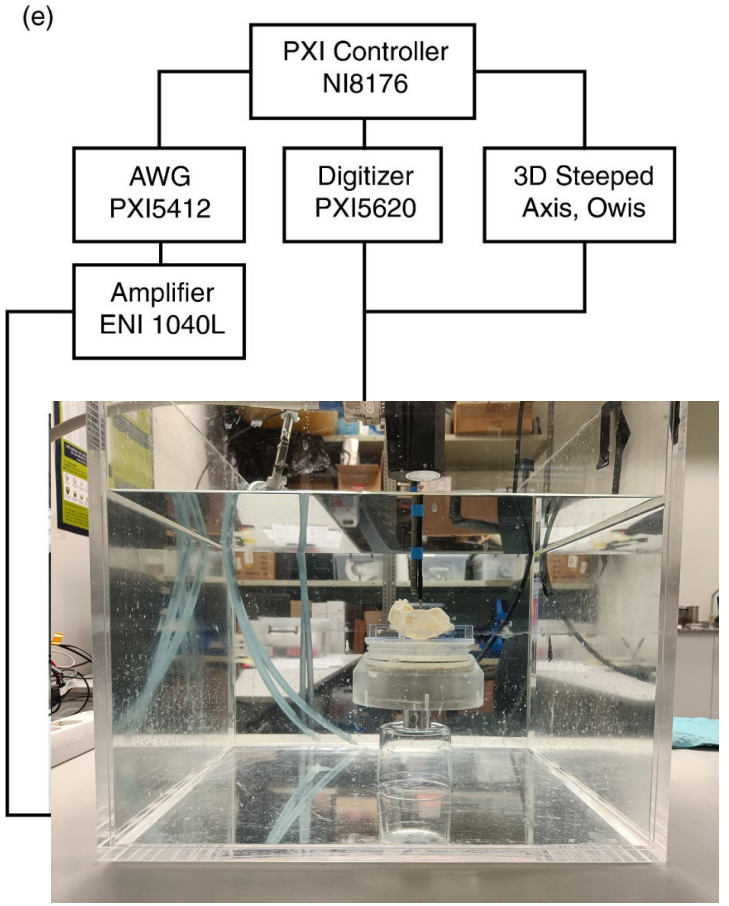
Acoustic holograms for the brain

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)





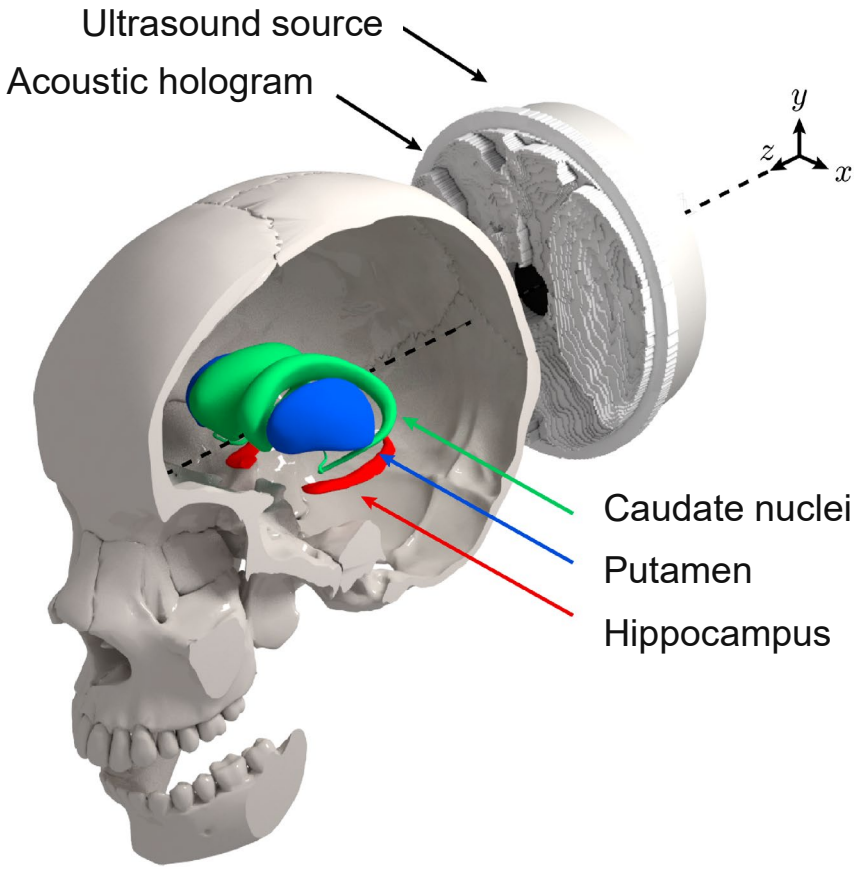




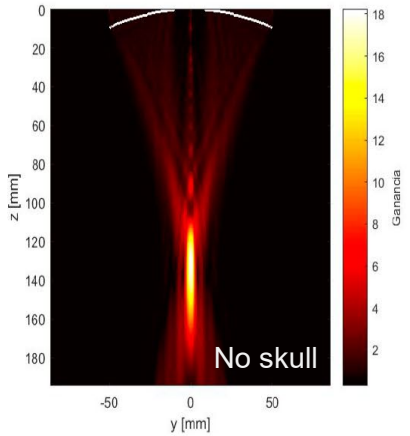
Acoustic holograms

Bilateral focusing

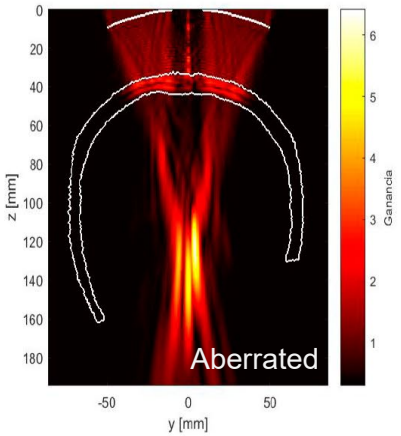
- Targeting at complex bilateral shapes



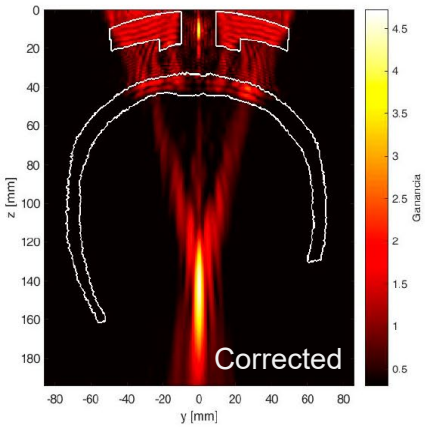
FUS transducer (500 kHz)



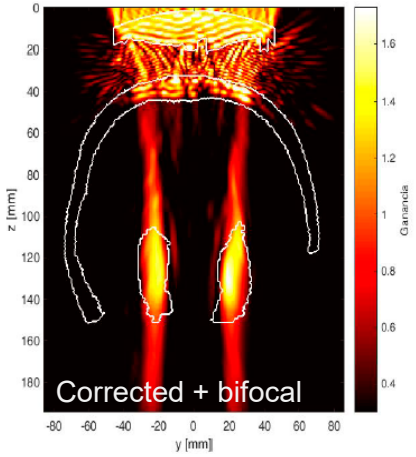
FUS transducer + skull



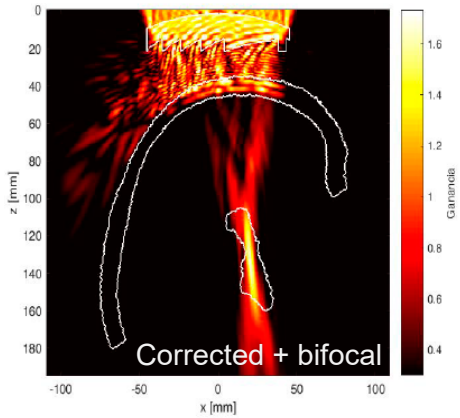
Hologram + skull



Bilateral focusing at hippocampus (coronal)



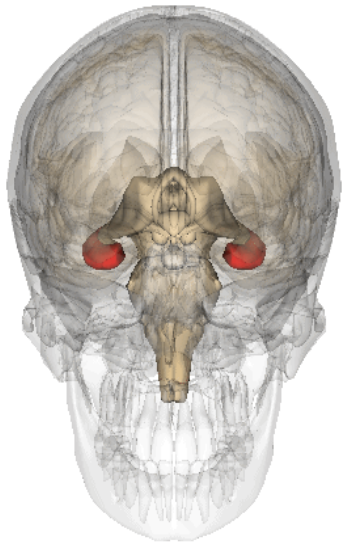
Bilateral focusing at hippocampus (sagittal)

