Metamaterials for therapeutic ultrasound applications

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Isaac Newton Institute for Mathematical Sciences

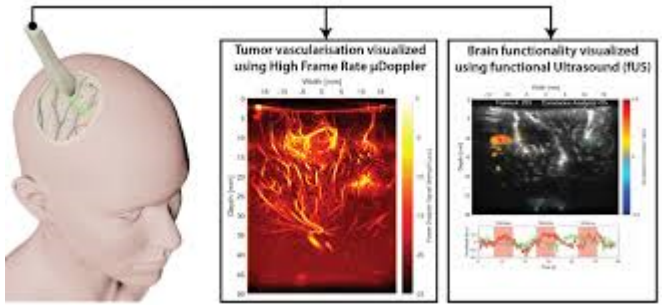
Multiple scattering in engineering and applied sciences MWSW04 22 May 2023 to 26 May 2023

Introduction

Ultrasound Imaging

Use a **low-amplitude** acoustic waves to image the tissue.

- Classical US: Morphology + flow
- New: Molecular contrast
- New: Functional ultrasound



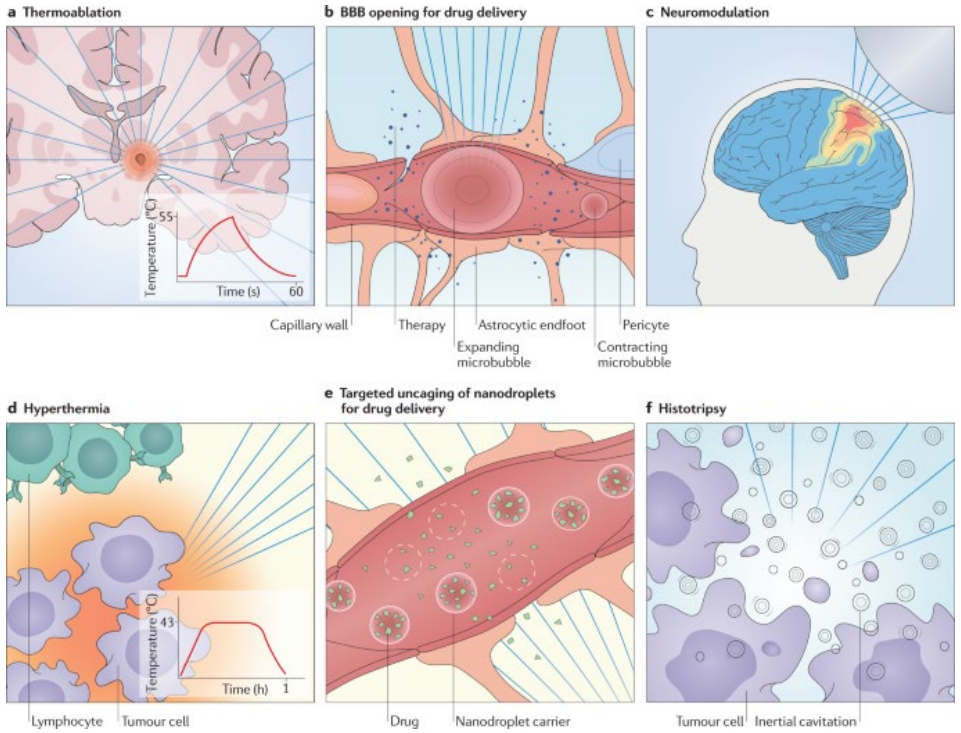
Therapeutic ultrasound

Use a **high-intensity** focused beam of acoustic waves to a biological effect on the tissues

- Thermal mechanism
- Mechanical mechanism

On the brain

- Thermoablation (HIFU)
- Hyperthermia
- Histotripsy
- Neuromodulation
- Drug delivery by BBBO
- Drug delivery carriers

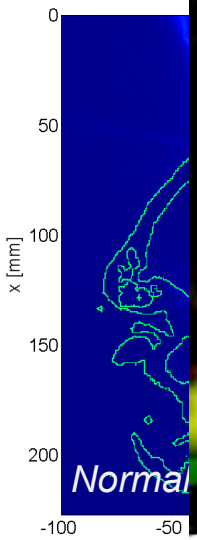



gentle motion
(in acoustics)
violent motion
(in acoustics)
almost at rest
(in acoustics)

Focus

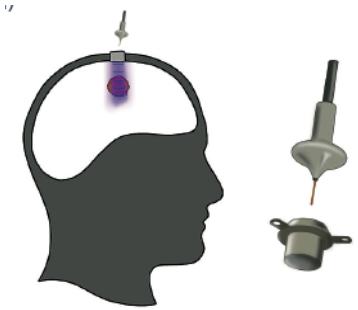
Transc

- 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



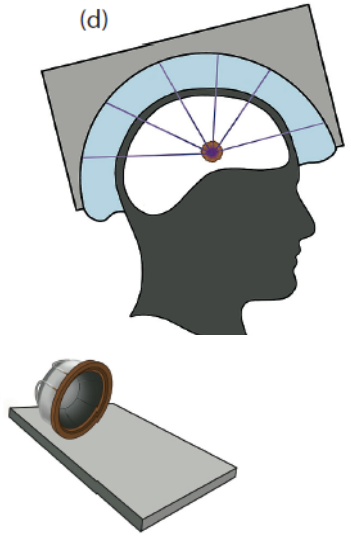
Single element transducer

- 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

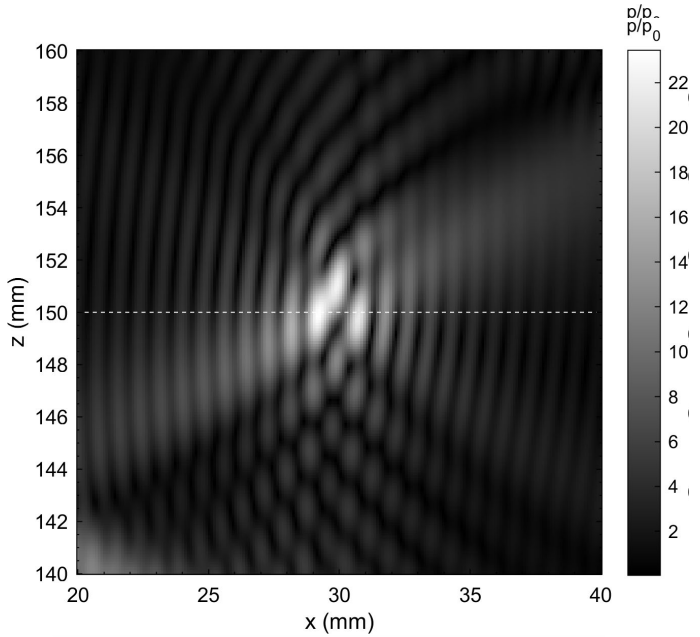
Focusing challenges

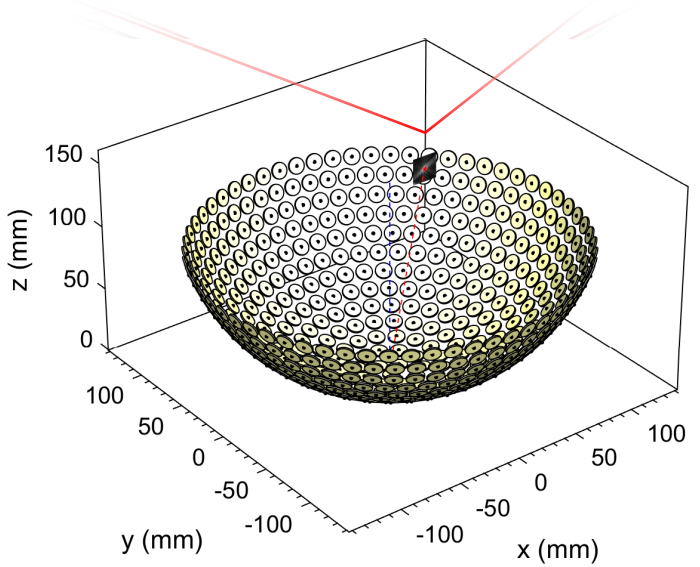
Focusing

- 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



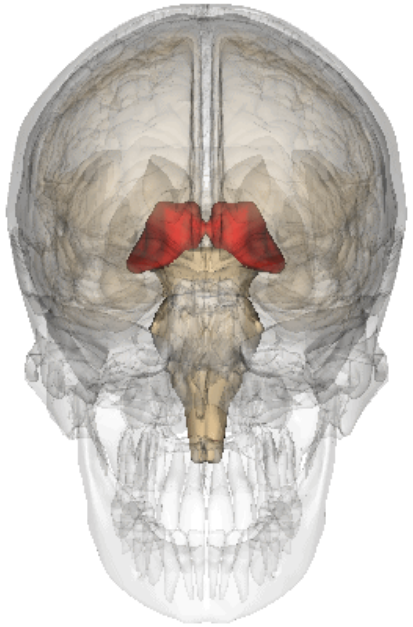


Focusing challenges

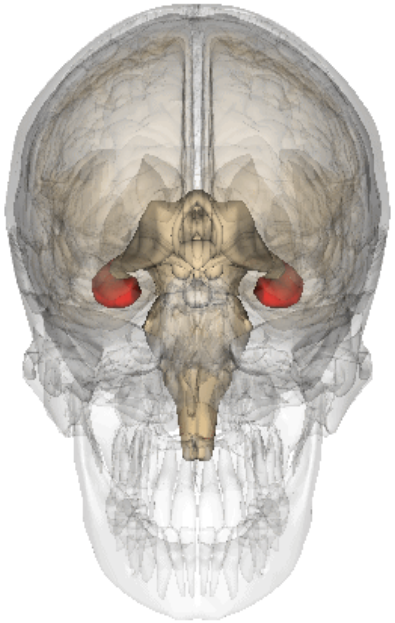
Complex target morphology

- Can we adapt the beam to the therapeutical target?

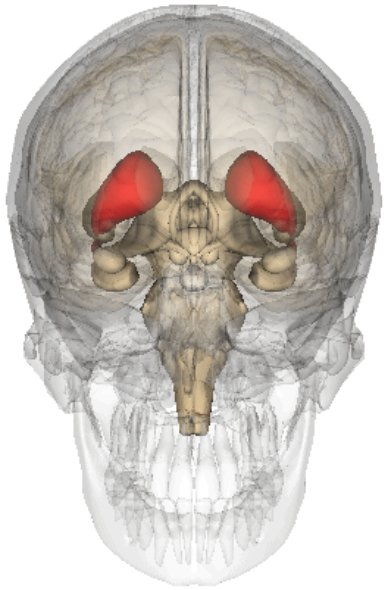
Thalamic nuclei



Hippocampus

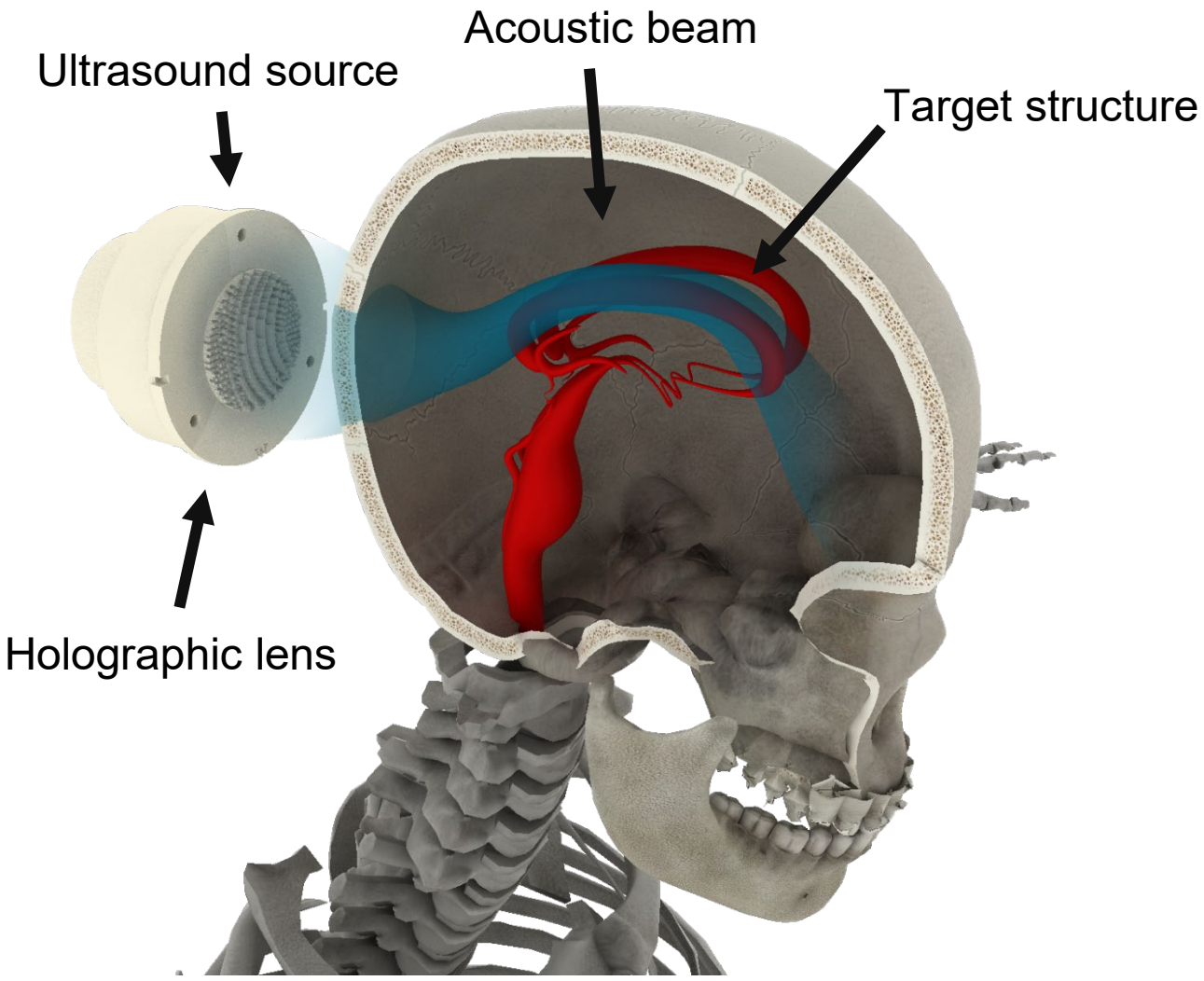


Caudate nucleus



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)

Why holograms?

High pixel density:

- Frecuency: 1 MHz → λ = 1.5 mm

No grating lobes.