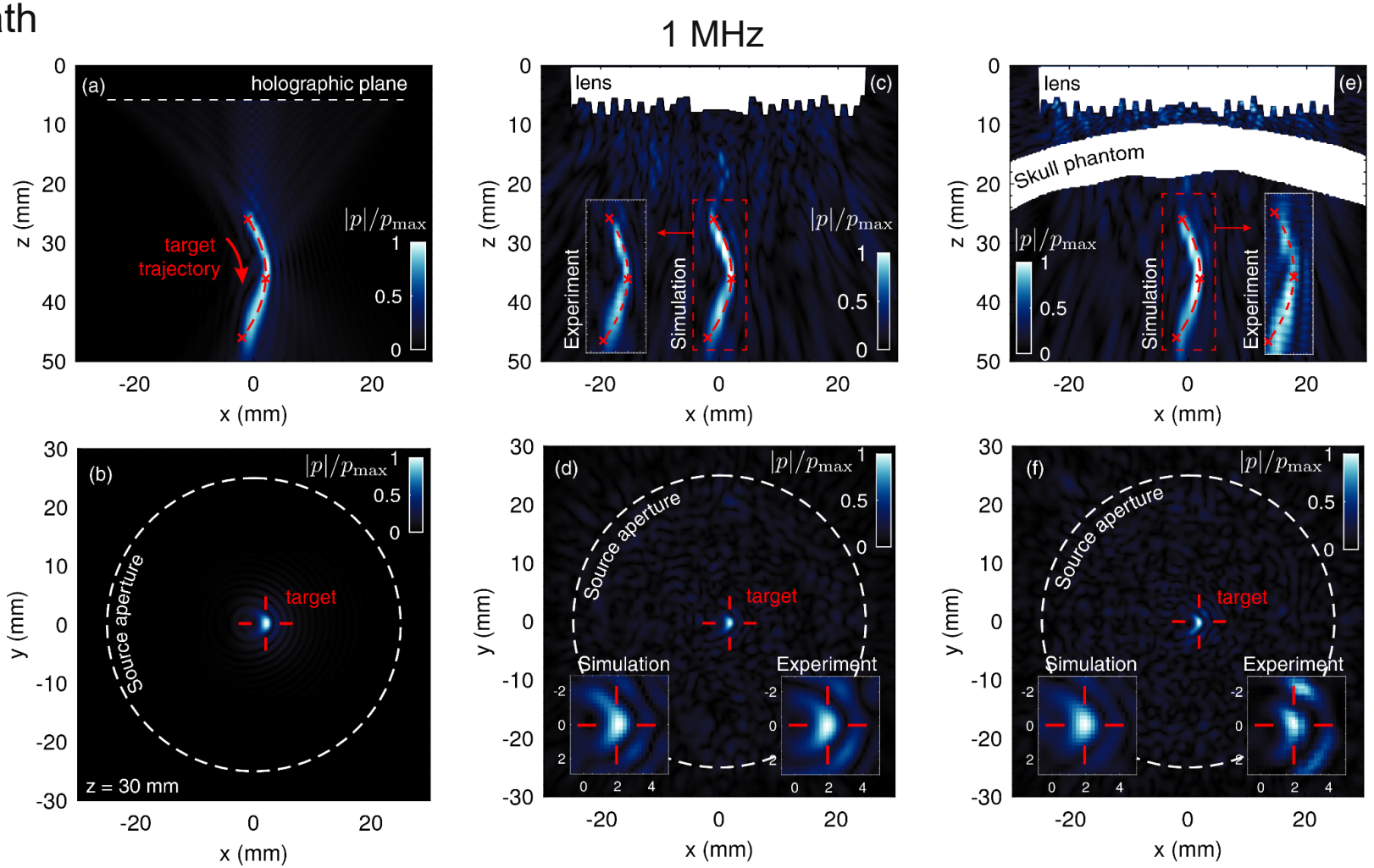


Acoustic holograms

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

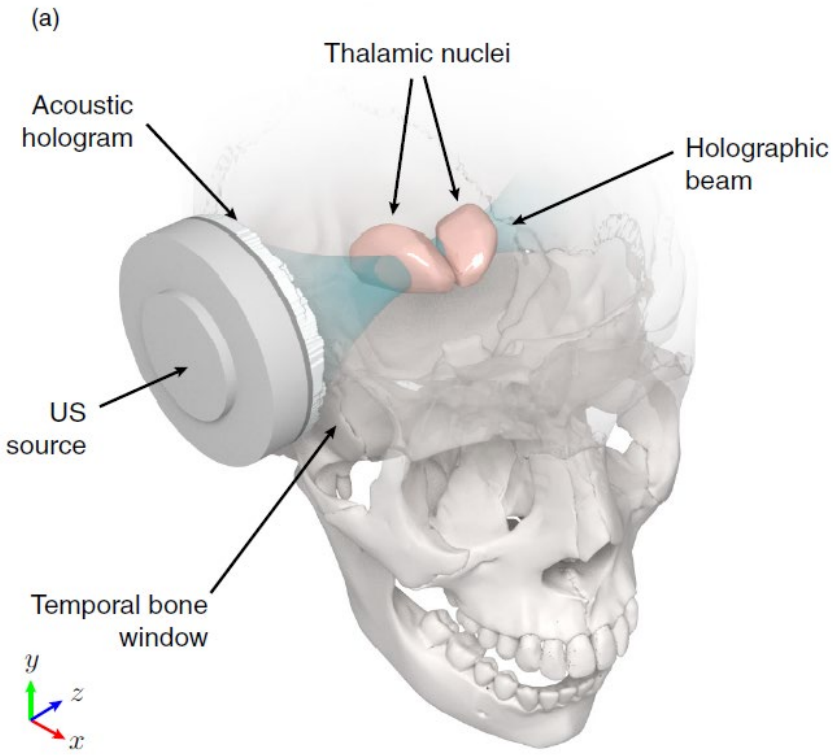
- Low thermal dose and deep-brain focusing



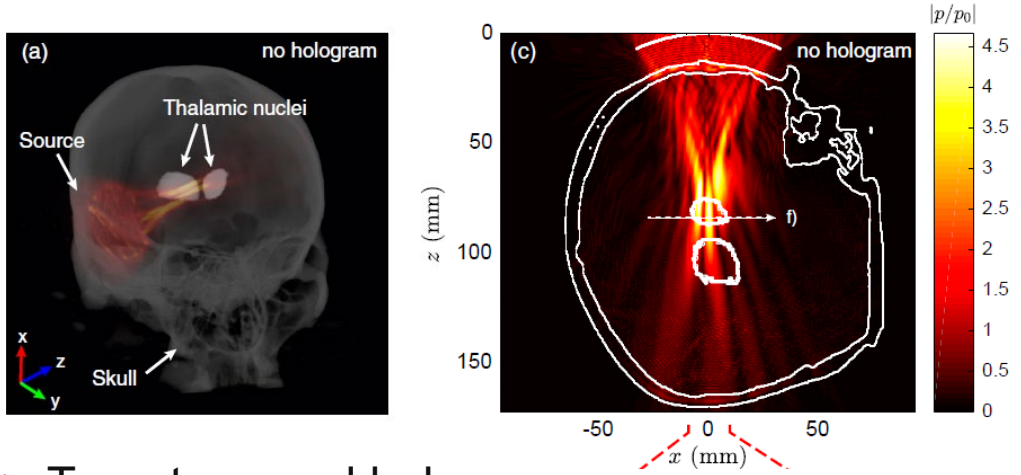
Acoustic holograms

Using the temporal window

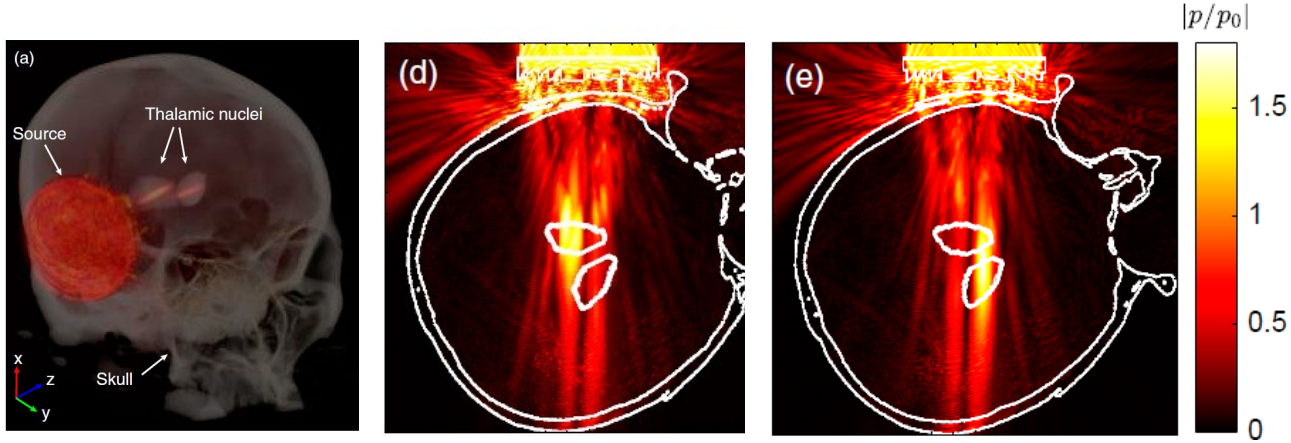
- Low thermal dose and deep-brain focusing



- Standard focused transducer (650 kHz)