- Separation < $\lambda/2$

Wide angular spectrum:

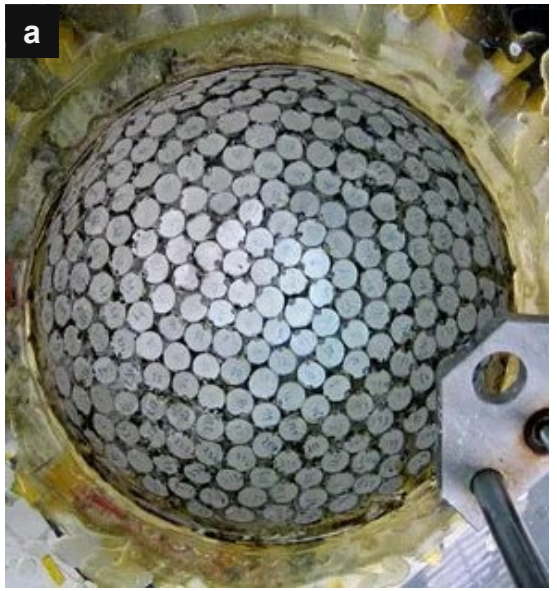
- Encode multiple scattering,
- Reflections,
- Reverberation.

Patient specific:

- Compensate refraction aberrations.

Treatment specific:

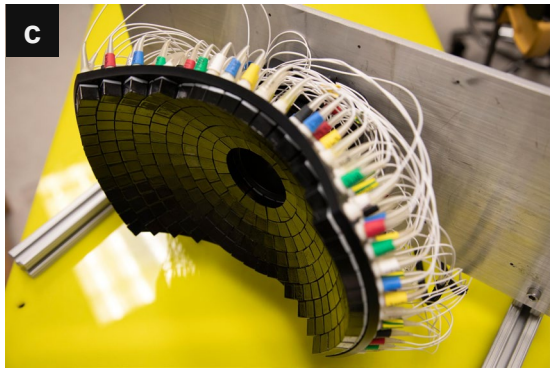
- Simultaneous focus on therapeutic target.



NaviFus: 1024 elements



Insightec Exablate: 2048 elements



Histosonics: 1024 elements

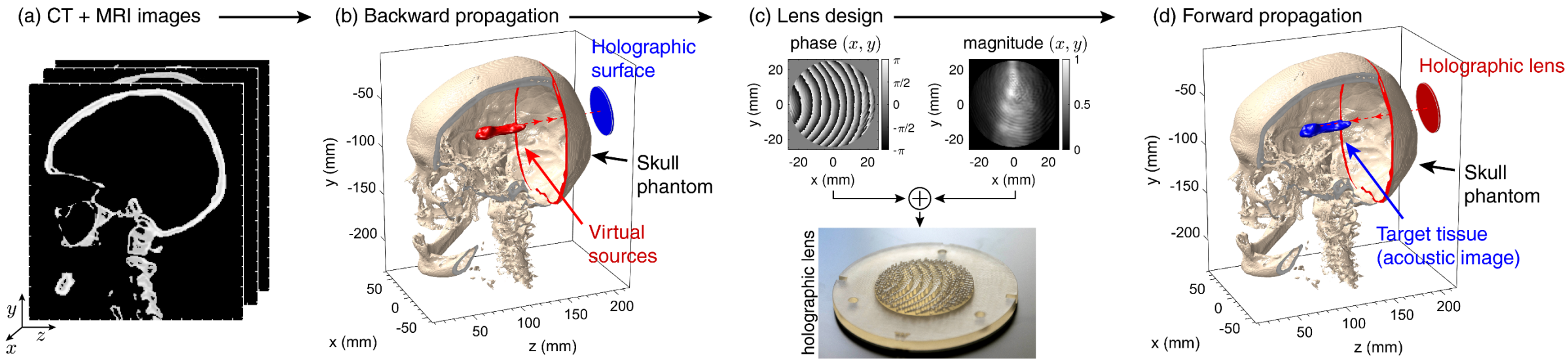


Holograms: > 100.000 elements

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)

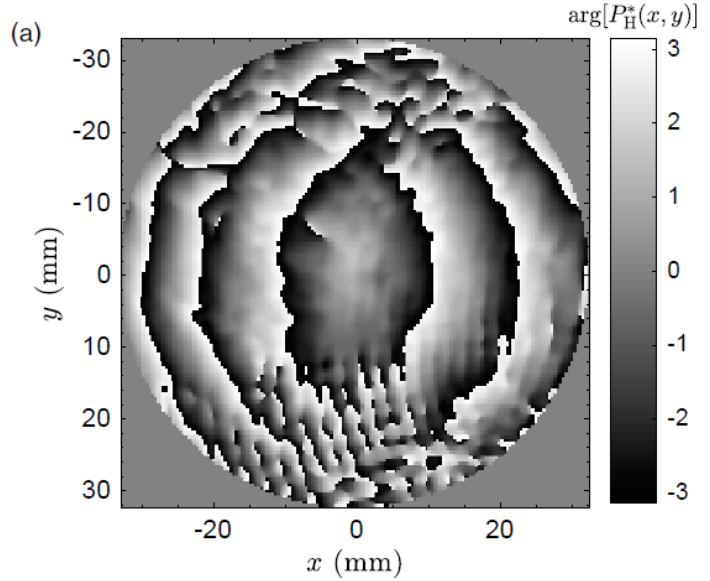
$$T(x, y) = \frac{2Ze^{-ik_0(d-h(x,y))}}{2Z\cos(k_L h(x, y)) + i(Z^2 + 1)\sin(k_L h(x, y))},$$

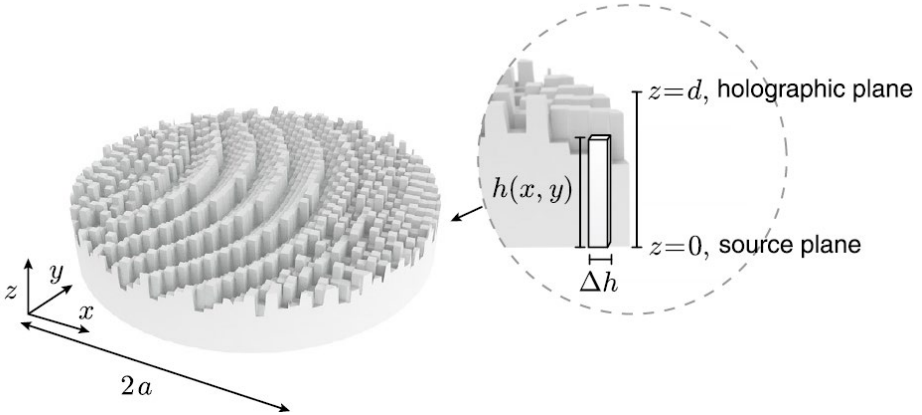
- Find the heigh function $h(x, y)$,producing

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

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

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





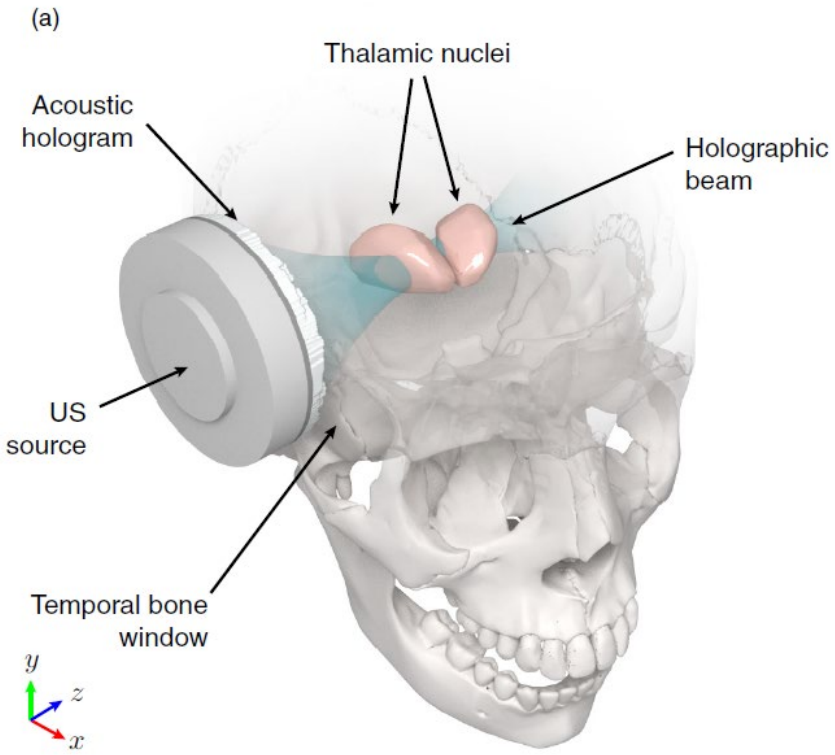
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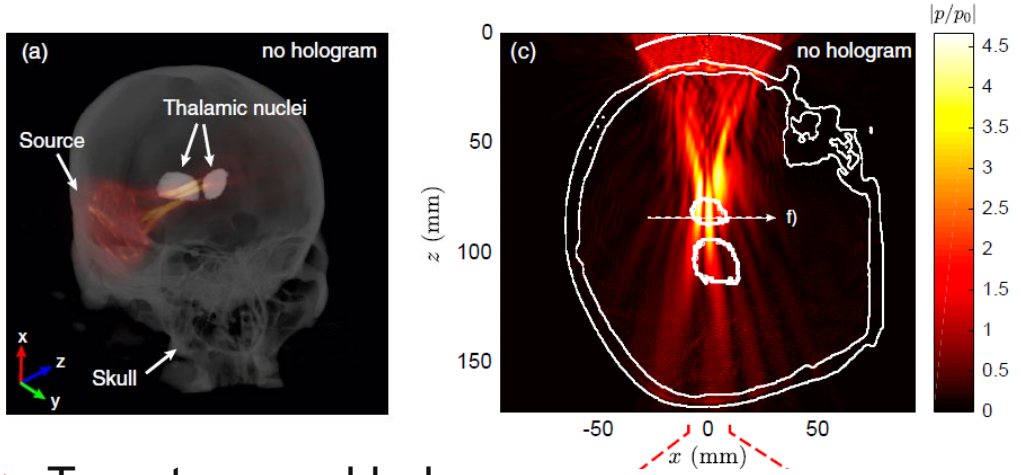
Acoustic holograms

Using the temporal window

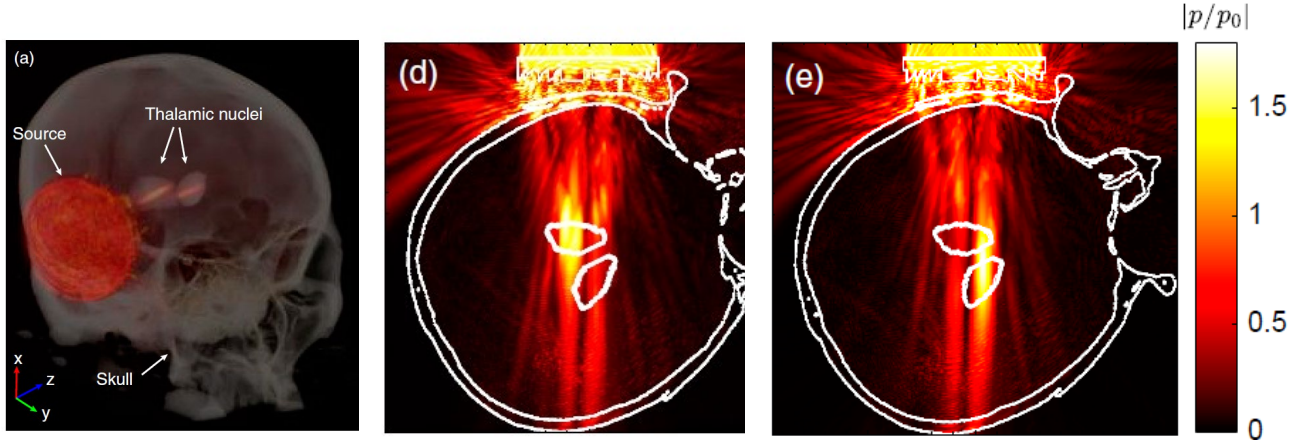
- Low thermal dose and deep-brain focusing



- Standard focused transducer (650 kHz)

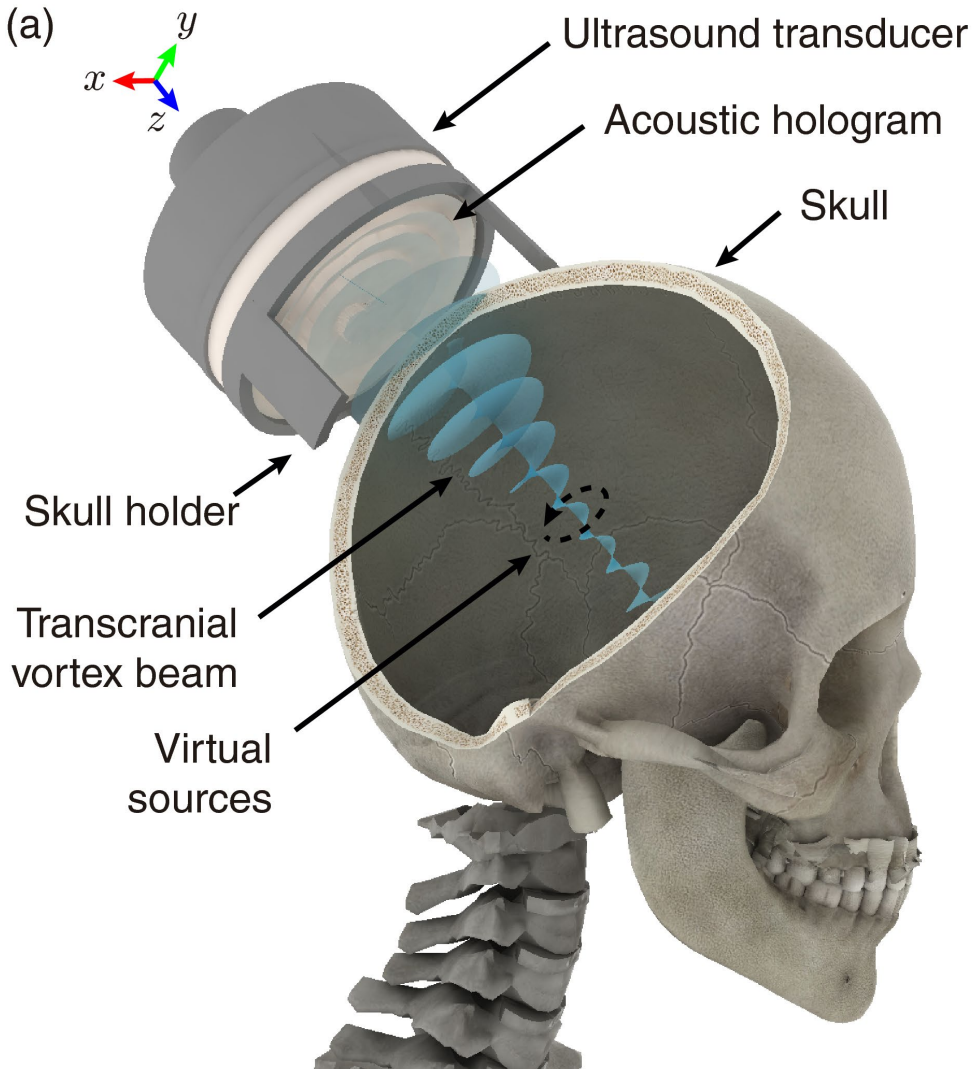


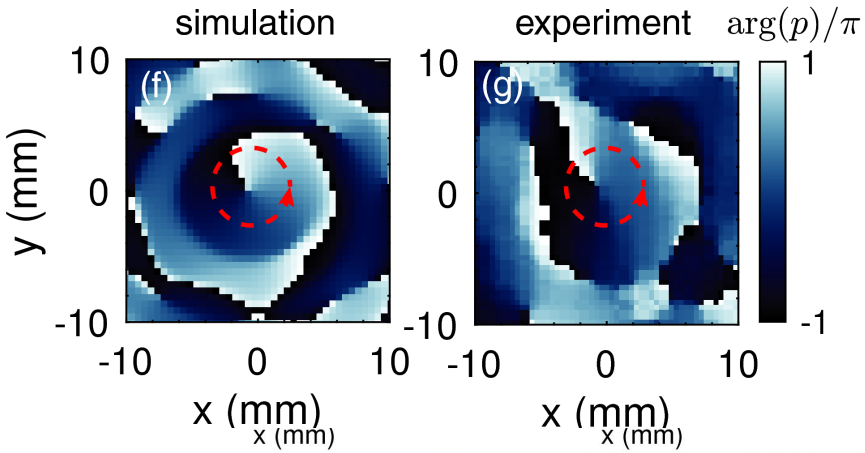
- Transtemporal hologram

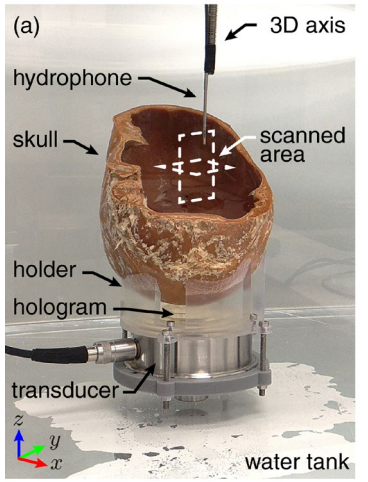


Diana Andrés, et al. *Ultrasound in Medicine & Biology* 48 (5) 872-886 (2022)

Focusing acoustic vortices through the skull







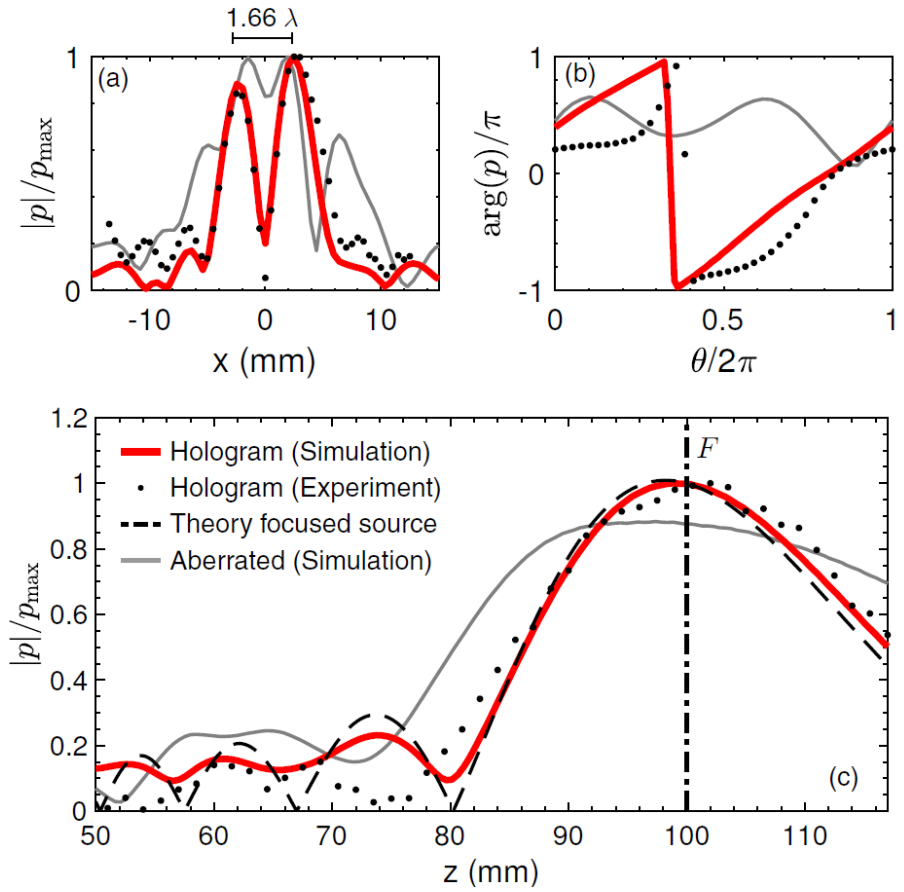


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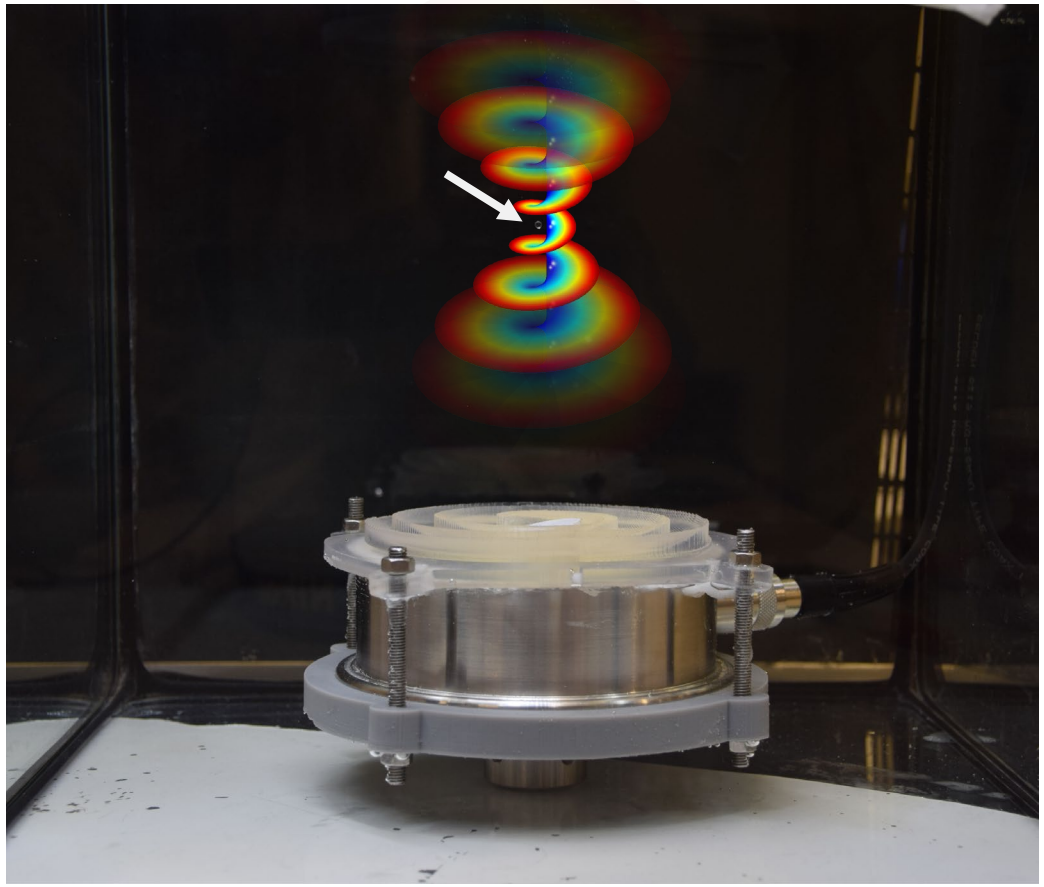
Focusing acoustic vortices through the skull

Topological charge can be tuned

- Aberration correction



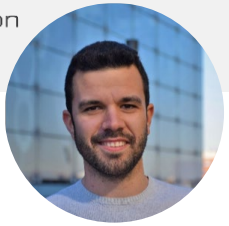
- Particle trapping: potential for clot manipulation



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

In-vivo validation for BBBO

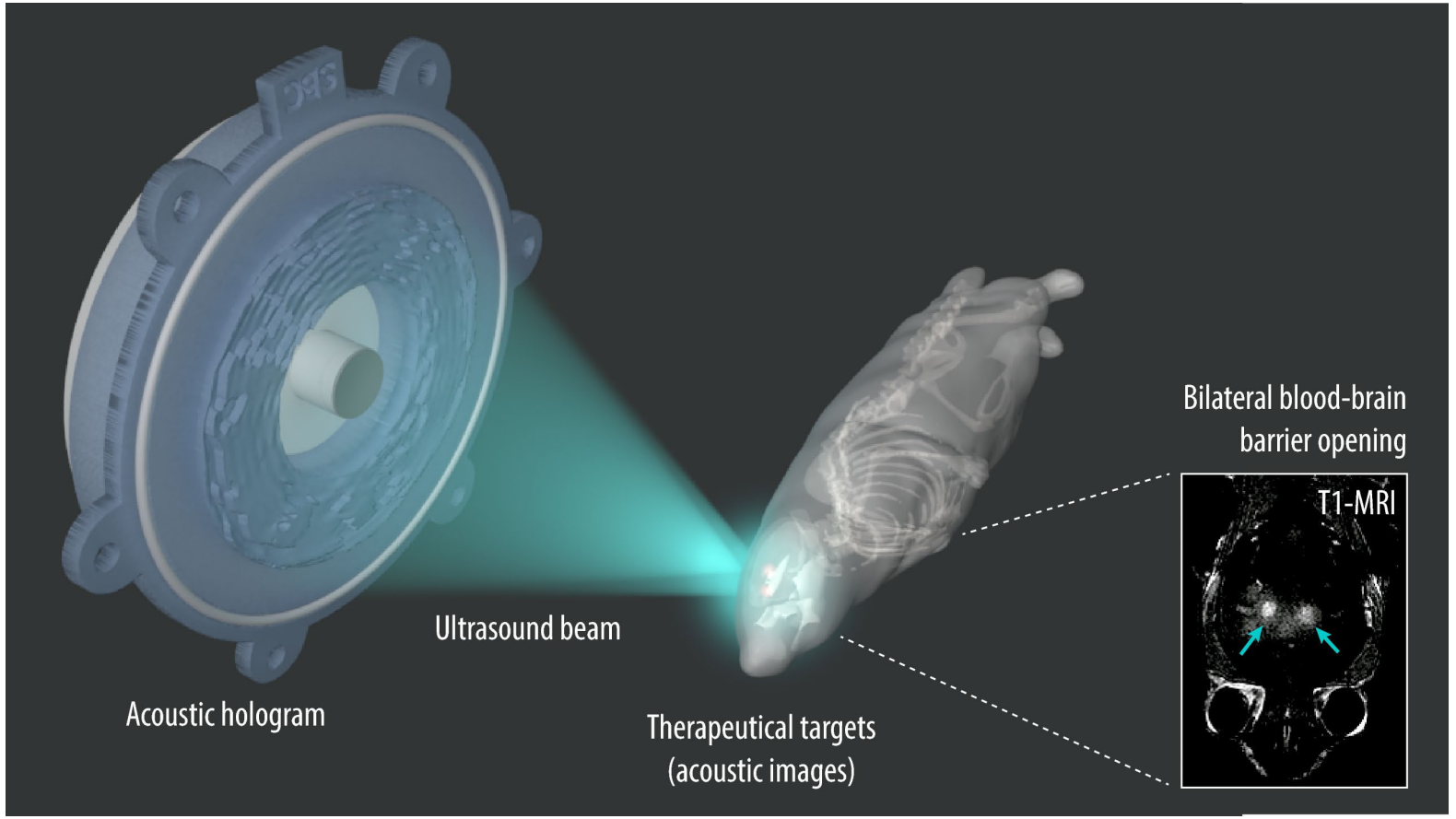
Instituto de Instrumentación para Imagen Molecular



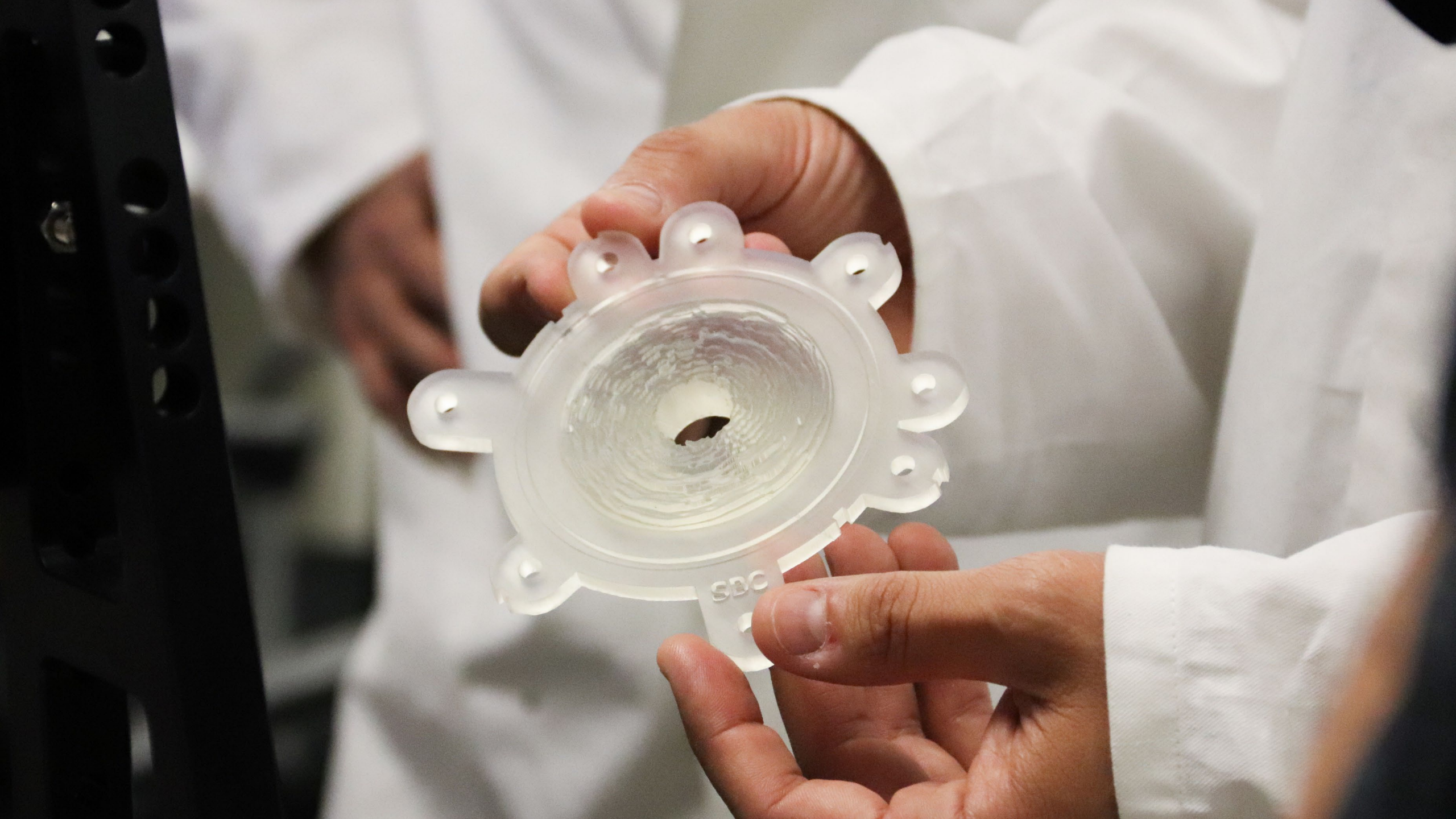
In collaboration with E.E. Konofagou, Columbia University (NYC, USA)