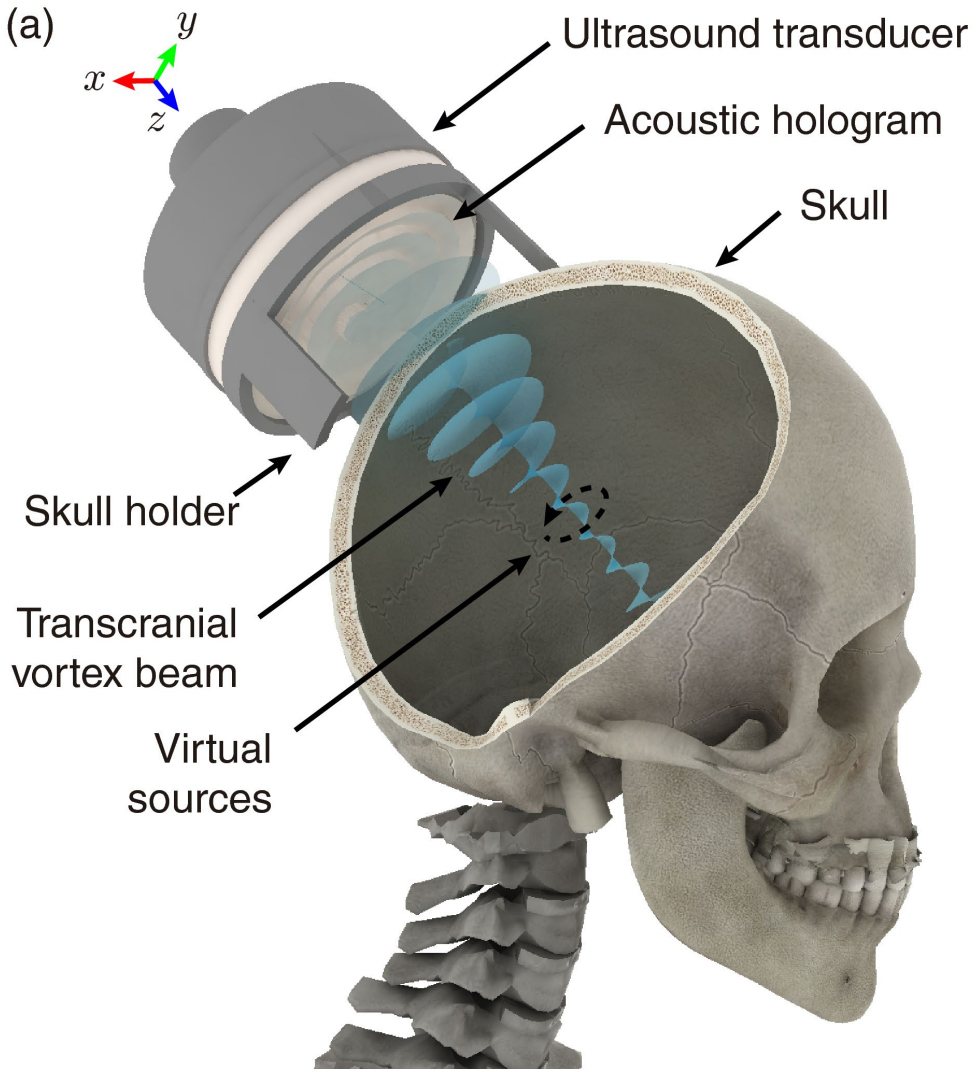


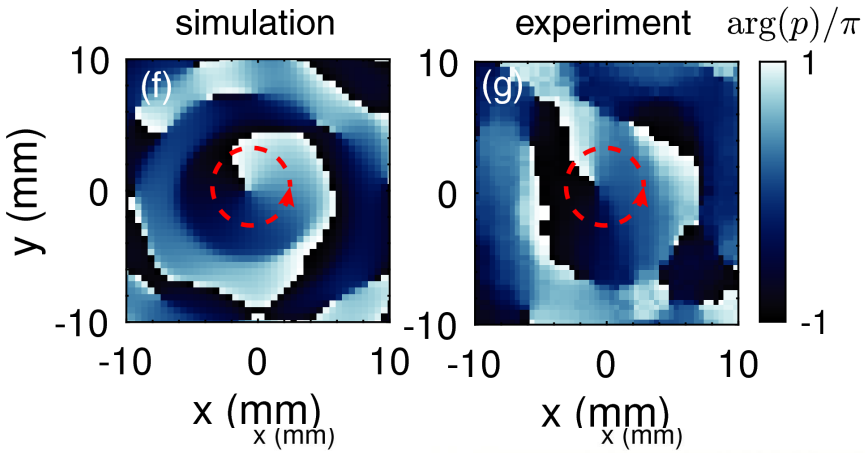
- Transtemporal hologram

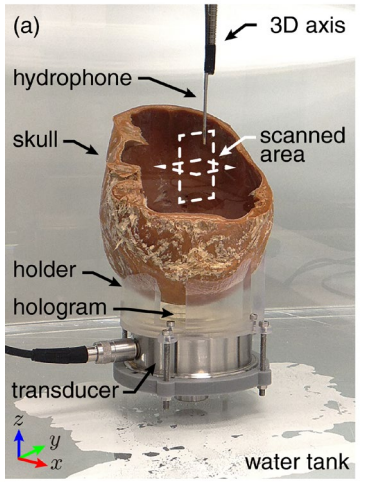


Diana Andrés, et al. *Ultrasound in Medicine & Biology* 48 (5) 872-886 (2022)

Focusing acoustic vortices through the skull







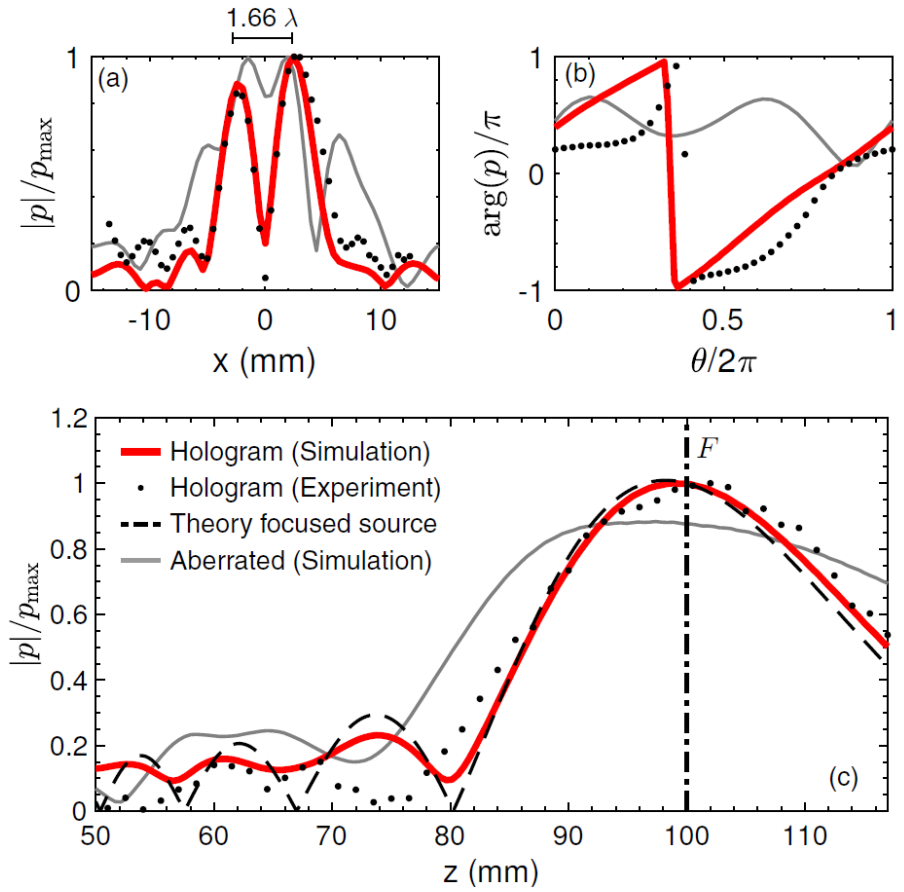


Jiménez-Gambín, et al. *Phys Rev Appl* 12 014016 (2019)

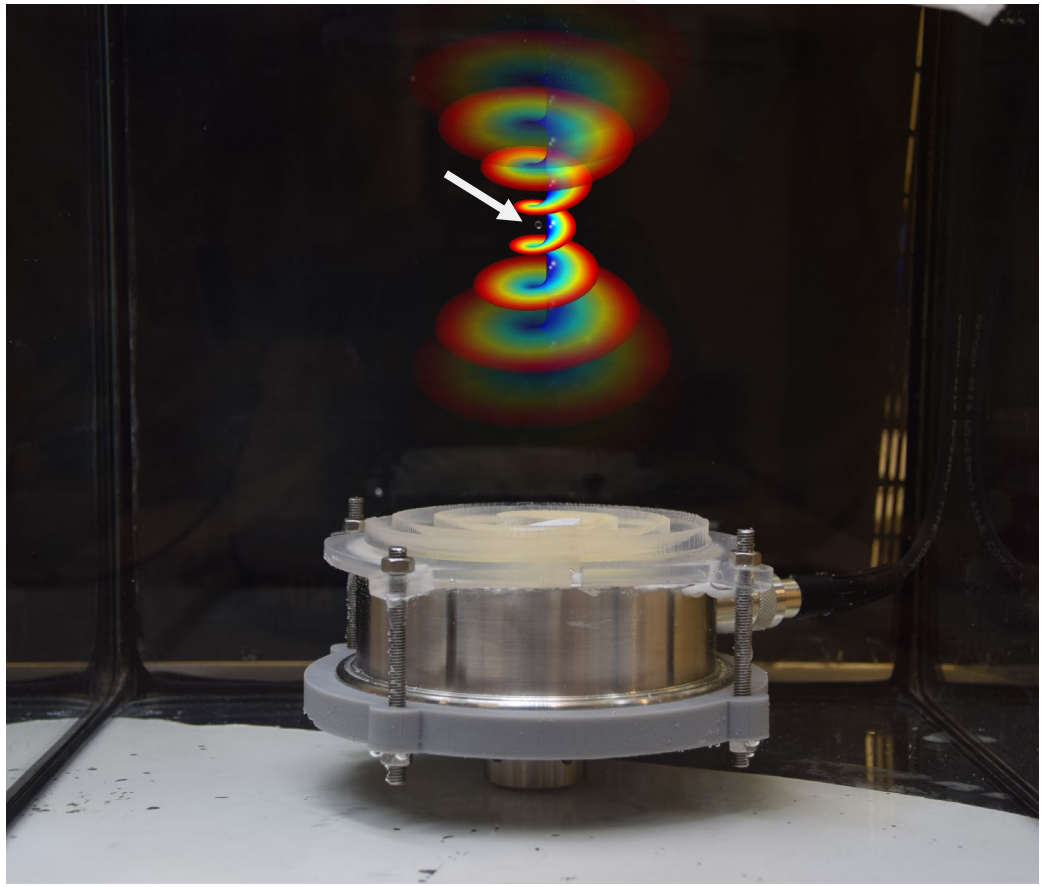
Focusing acoustic vortices through the skull

Topological charge can be tuned

- Aberration correction



- Particle trapping: potential for clot manipulation



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

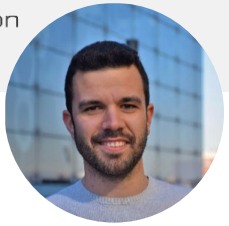
Focusing acoustic vortices through the skull