Bilateral blood-brain barrier opening

- First in-vivo application of acoustic holograms



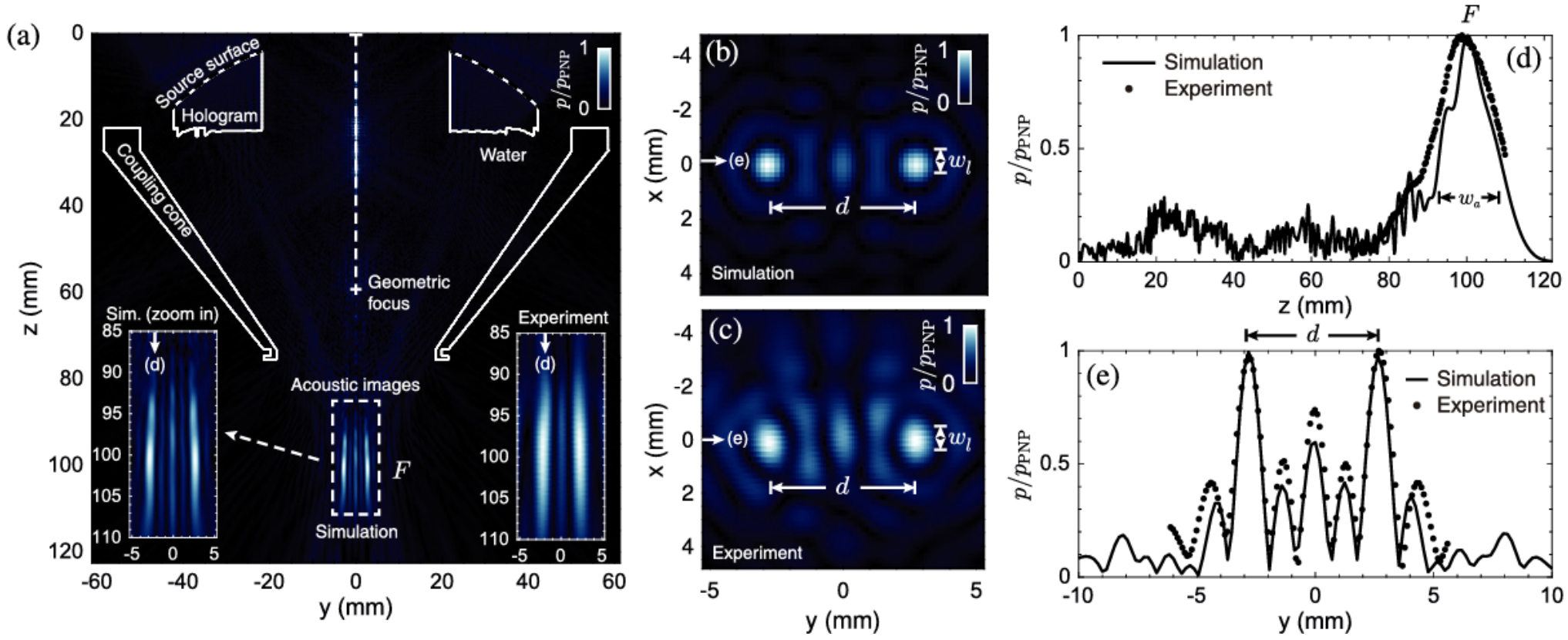
Jiménez-Gambín, et al. IEEE Transactions on Biomedical Engineering 69 (4) 2022
(featured at the cover May 2022)


SBC

In-vivo validation for BBBO

Lens performance in water

- Bilateral elongated focal spots

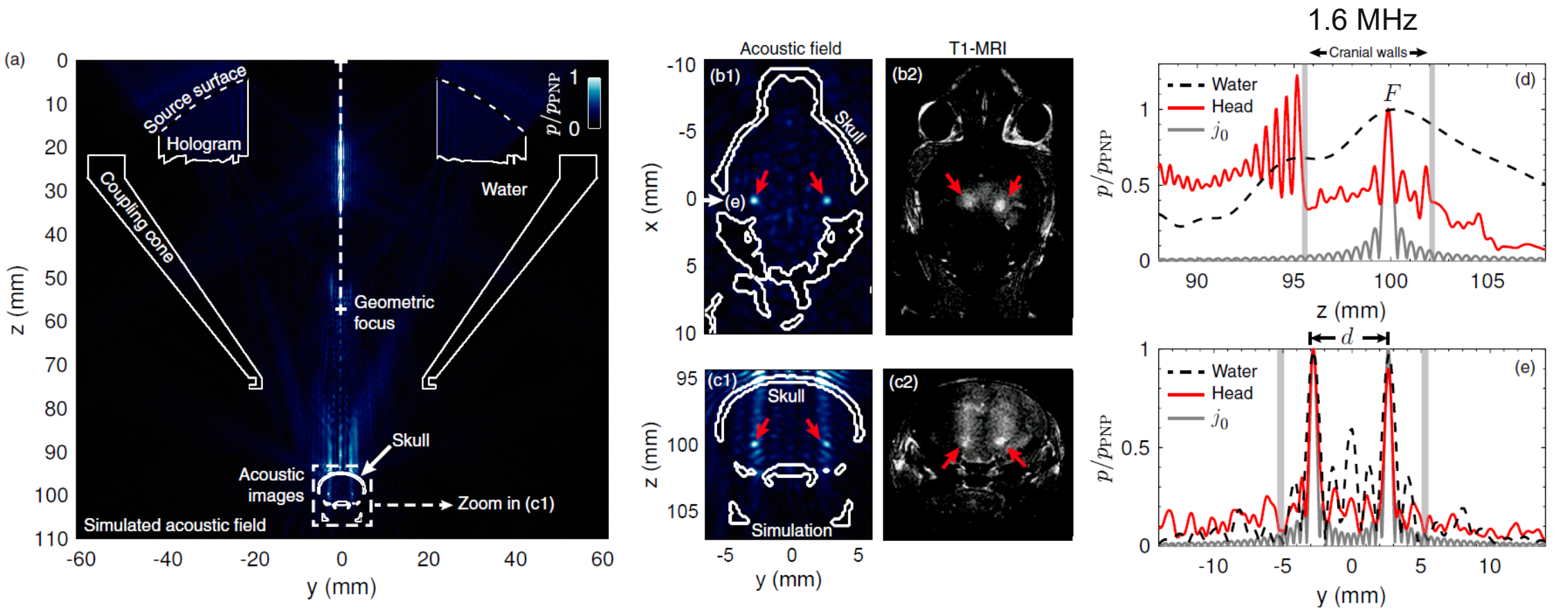


Jiménez-Gambín, et al. IEEE Transactions on Biomedical Engineering 69 (4) 2022

In-vivo validation for BBBO

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

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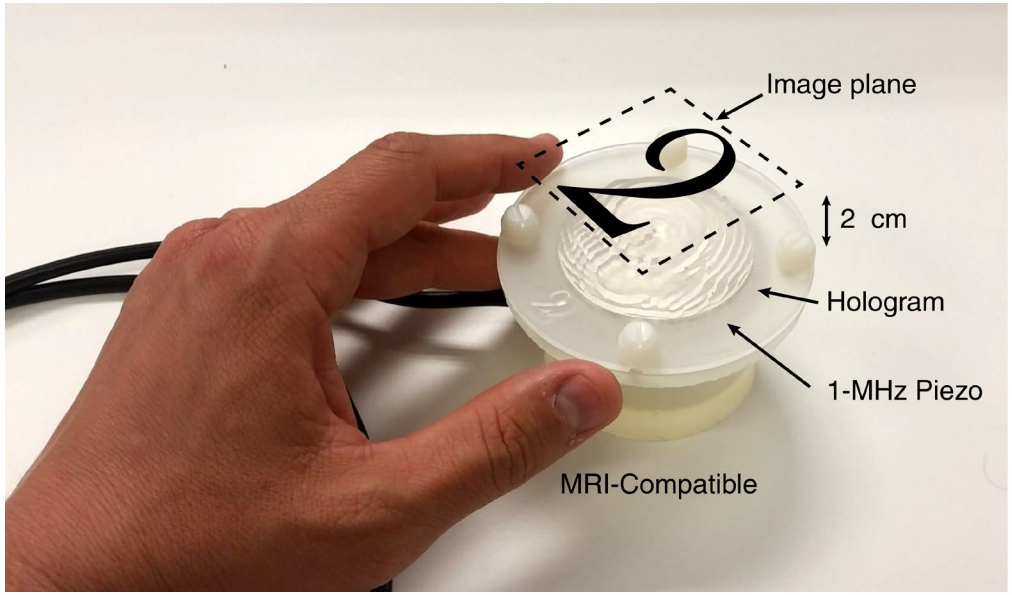
In collaboration with Jonathan Vappou, CNRS (France)



Thermal patterns for ultrasound hyperthermia

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

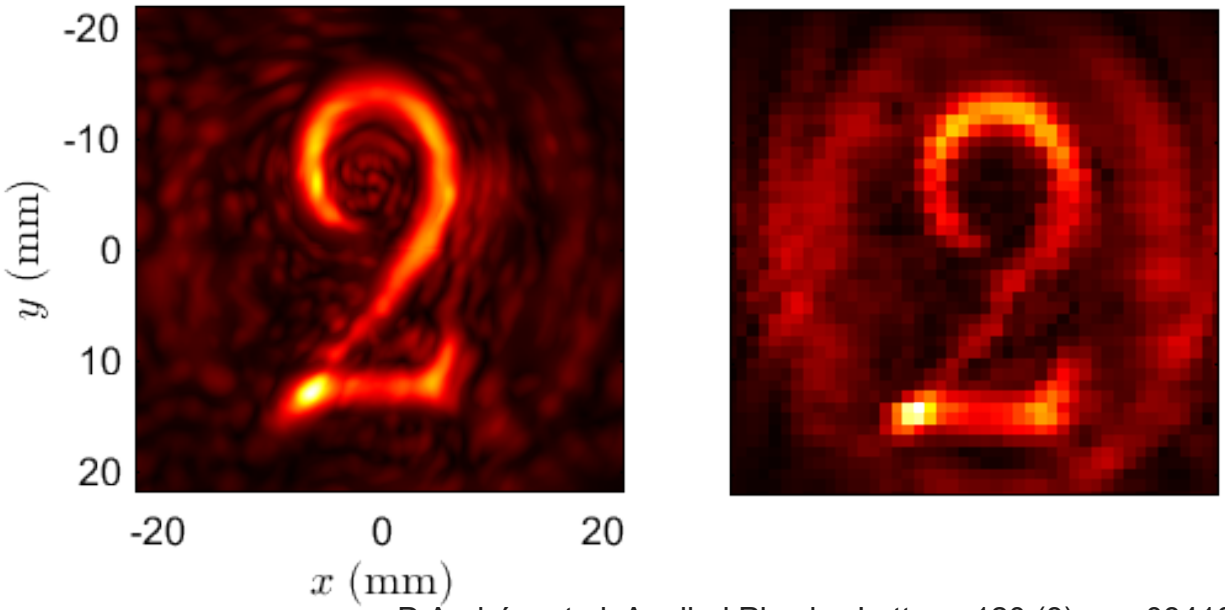
Experimental setup



Acoustic field

Simulation

Experiment



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

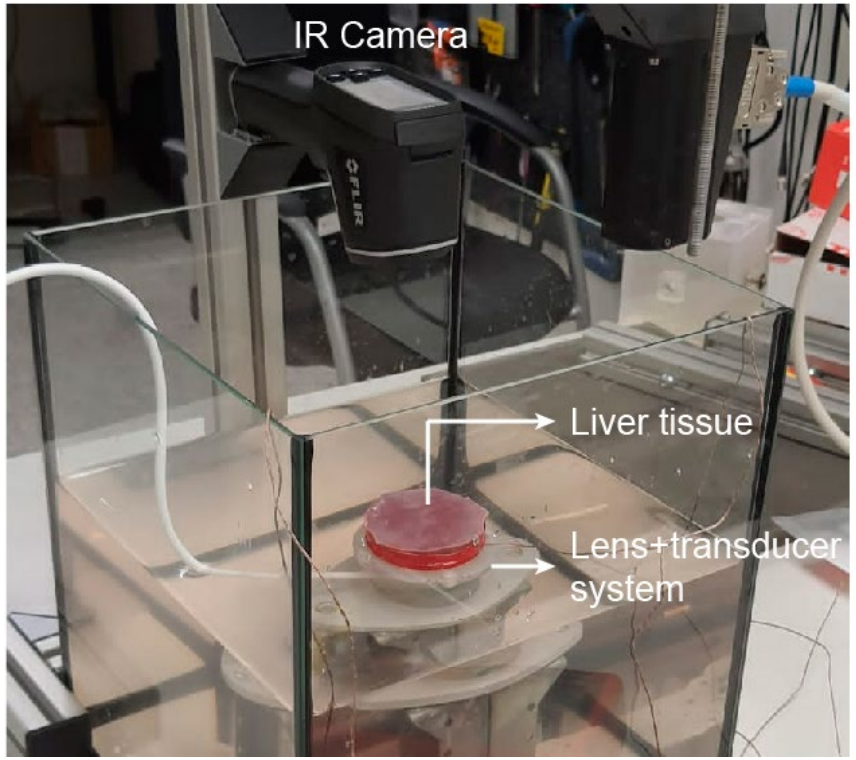
Holographic thermal patterns

Experimental demonstration (weakly nonlinear regime)