Vortex focusing by holograms

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

In-vivo validation for BBBO

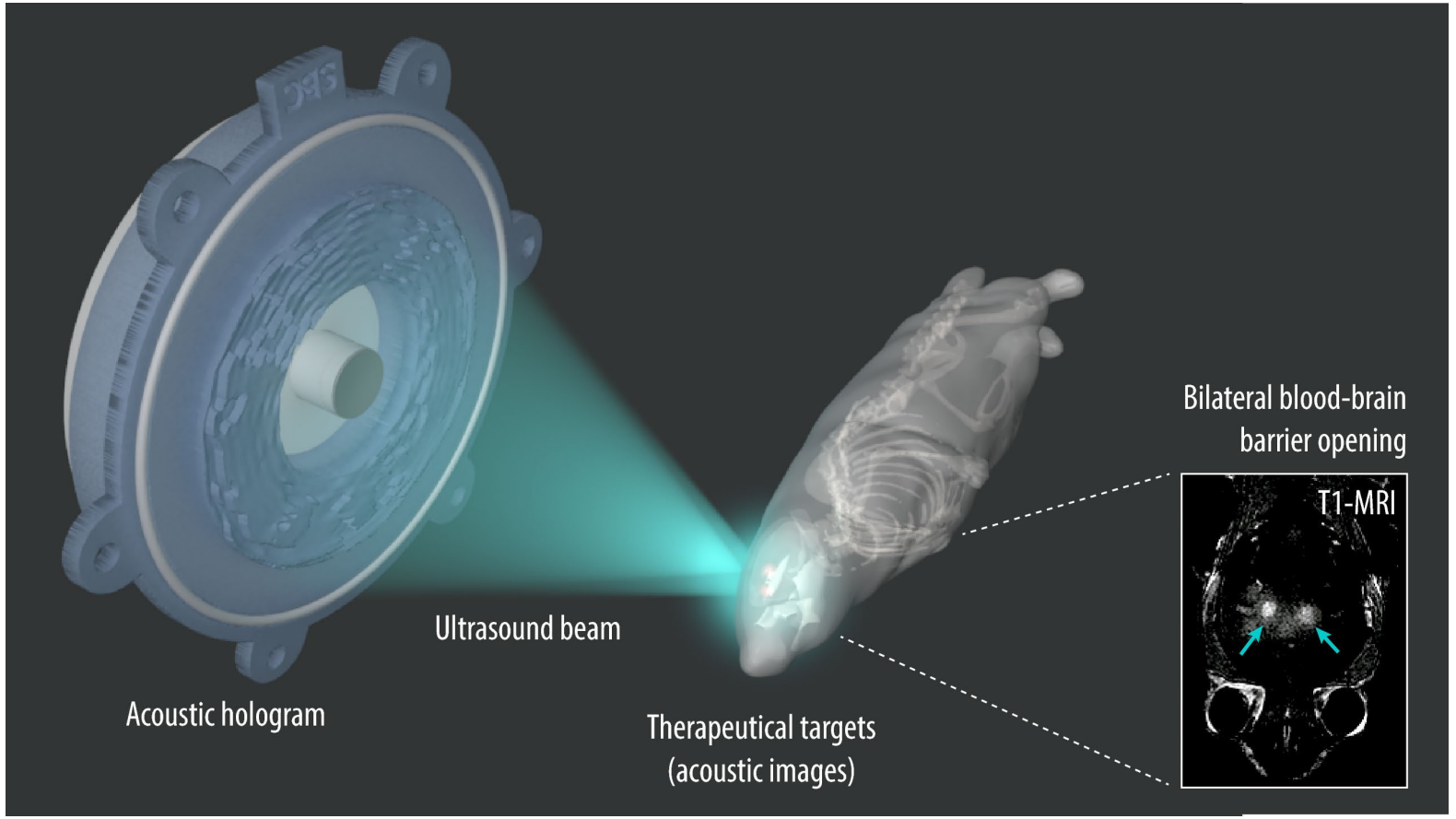
i3M Instituto de Instrumentación para Imagen Molecular



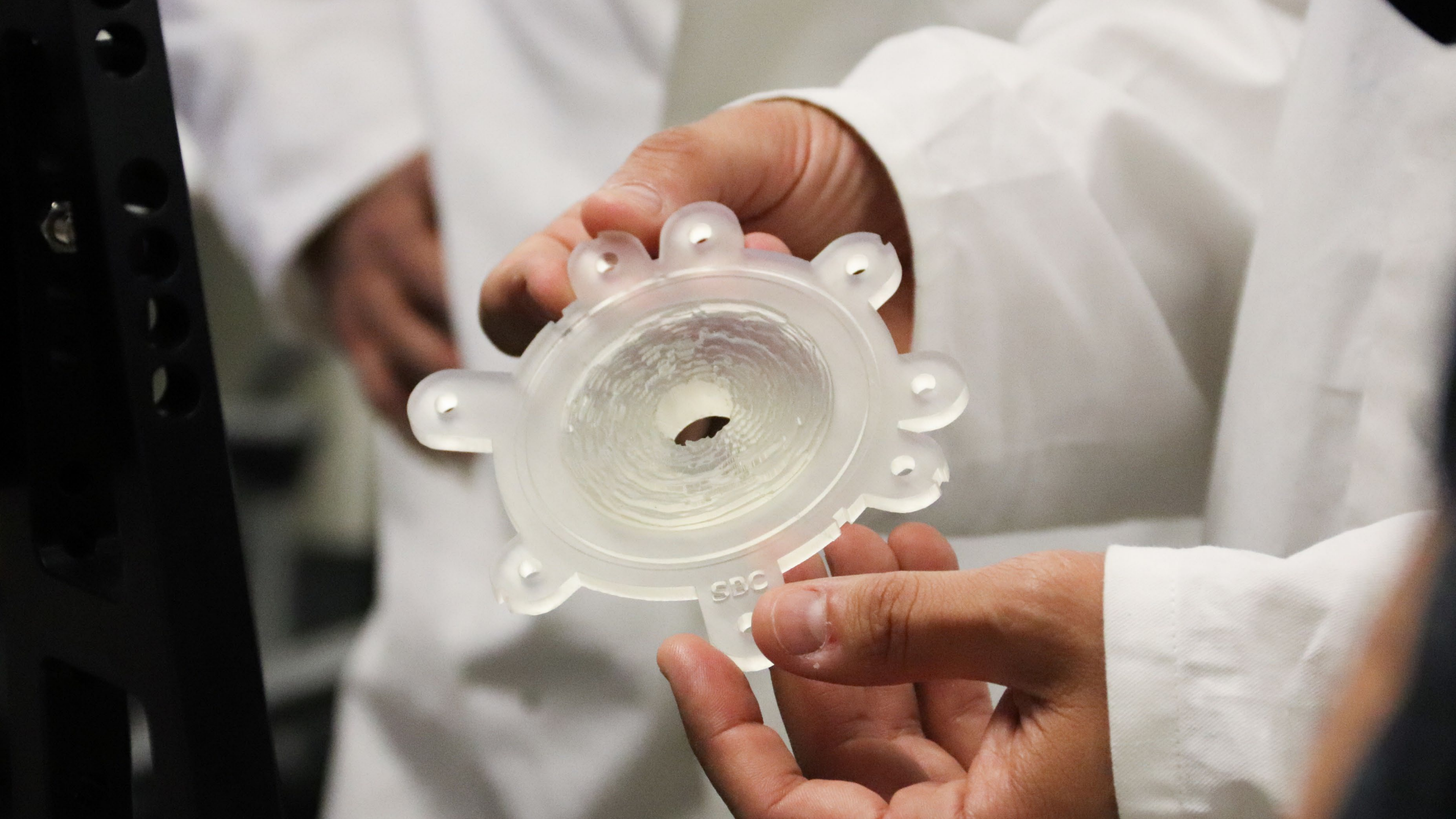
In collaboration with E.E. Konofagou, Columbia University (NYC, USA)

Bilateral blood-brain barrier opening

- First in-vivo application of acoustic holograms

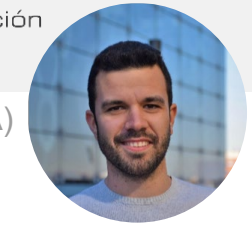


Jiménez-Gambín, et al. IEEE Transactions on Biomedical Engineering 69 (4) 2022 (featured at the cover May 2022)


SBC

In-vivo validation for BBBO

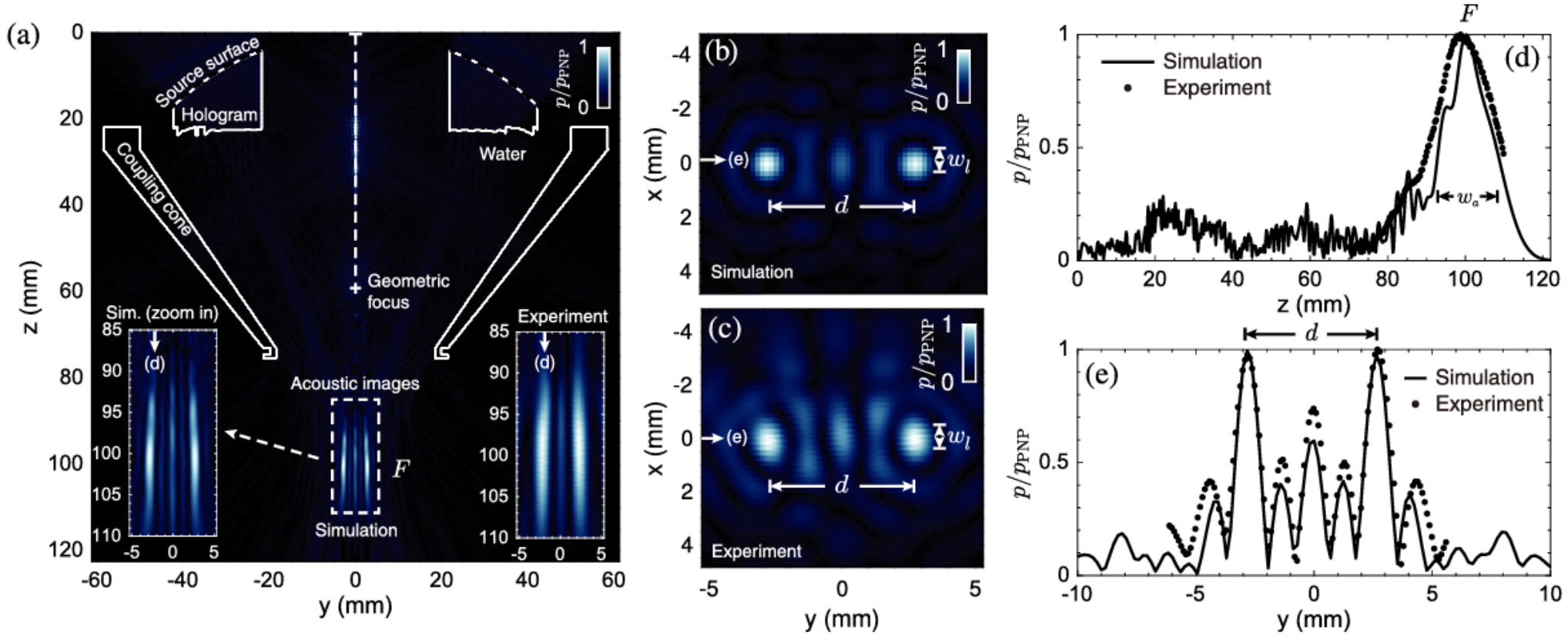
Instituto de Instrumentación para Imagen Molecular



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

Lens performance in water

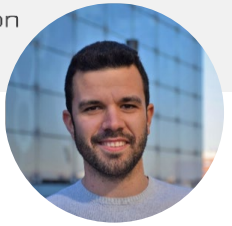
- Bilateral elongated focal spots



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

In-vivo validation for BBBO

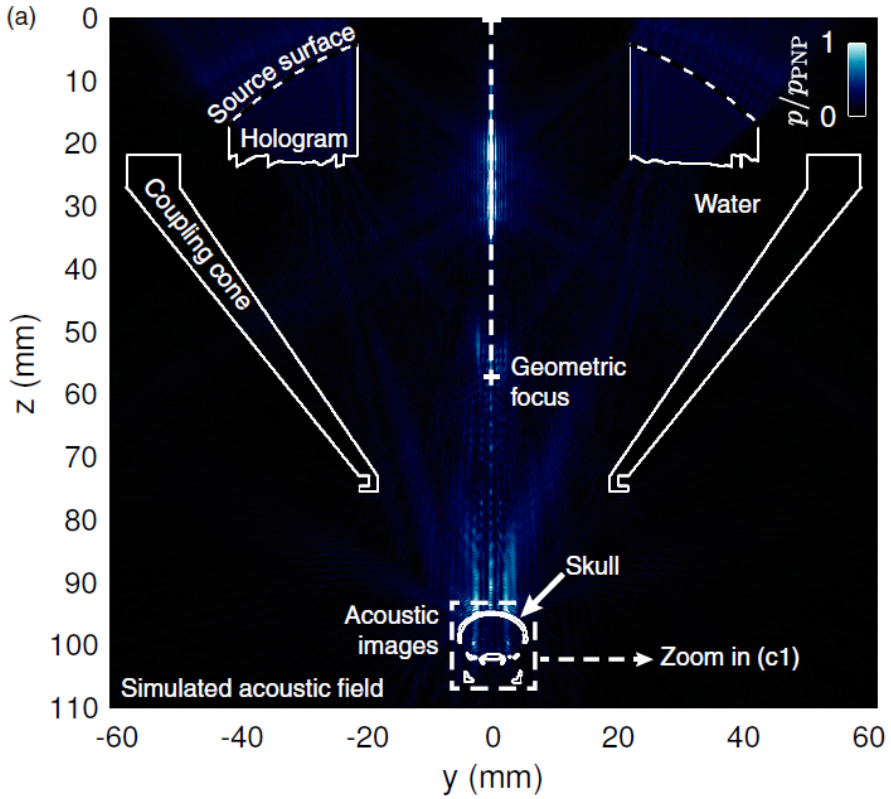
Instituto de Instrumentación para Imagen Molecular

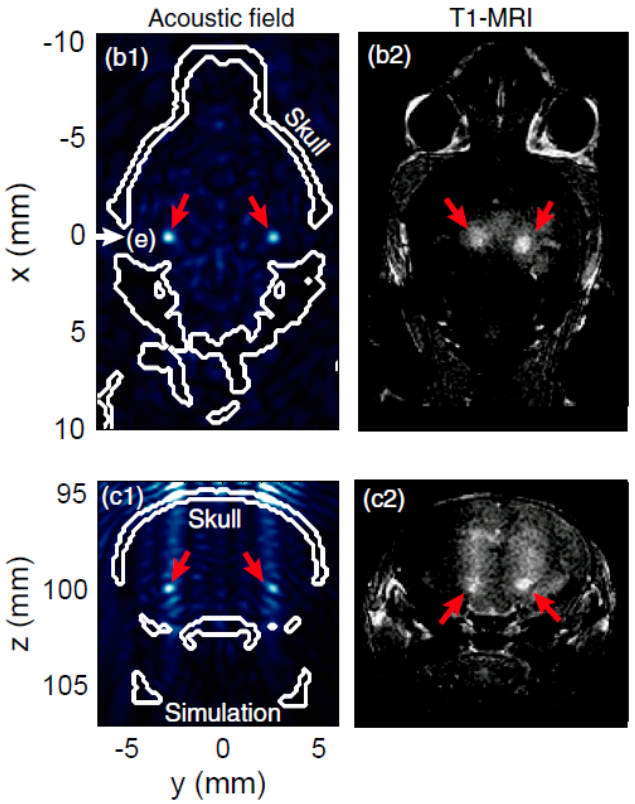


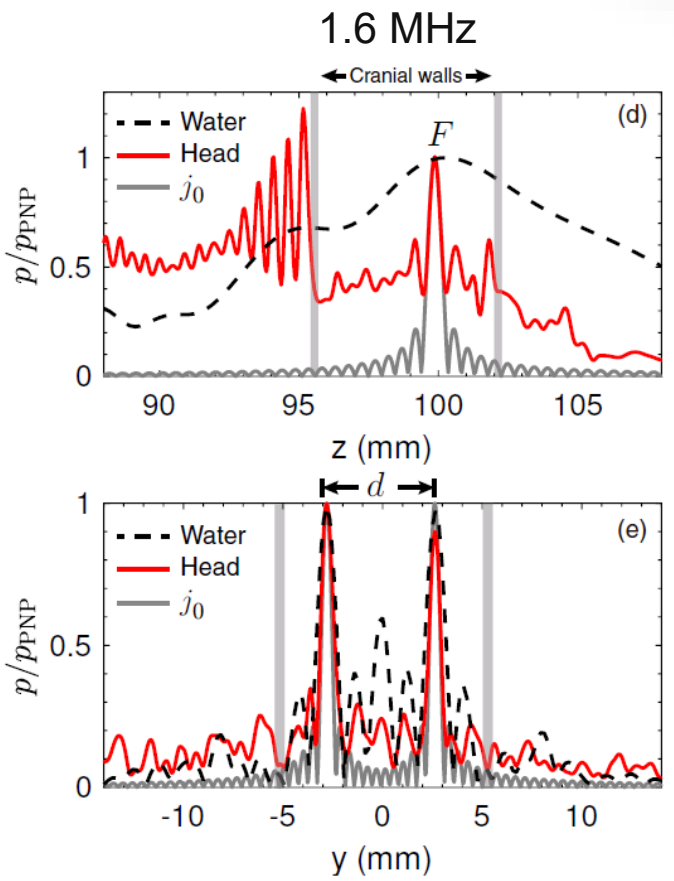
In collaboration with E.E. Konofagou, Columbia University (NYC, USA)

Bilateral blood-brain barrier opening

- First in-vivo application of acoustic holograms
- Kaleidoscopic TR focusing: Diffraction-limited focal spots







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

Thermal holograms

Instituto de Instrumentación para Imagen Molecular

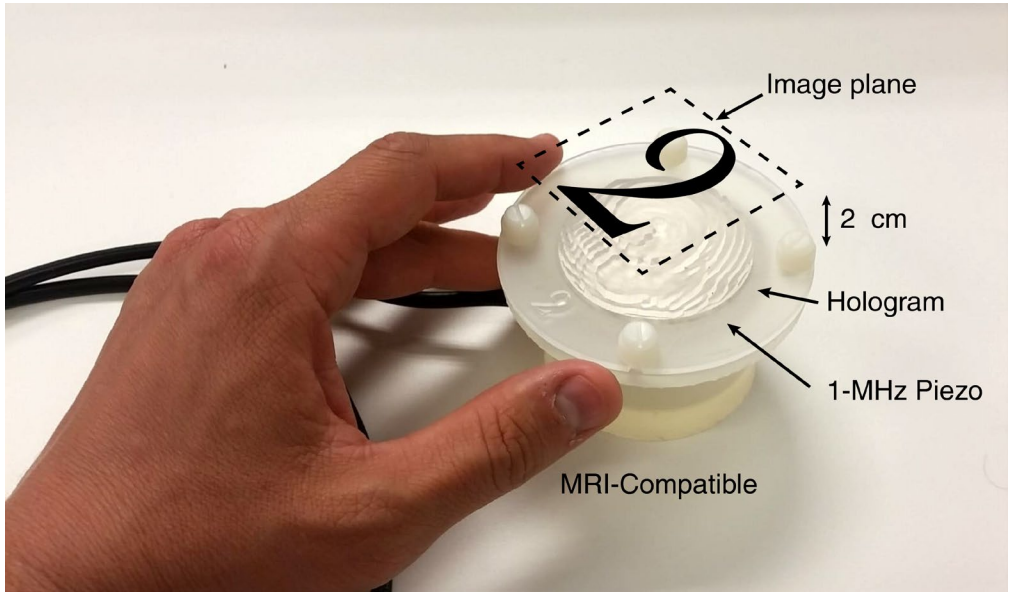
In collaboration with Jonathan Vappou, CNRS (France)



Thermal patterns for ultrasound hyperthermia

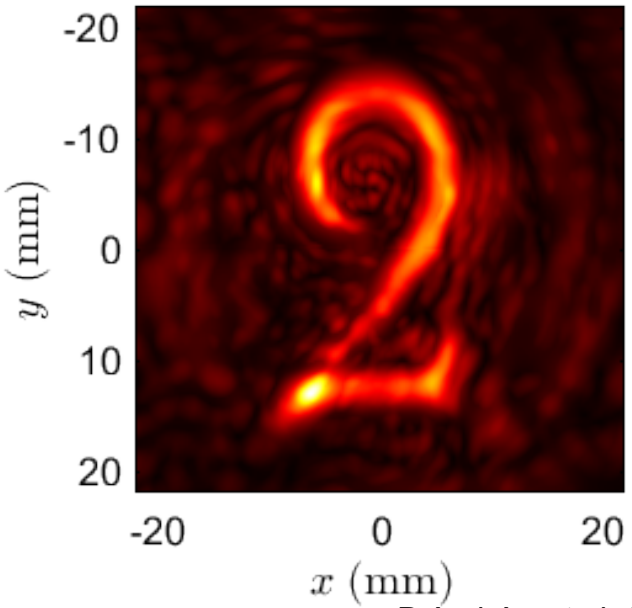
- Mild and local rise temperature
- Activate immune system
- Enhance drug administration
- Enhance chemotherapy