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

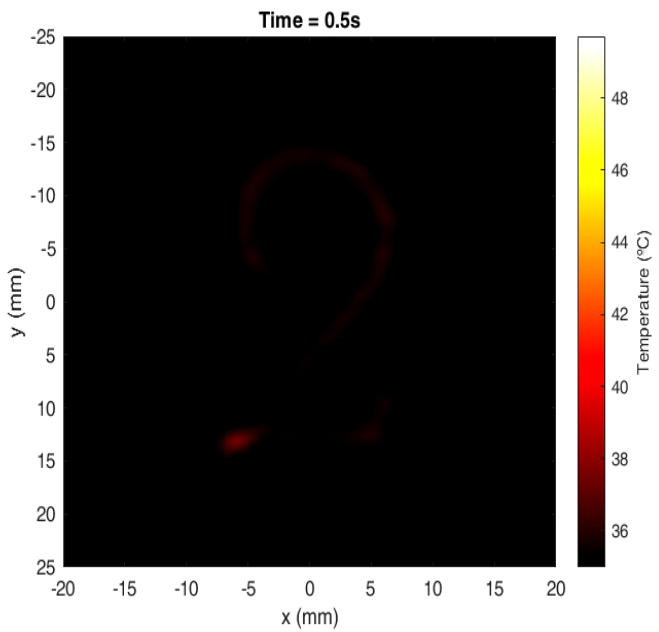
- Cow liver tissue
- Measurements: thermal imaging infrared camera

IR camera (FLIR TG165)

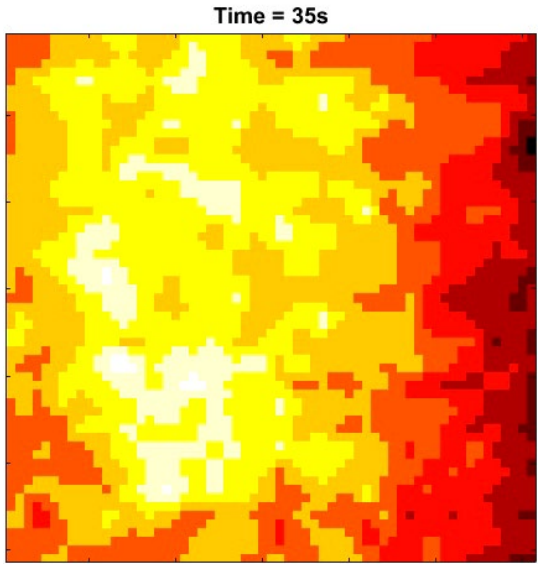


Thermal pattern

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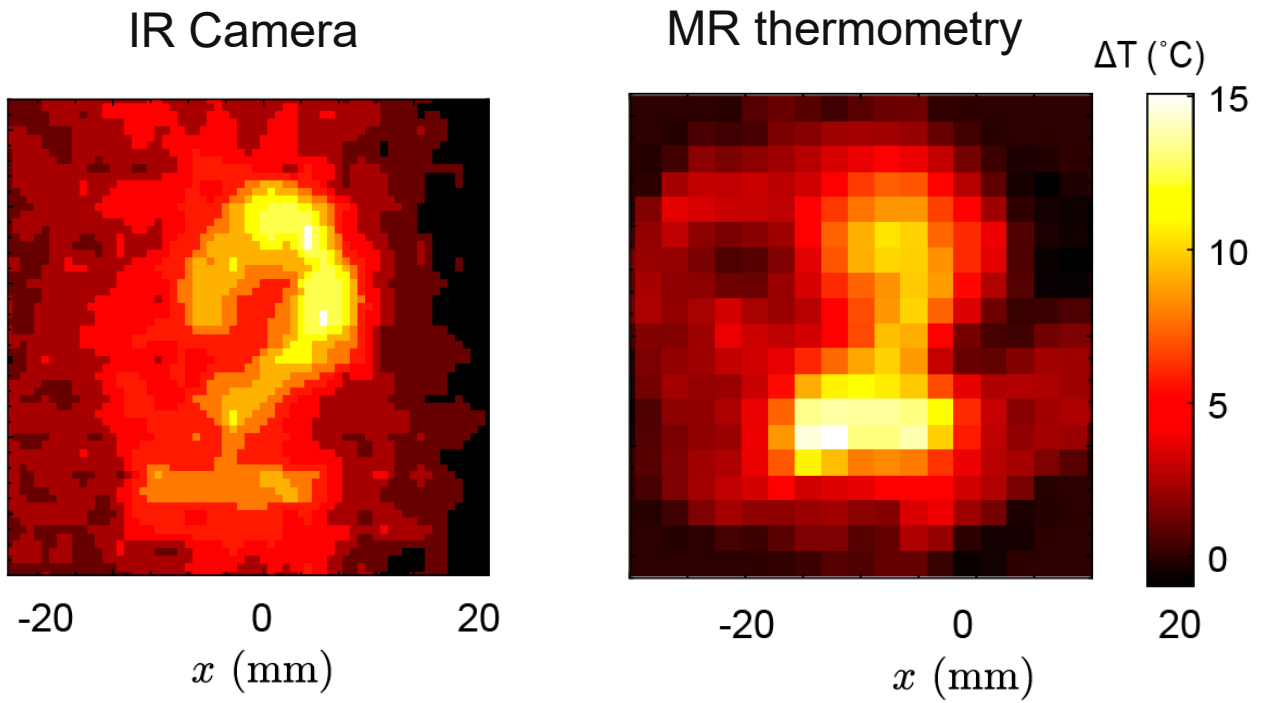
- 3D printed hologram
- Plane transducer: 2a = 50 mm, f = 1,1 MHz
- Max pressure ~ 2 MPa (weakly nonlinear)

- Gelatin + milk phantom
- Measurements: 1.5-Tesla MRI thermometry

1.5T Aera MRI (Siemens)
Strasbourg facility



Thermal pattern

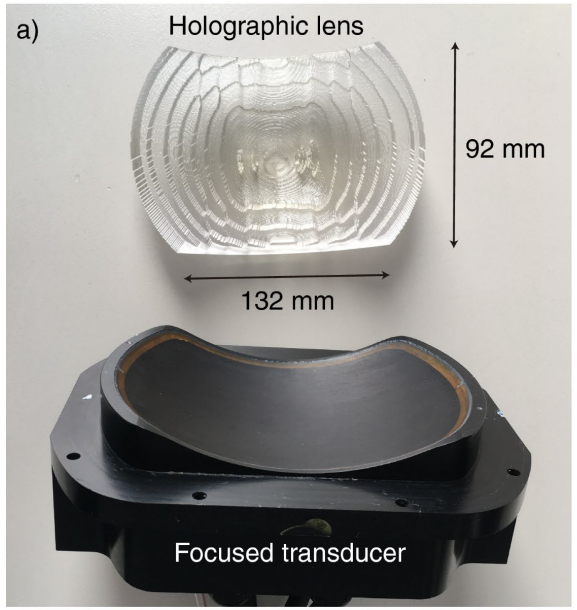


Thermal holograms

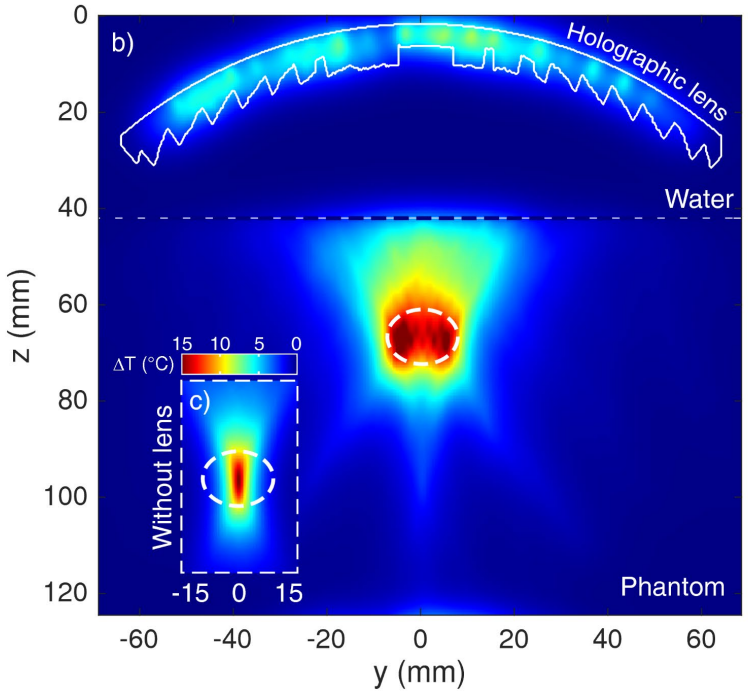
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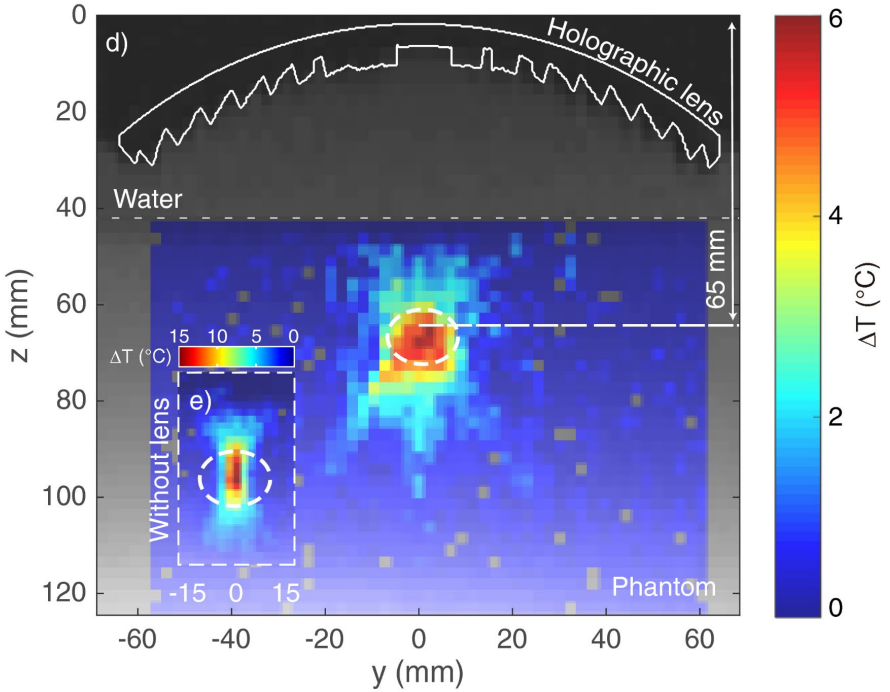
Experimental setup



Thermal simulation



1.5-Tesla MRI thermometry



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

Thermal holograms

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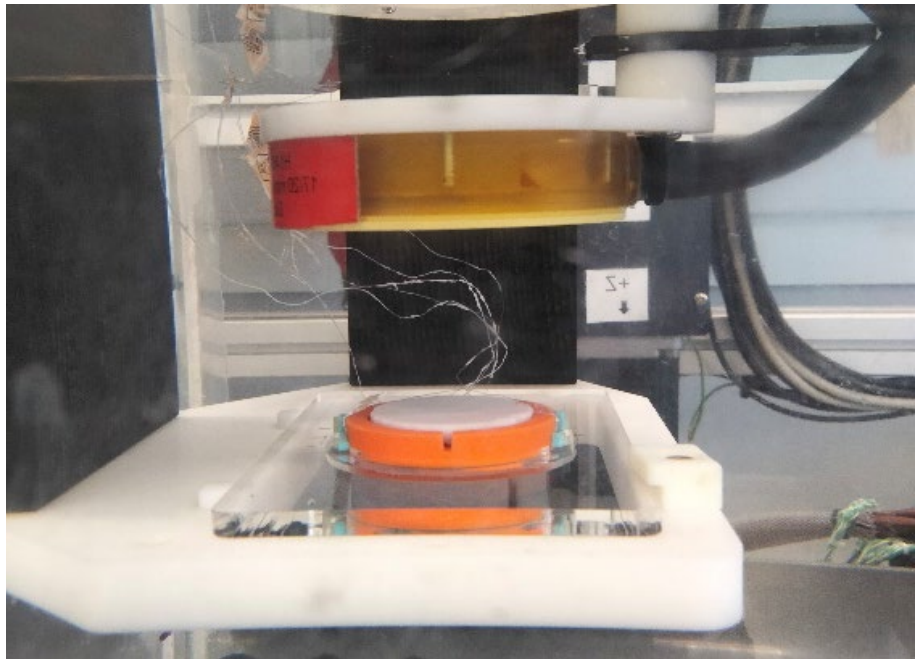


In collaboration with Gail Ter Haar, ICR (UK)

Thermal patterns for ultrasound hyperthermia

- In-vitro tested on human U87-MG glioma spheroids (glioblastoma)







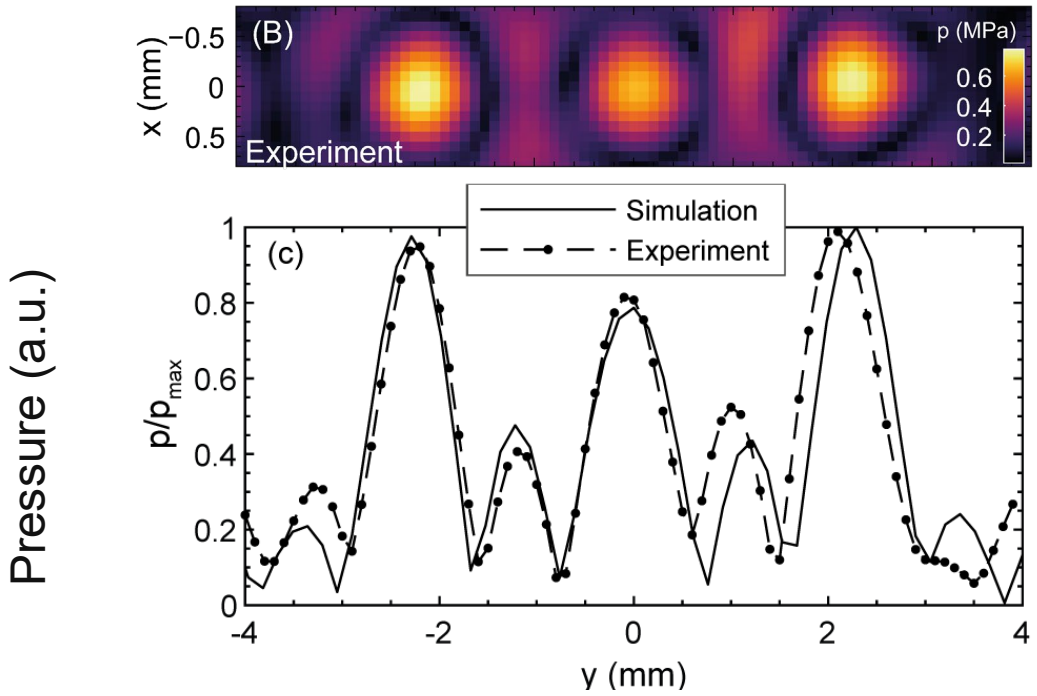
Andrés, et al. Cancers, 15(9), 2540 (2023)

Thermal holograms

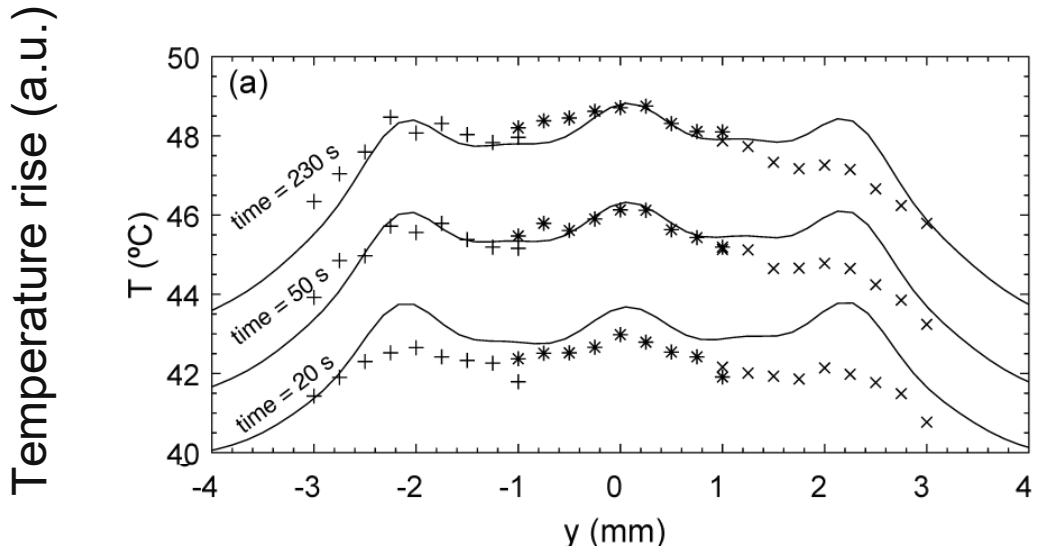
Look for uniform thermal dose on spheroids

- What is the optimal field?

Uniform field at targets



Nonuniform temperature distribution



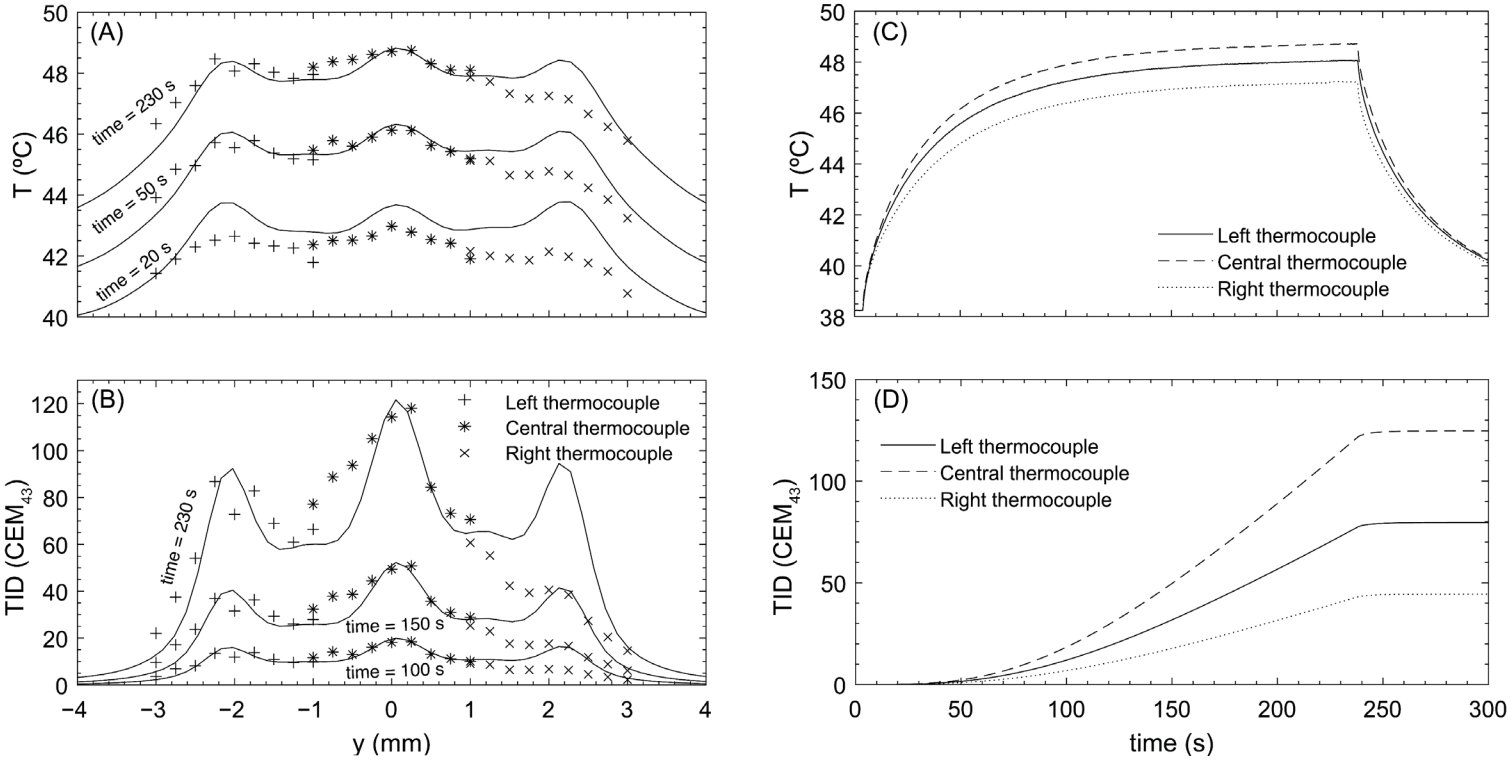
Andrés, et al. Cancers, 15(9), 2540 (2023)

Thermal holograms

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  Uniform field at targets
  Nonuniform temperature distribution



Andrés, et al. Cancers, 15(9), 2540 (2023)

Thermal holograms

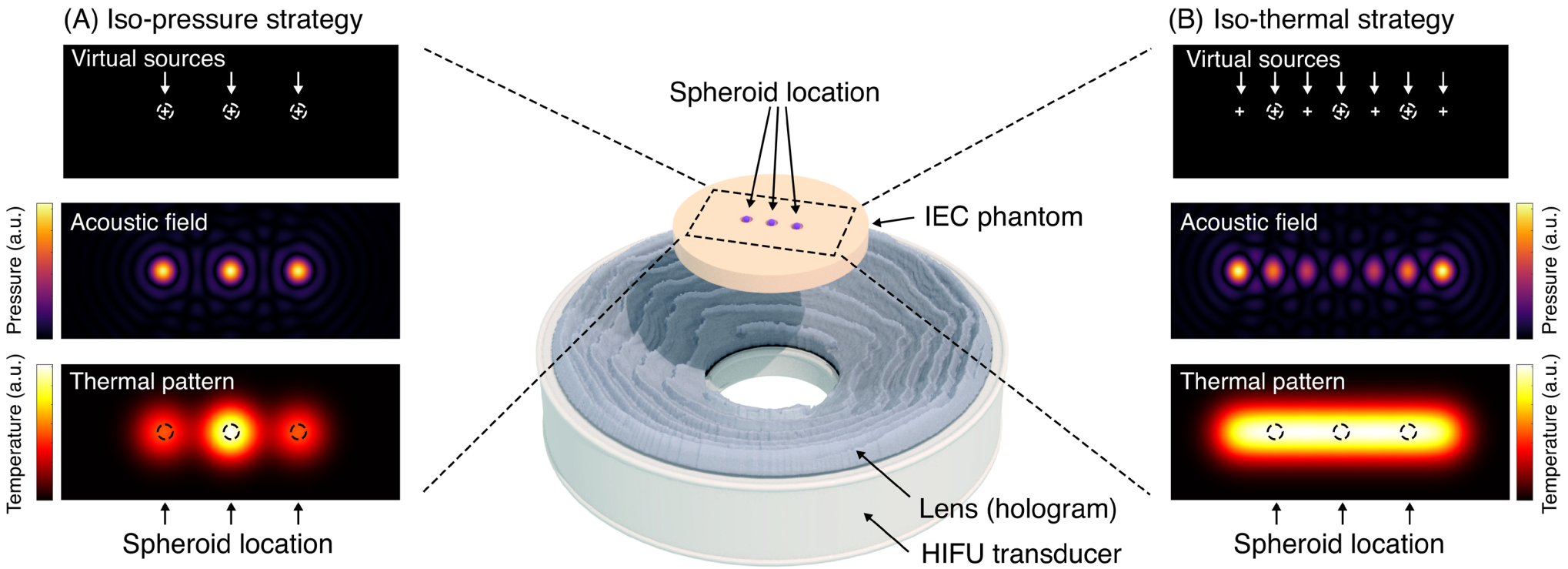
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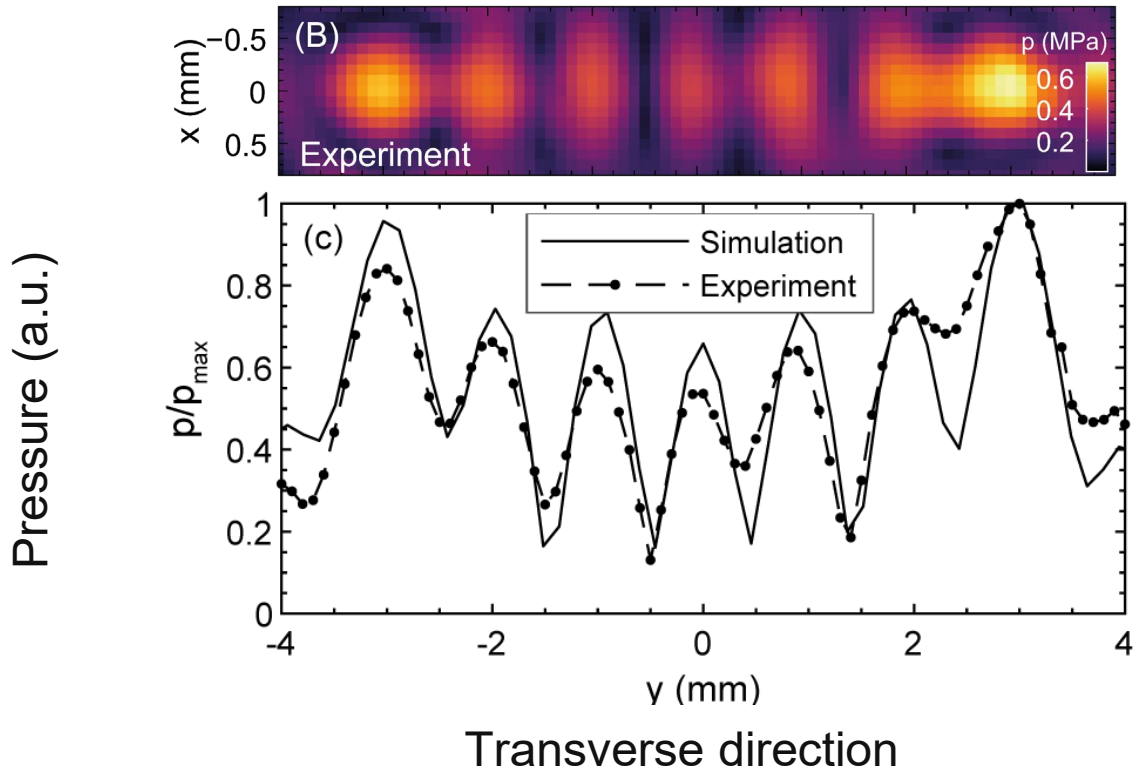
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Thermal holograms

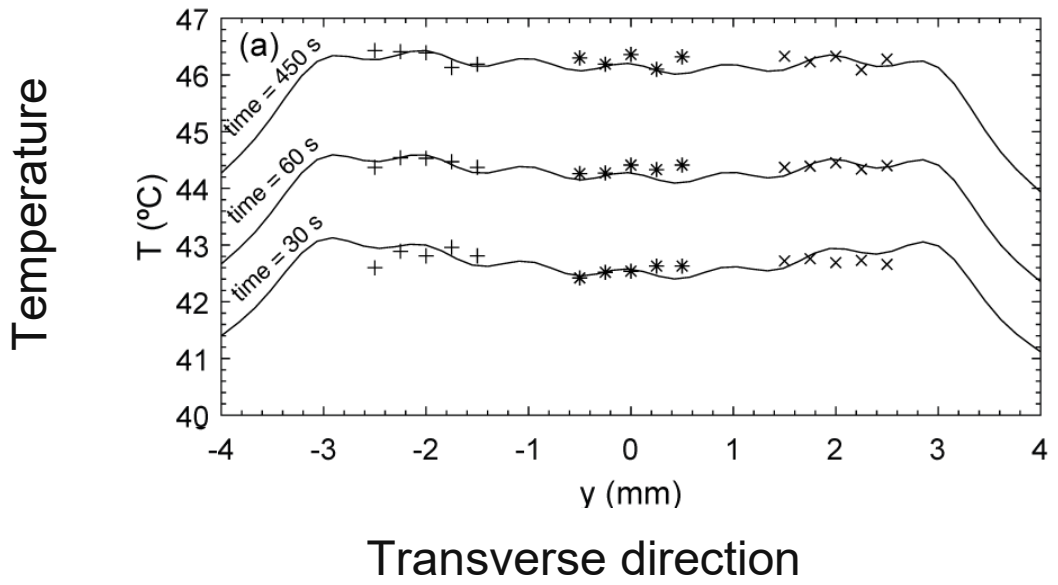
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Nonuniform field at targets



Uniform temperature distribution



Andrés, et al. Cancers, 15(9), 2540 (2023)

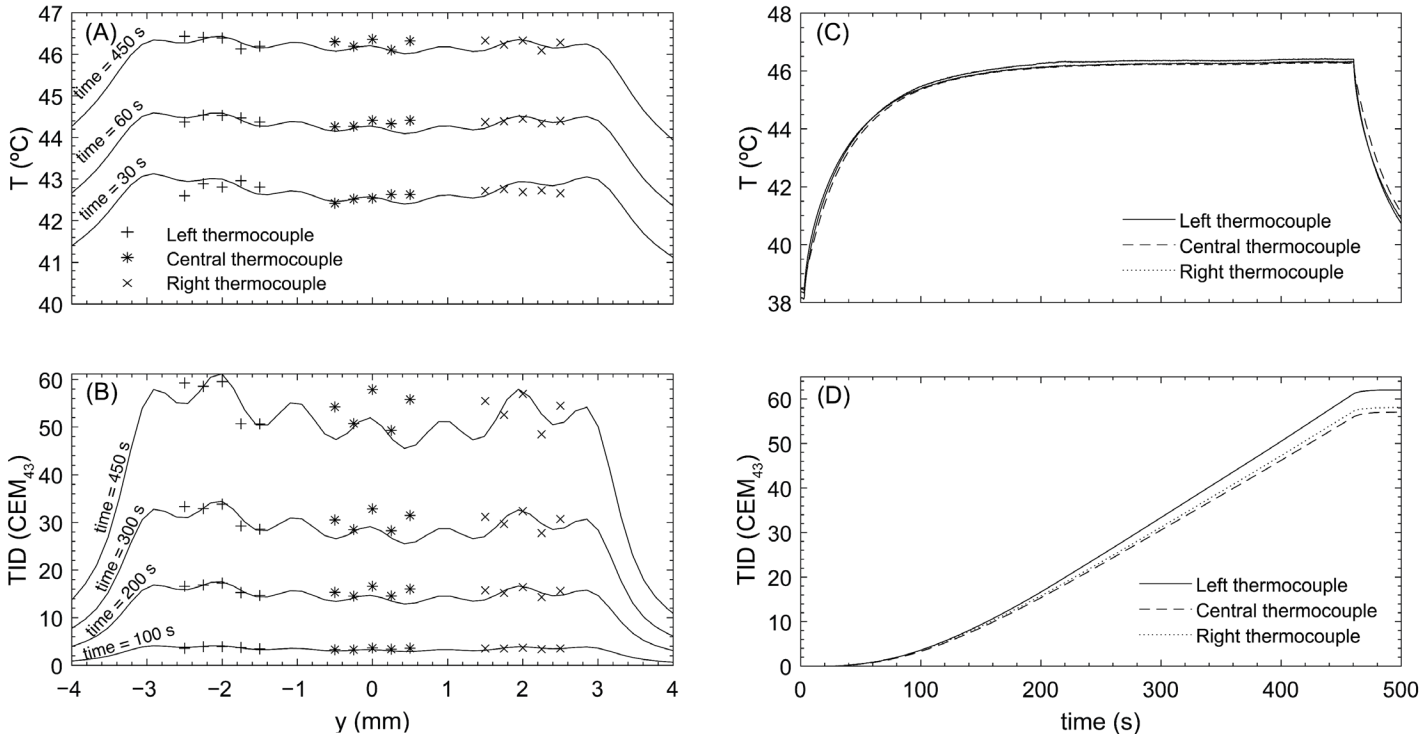
Thermal holograms

Thermal patterns for ultrasound hyperthermia

- What is the optimal field?