Experimental setup

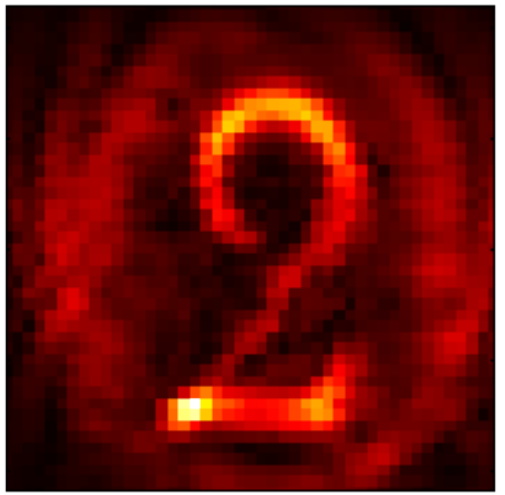


Acoustic field

Simulation



Experiment



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

Holographic thermal patterns

Instituto de Instrumentación para Imagen Molecular



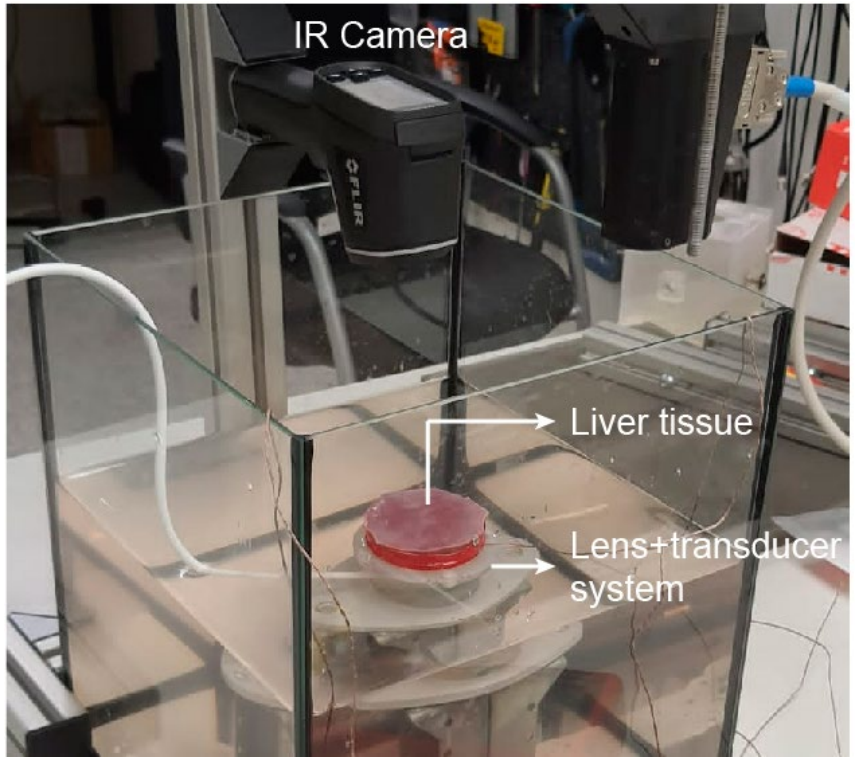
In collaboration with Jonathan Vappou, CNRS (France)

Experimental demonstration (weakly nonlinear regime)

- 3D printed hologram
- Plane transducer: 2a = 50 mm, f = 1,1 MHz
- Max pressure ~ 2 MPa (weakly nonlinear)

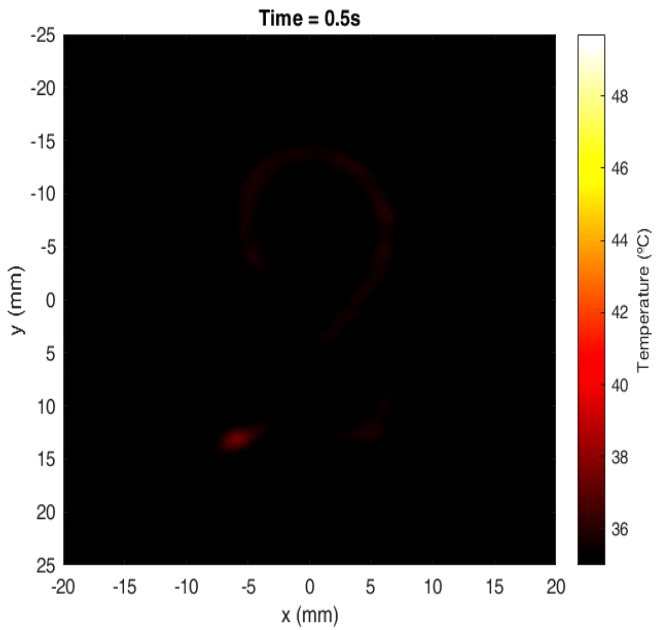
- Cow liver tissue
- Measurements: thermal imaging infrared camera

IR camera (FLIR TG165)

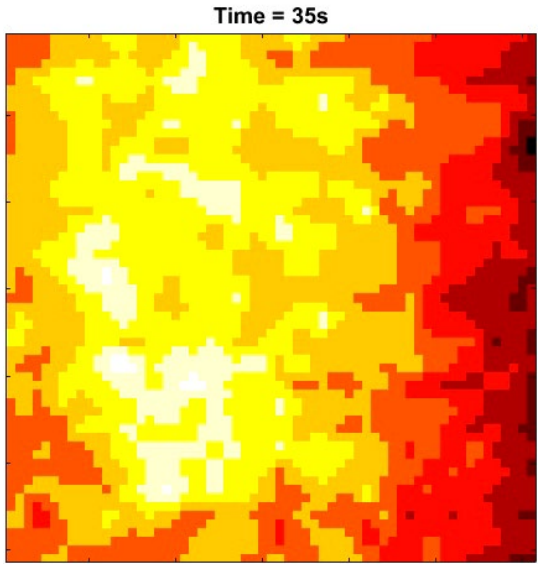


Thermal pattern

Simulation



Experiment



Holographic thermal patterns

Instituto de Instrumentación para Imagen Molecular



In collaboration with Jonathan Vappou, CNRS (France)

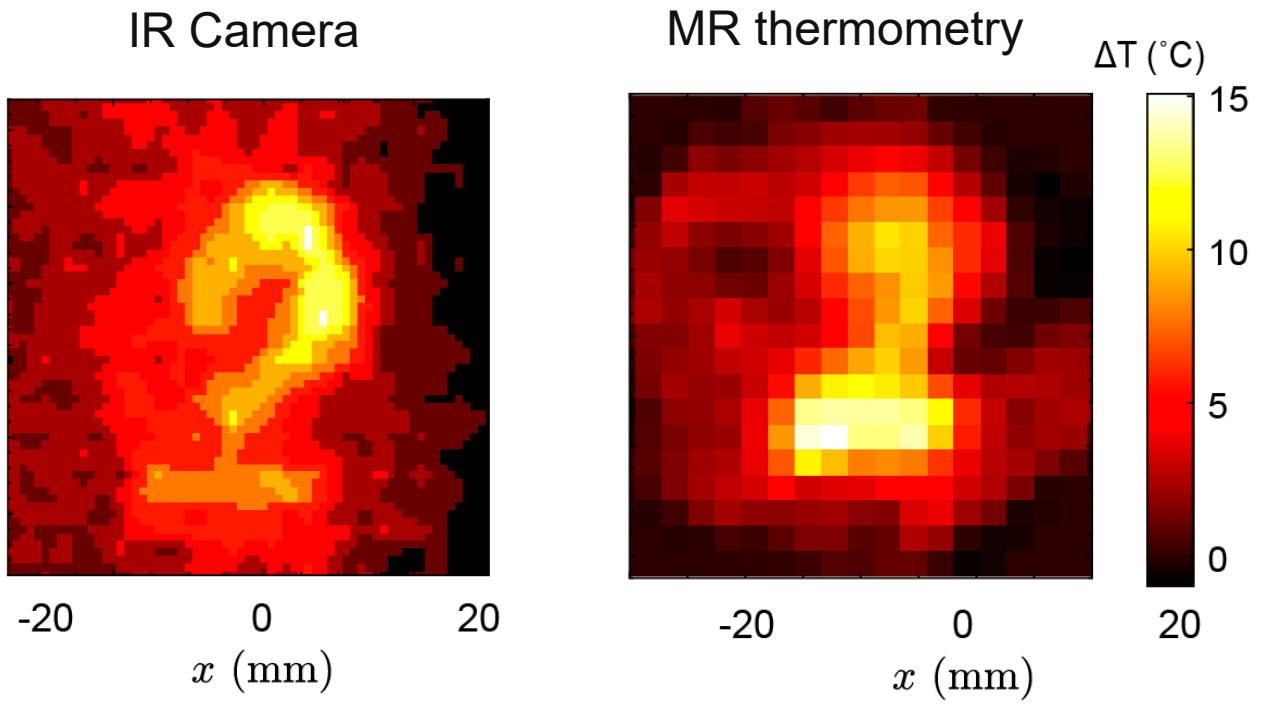
Experimental demonstration (weakly nonlinear regime)

- 3D printed hologram
- Plane transducer: 2a = 50 mm, f = 1,1 MHz
- Max pressure ~ 2 MPa (weakly nonlinear)
- Gelatin + milk phantom
- Measurements: 1.5-Tesla MRI thermometry

1.5T Aera MRI (Siemens)
Strasbourg facility



Thermal pattern



Thermal holograms

Instituto de Instrumentación para Imagen Molecular

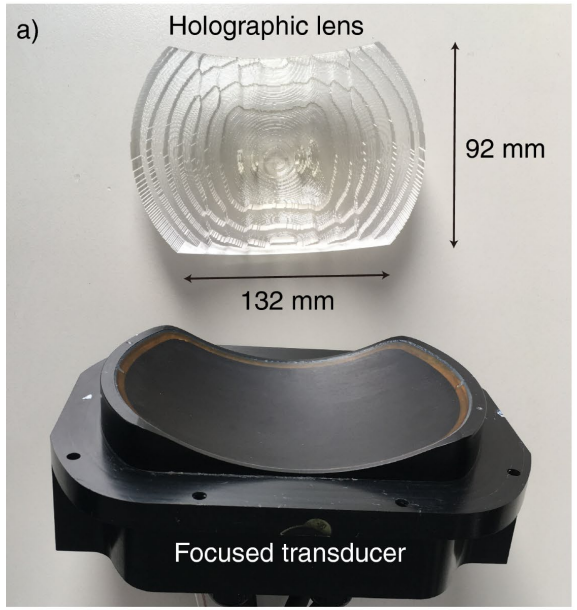
In collaboration with Jonathan Vappou, CNRS (France)



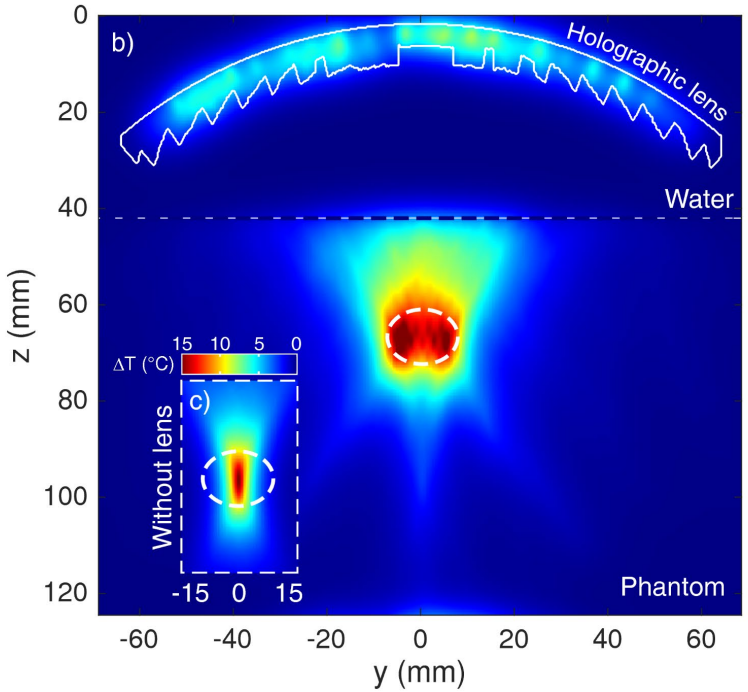
Thermal patterns for ultrasound hyperthermia