Nonuniform field at targets

Uniform temperature distribution

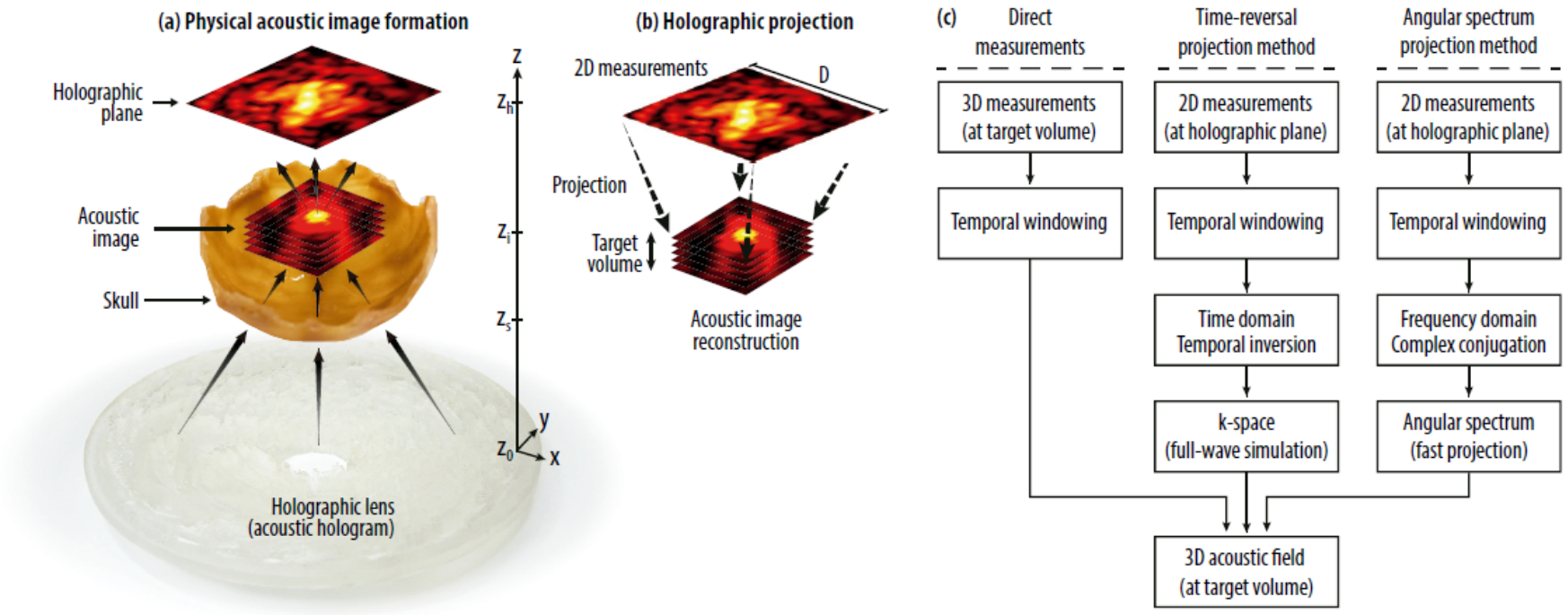


Andrés, et al. Cancers, 15(9), 2540 (2023)

Phase and magnitude holograms

Are holograms synthesizing the exact wavefront?

- Use holography to measure holograms

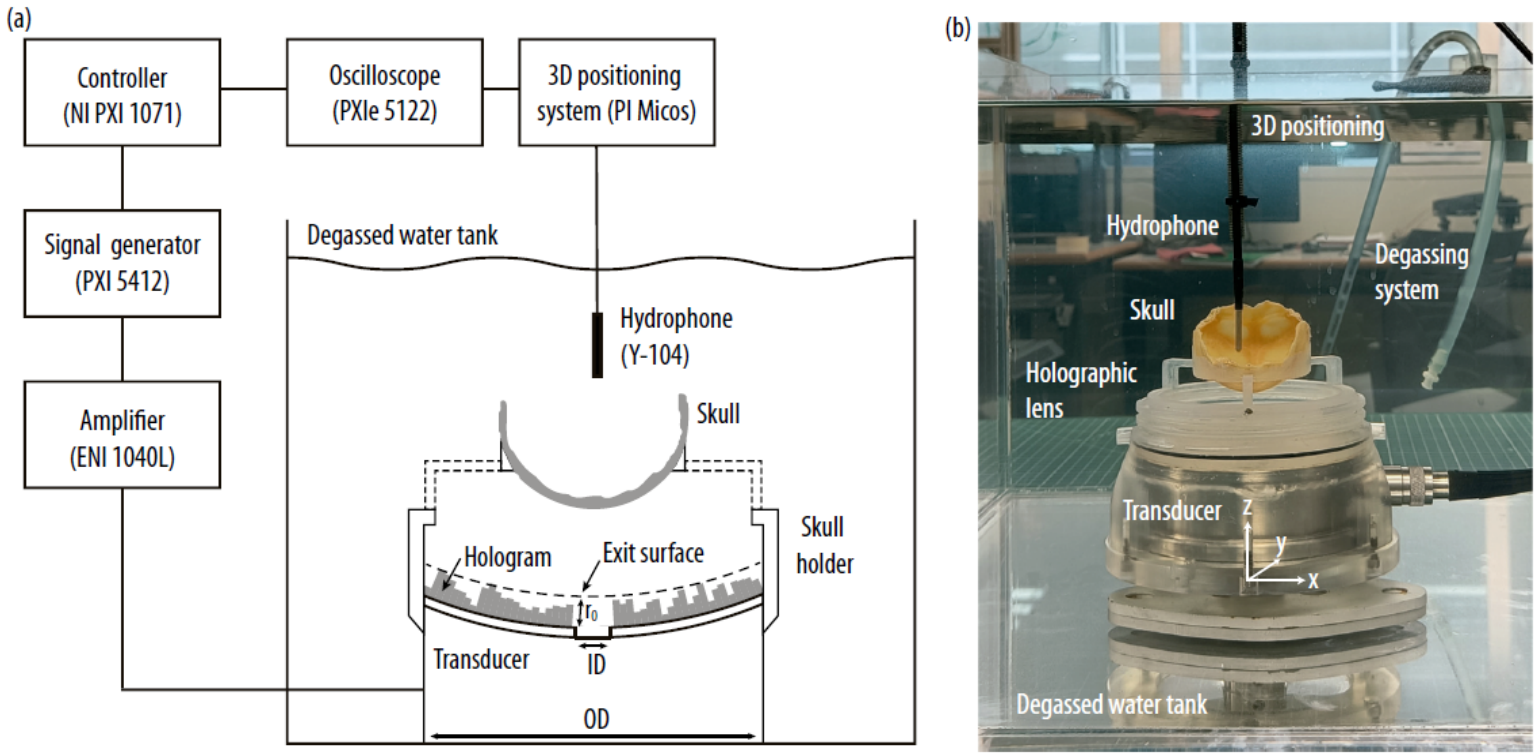


Andrés, submitted (2023)

Phase and magnitude holograms

Are holograms synthesizing the exact wavefront?

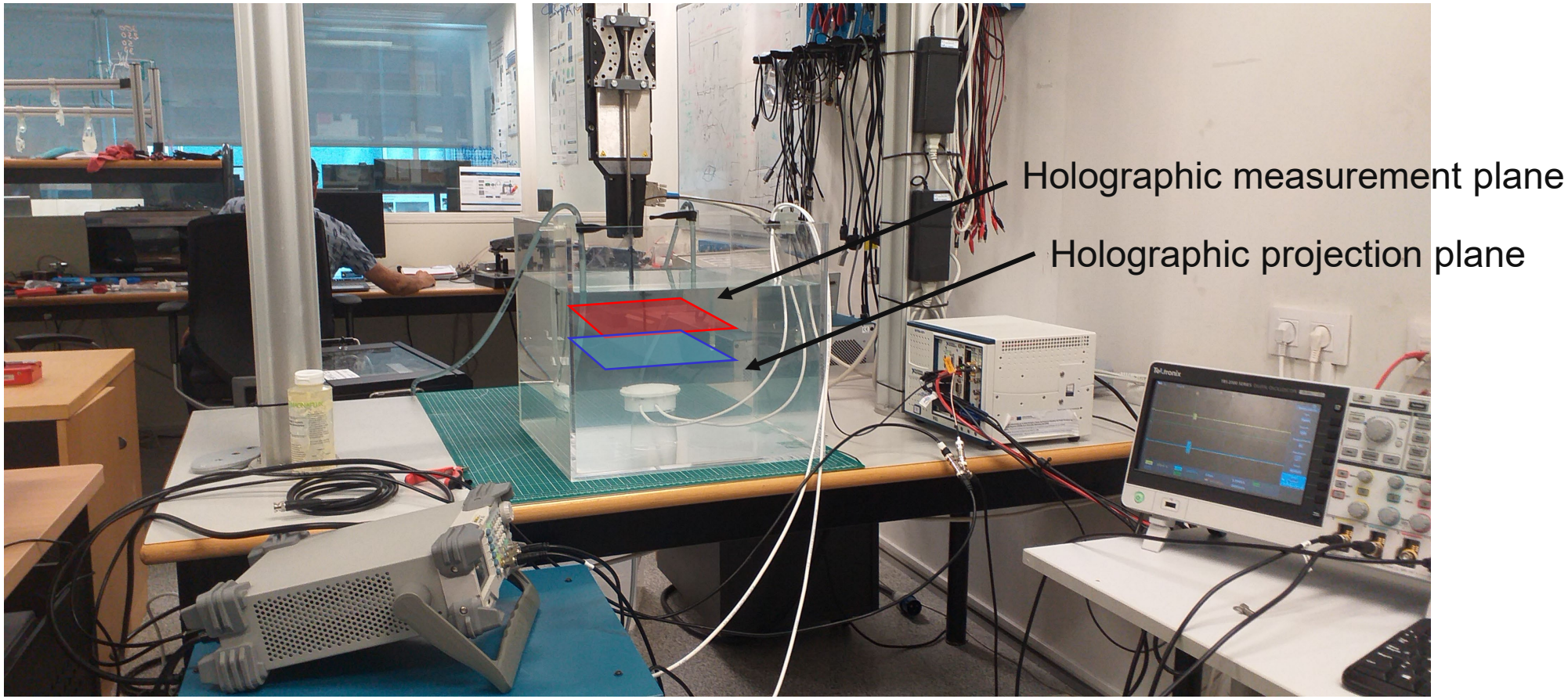
- Use holography to measure holograms



Andrés, submitted (2023)

Phase and magnitude holograms

Are holograms synthesizing the exact wavefront?



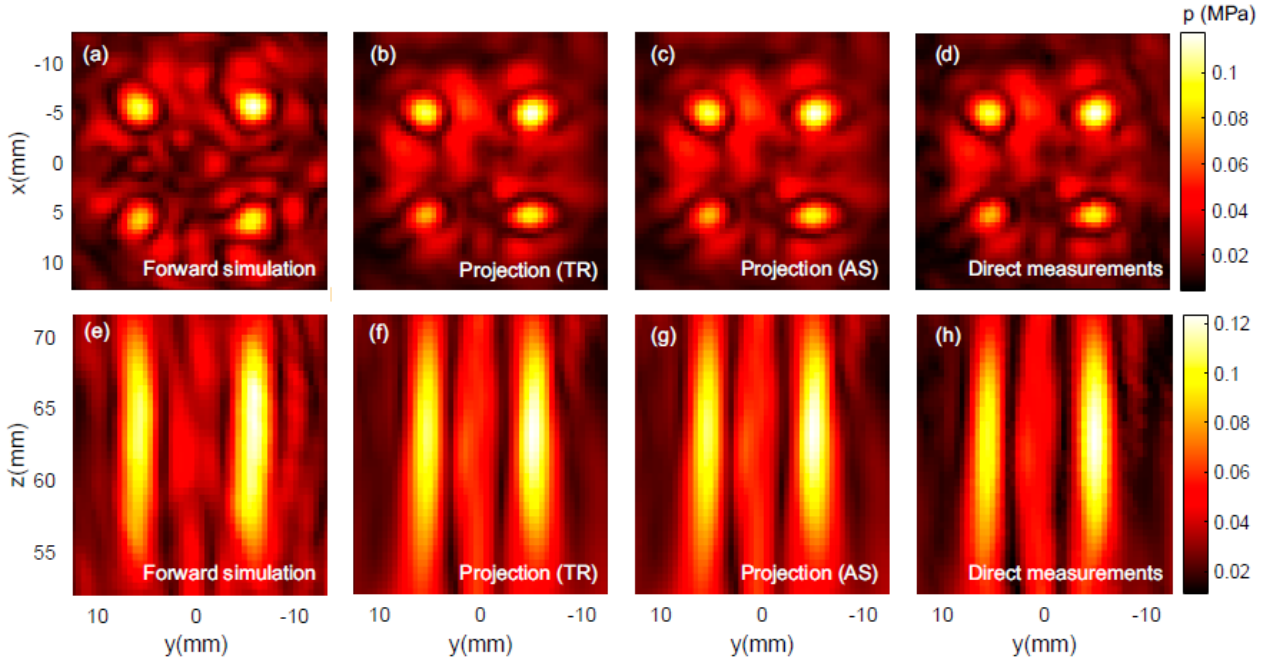
Andrés, submitted (2023)

Phase and magnitude holograms

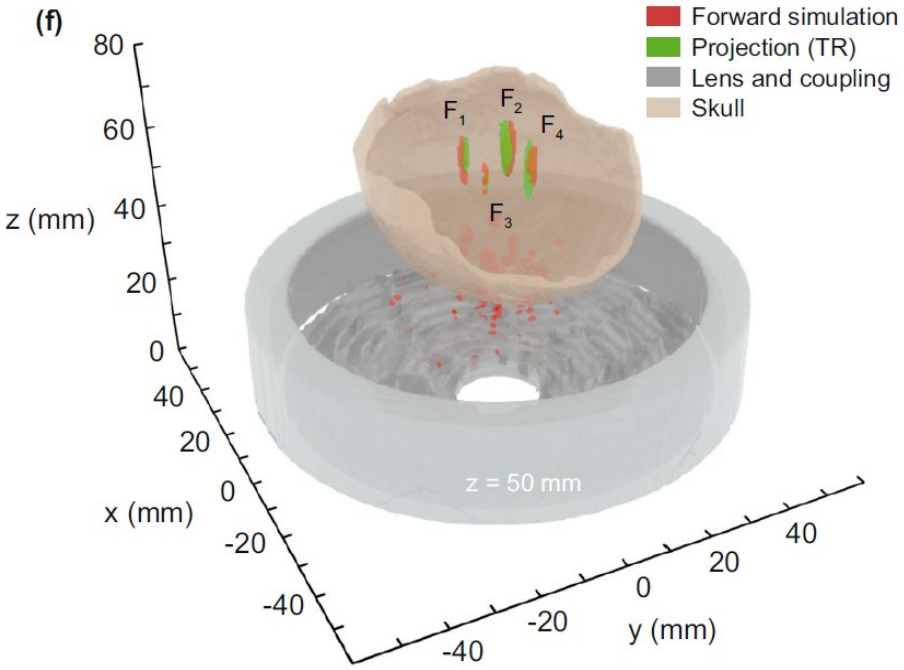
Are holograms synthesizing the exact wavefront?