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

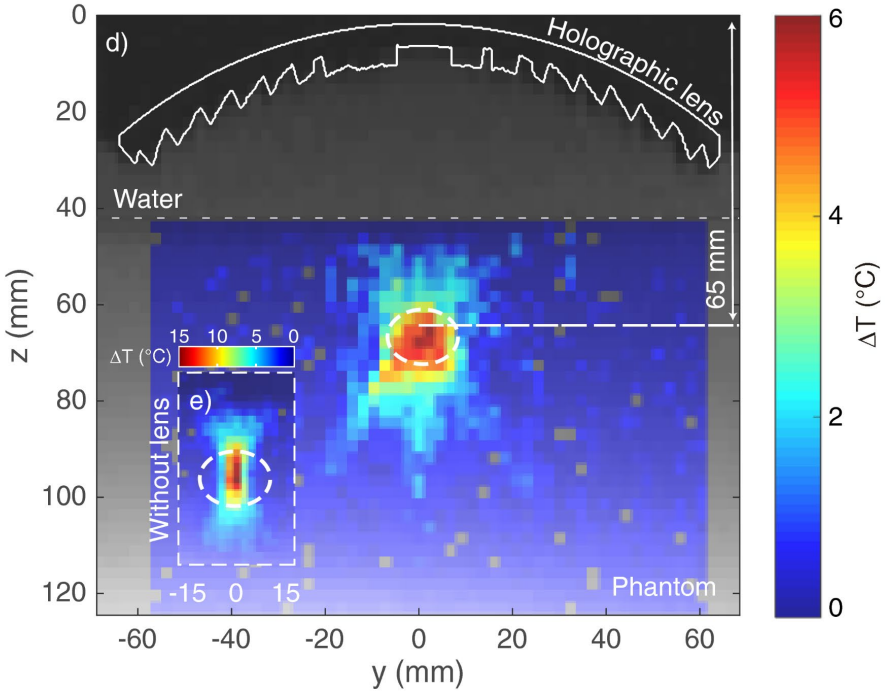
Experimental setup



Thermal simulation



1.5-Tesla MRI thermometry



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

Thermal holograms

Instituto de Instrumentación para Imagen Molecular

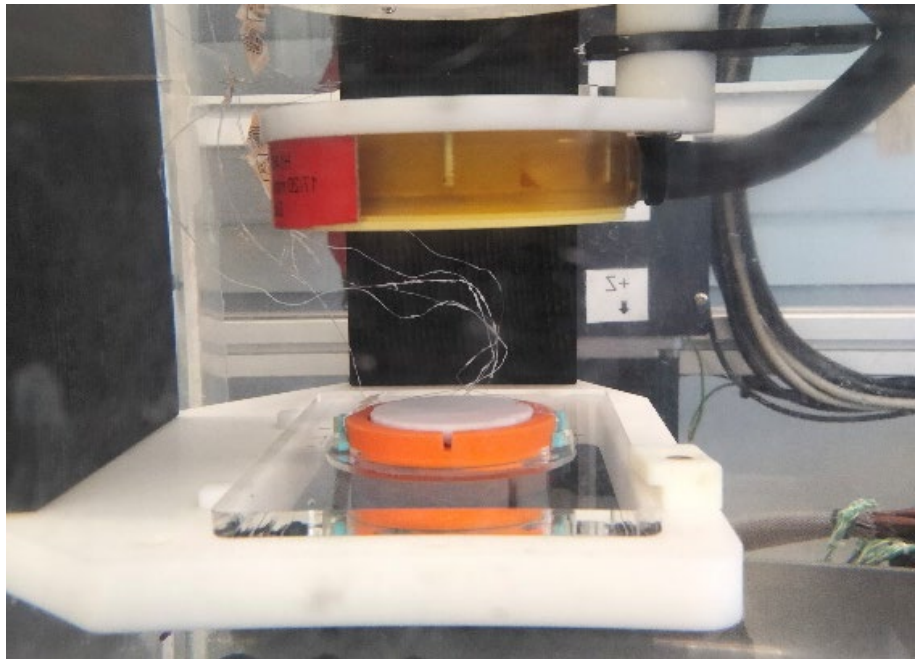


In collaboration with Gail Ter Haar, ICR (UK)

Thermal patterns for ultrasound hyperthermia

- In-vitro tested on human glioma spheroids







Thermal holograms

Instituto de Instrumentación para Imagen Molecular

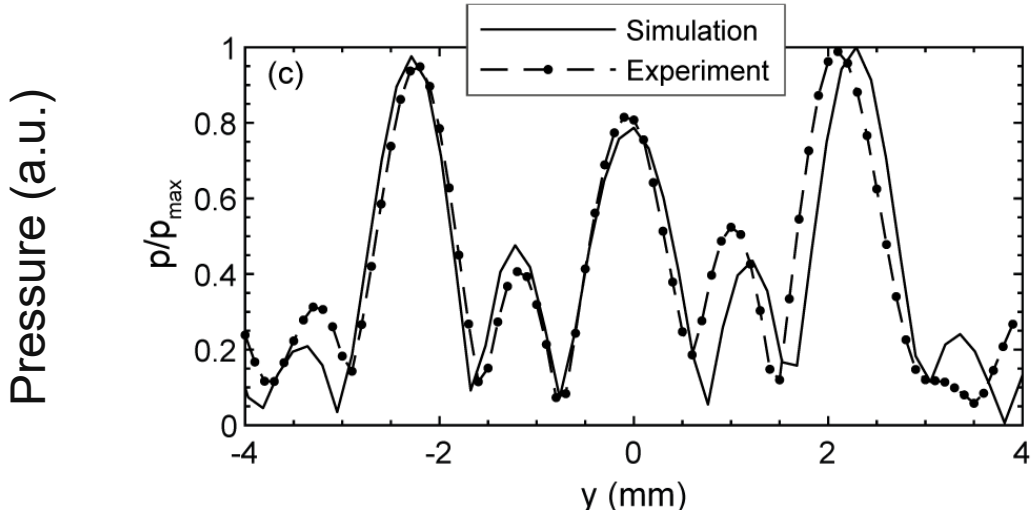
In collaboration with Gail Ter Haar, ICR (UK)



Look for uniform thermal dose on spheroids

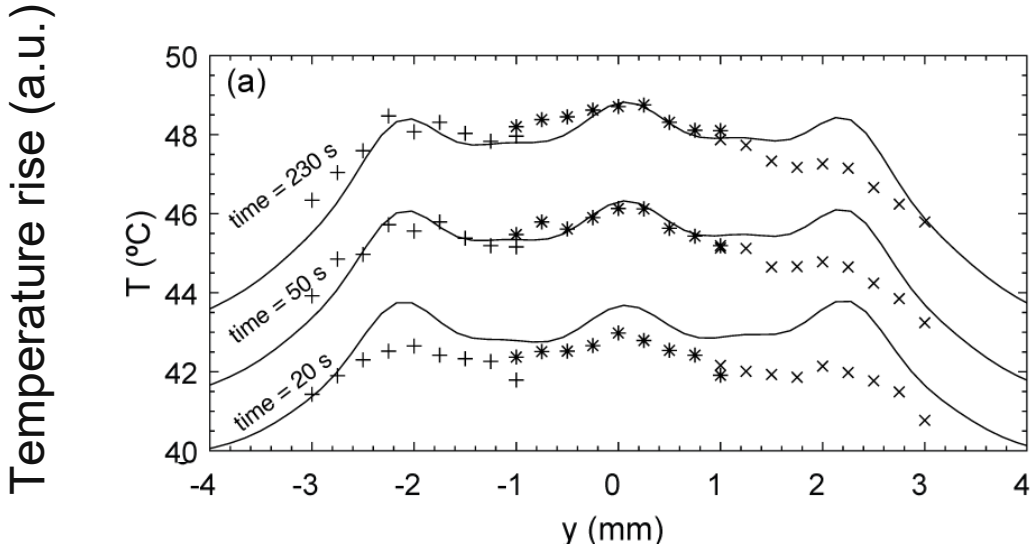
- What is the optimal field?

Uniform field at targets



Transverse direction

Nonuniform temperature distribution



Transverse direction

Thermal holograms

Instituto de Instrumentación para Imagen Molecular

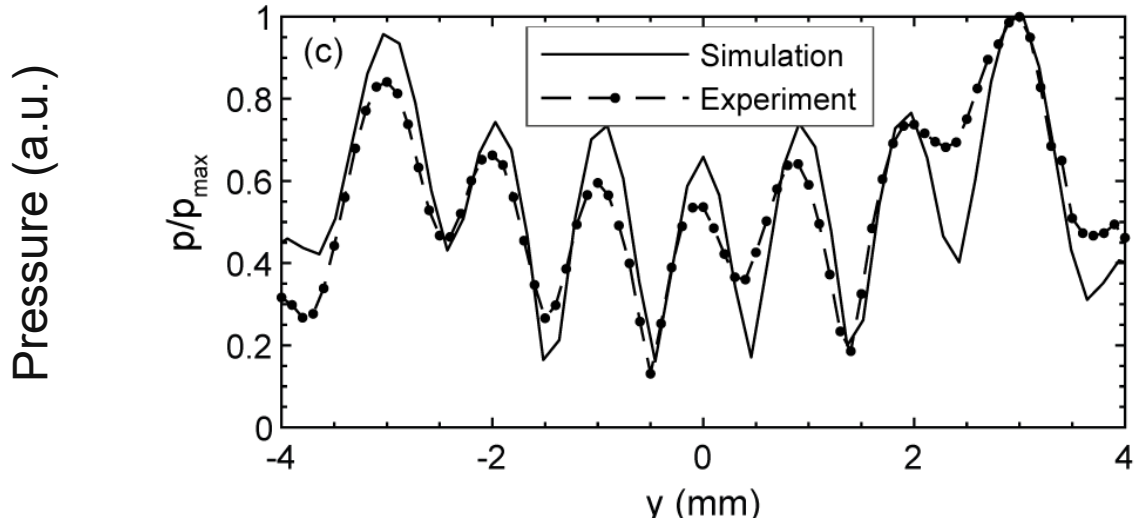
In collaboration with Gail Ter Haar, ICR (UK)



Thermal patterns for ultrasound hyperthermia

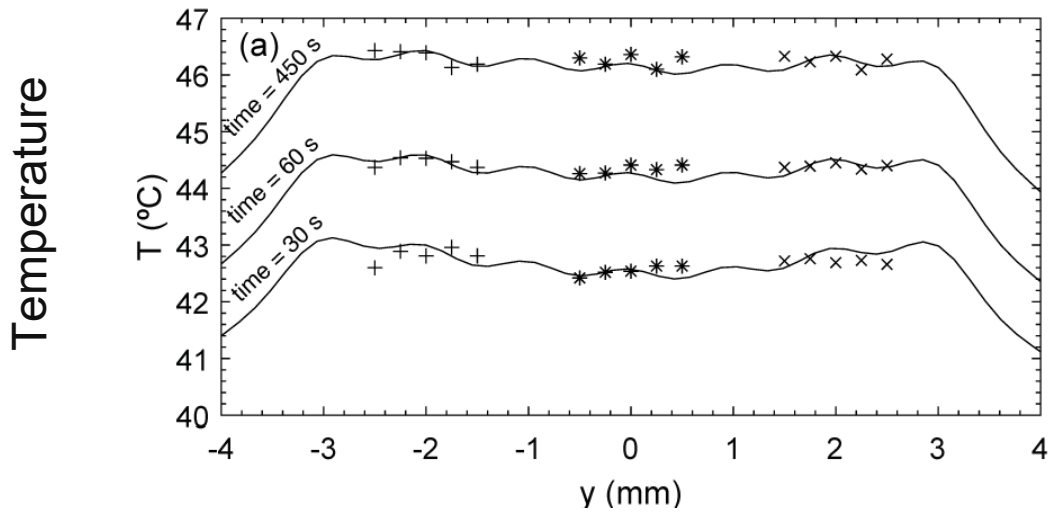
- What is the optimal field?

Nonuniform field at targets



Transverse direction

Uniform temperature distribution



Transverse direction

Thermal holograms

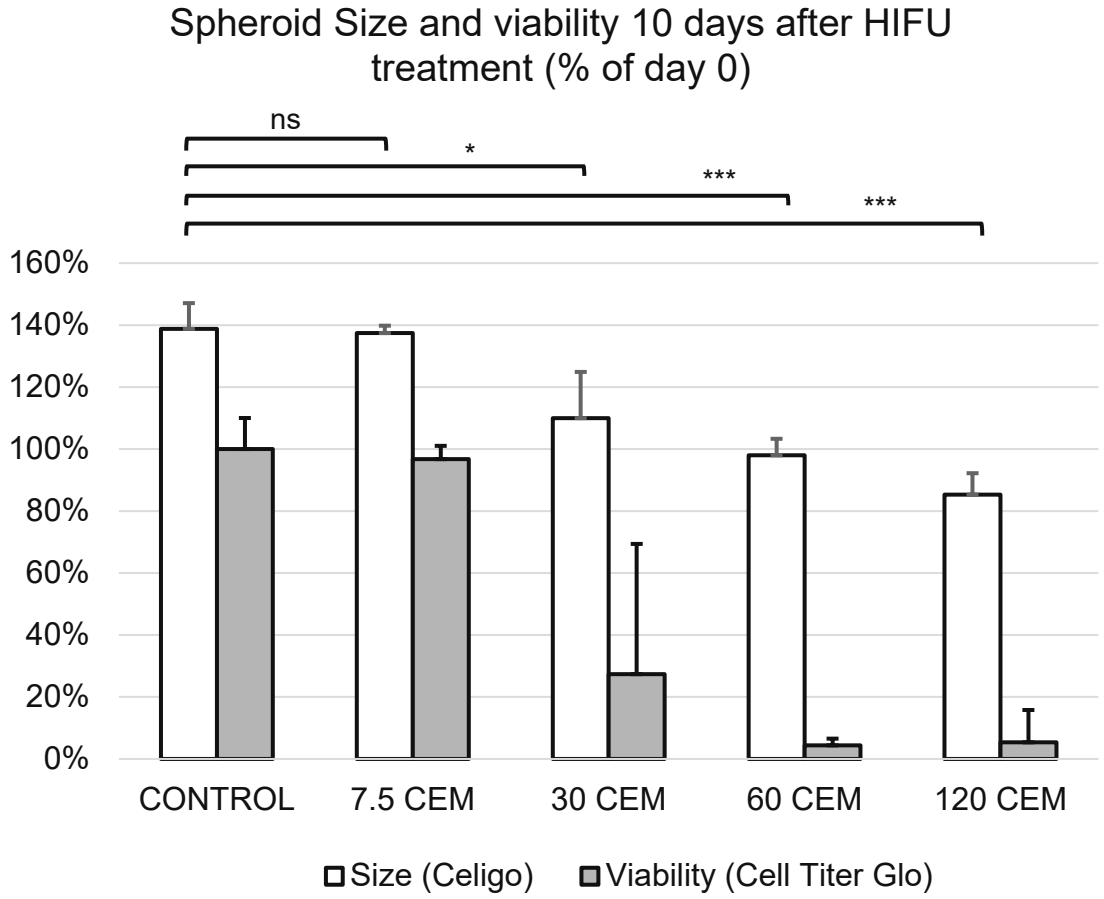
Instituto de Instrumentación para Imagen Molecular

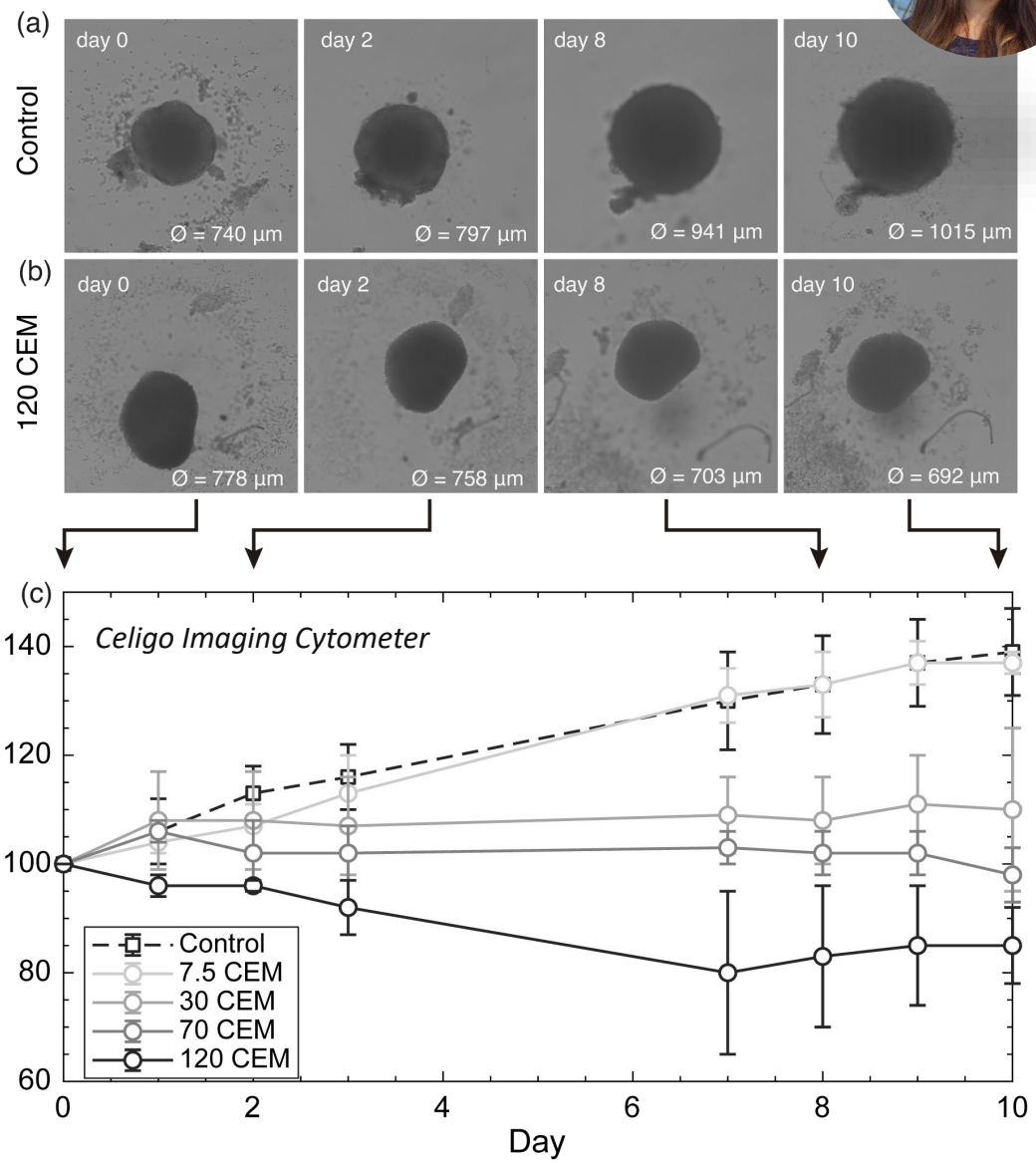


In collaboration with Gail Ter Haar, ICR (UK)

Thermal patterns for ultrasound hyperthermia

- In-vitro tested on human glioma spheroids





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 (CINAC)** and **human trials (NYC)**
- Broadband / phase and amplitude holograms: **phononic crystals** and **metamaterials**
- Reconfigurable holograms: Towards active **spatial-sound modulators (for high-amplitude US)**



Publications

Papers

- 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)
- 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 (2021)
- 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. “Holograms to focus arbitrary ultrasonic fields through the skull.” Physical Review Applied, 12 (1), pp. 014016, (2019)
- 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

Never walk alone…

- Sergio Jimenez-Gambín (I3M, Valencia) (Now PostDoc at Columbia University)
- Diana Andrés (PhD Student) (I3M, Valencia)
- Nathalie Lamothe (PhD Student) (I3M, Valencia)
- Francisco Camarena (Prof. UPV) (I3M, Valencia)
- José María Benlloch (Prof. CSIC) (I3M, Valencia)
- Antonios Pouliopoulos, (King's College, London, UK)
- Elisa E. Konofagou (Columbia University, NYC, USA)
- Jonathan Vappou (Université d'Strasbourg / NCRS, Strasbourg, France)
- Gail Ter Haar, Institute of Cancer Research (London, UK)
- Ian Rivens, Institute of Cancer Research (London, UK)



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- Agència Valenciana de la Innovació: INNVAL10/19/016, INNCON/2020/009.
- Generalitat Valenciana: ACIF/2017/045.
- European Union: IDIFEDER/2018/022