- Use holography to measure holograms

Projection inside the skull



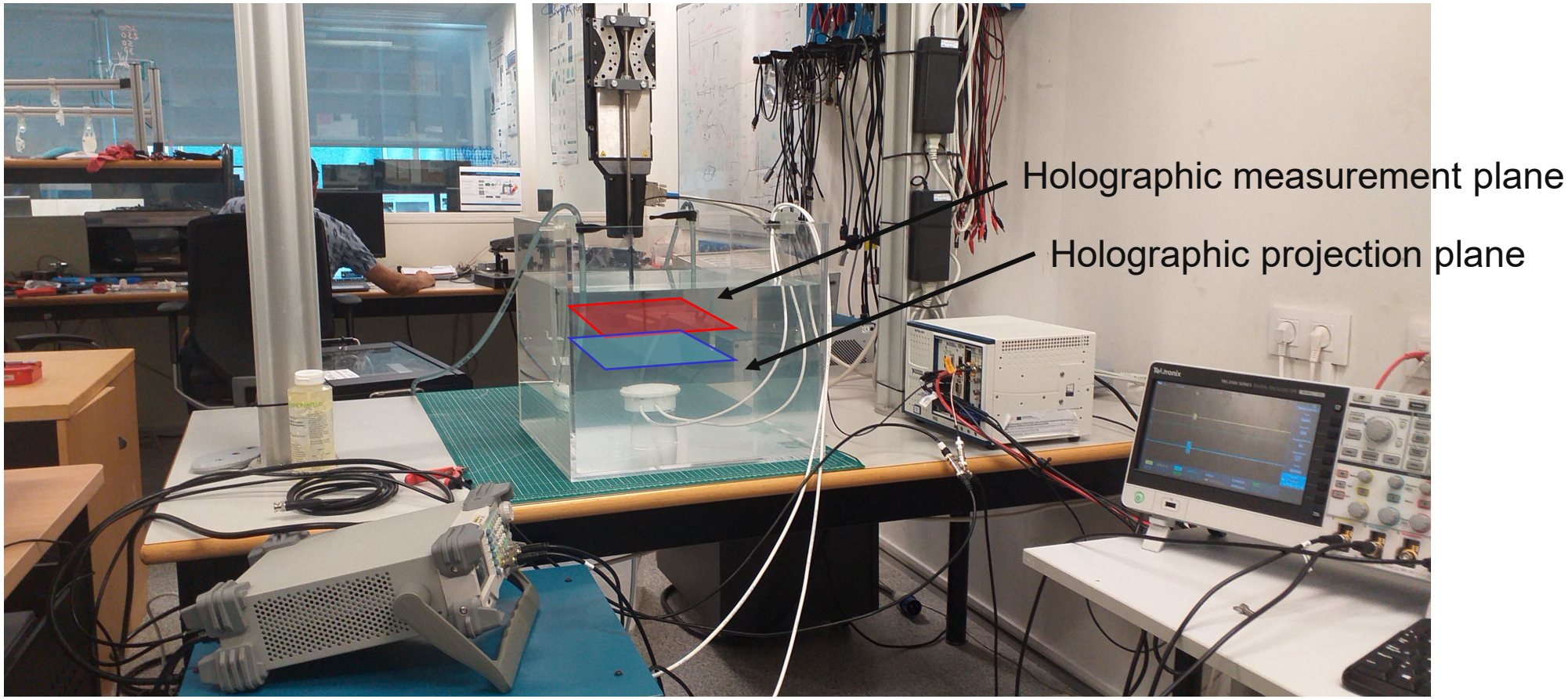
Volumetric field rendering



Andrés, submitted (2023)

Phase and magnitude holograms

Are holograms synthesizing the exact wavefront?

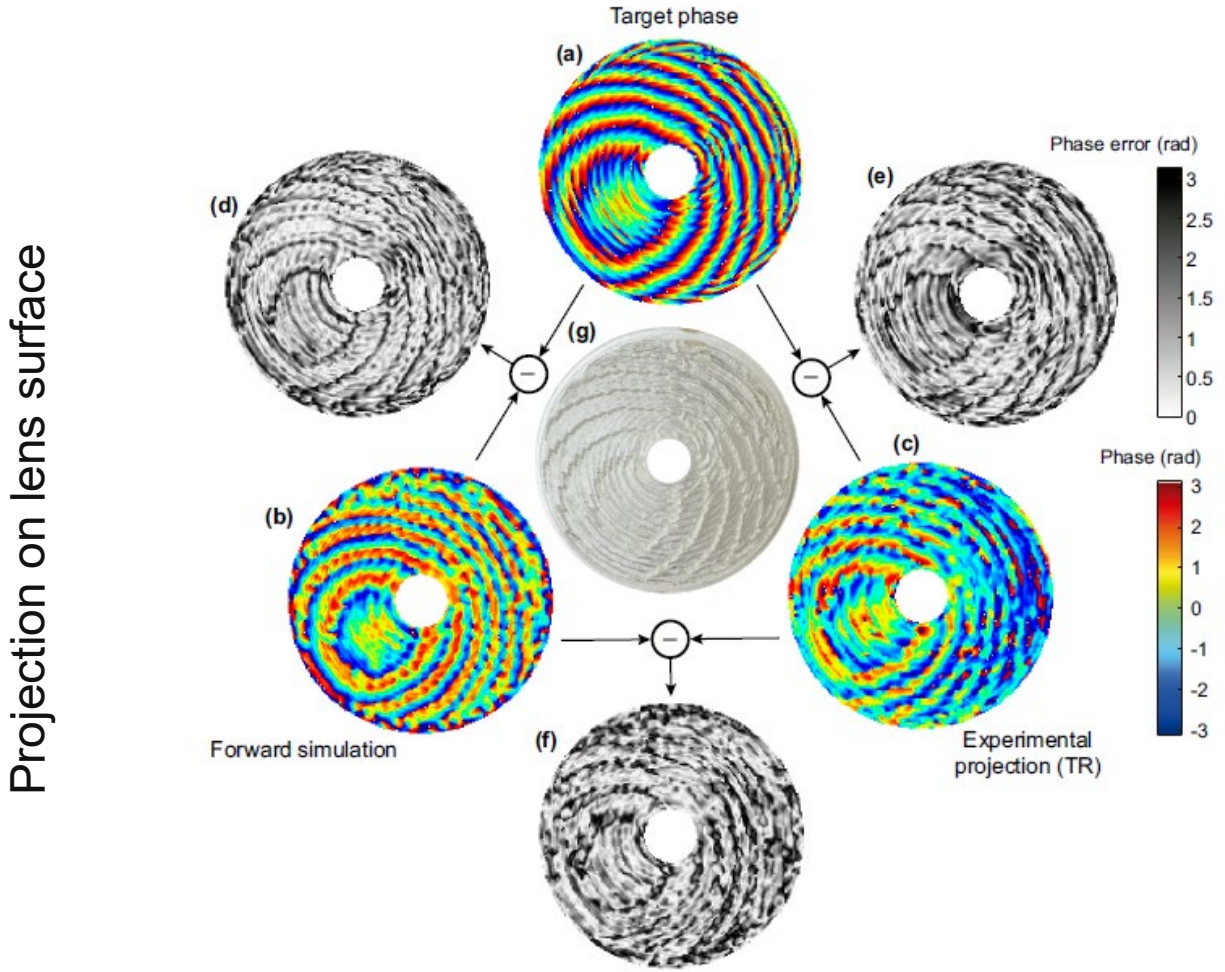


Andrés, submitted (2023)

Phase and magnitude holograms

Are holograms synthesizing the exact wavefront?

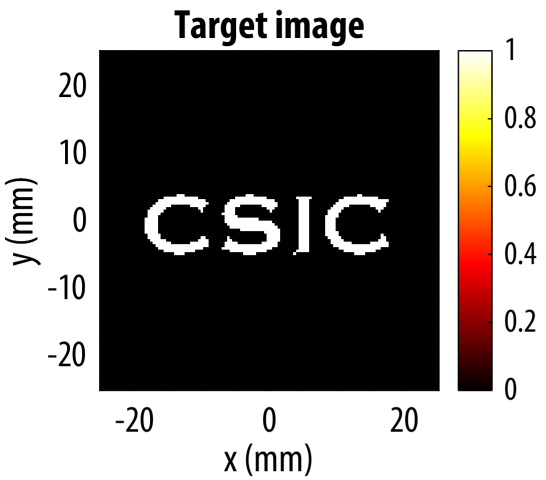
- Use holography to measure holograms



Andrés, submitted (2023)

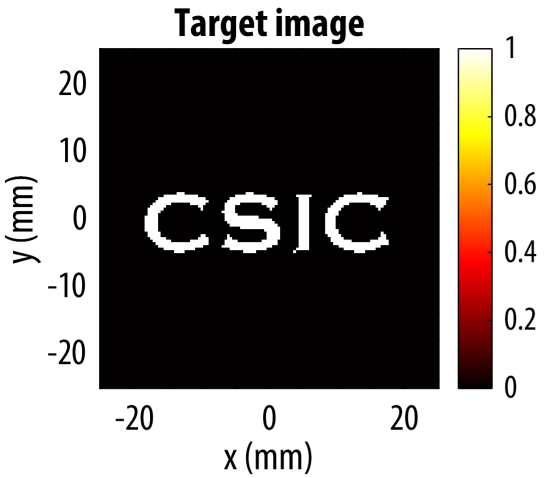
Metamaterial holograms

Tune magnitude and phase



Metamaterial holograms

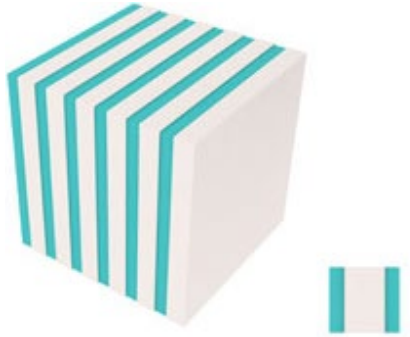
Tune magnitude and phase

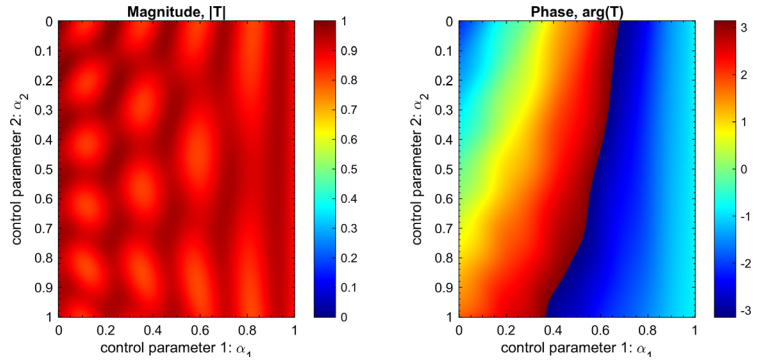


Phononic-crystal holograms

Tune magnitude and phase

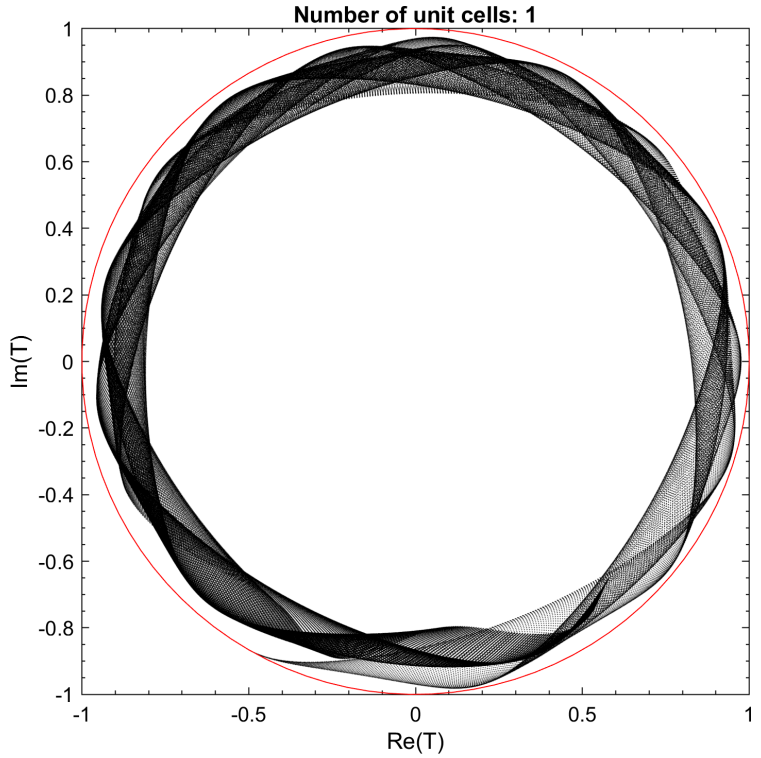
- Topology: a two-layer phononic crystal
- Unit cell: (two plastics for Polyjet ® printers)
- Unit cell (~ 5mm), air voids (~50 um)
- Analytical TMM unit cell model.





Argand diagram

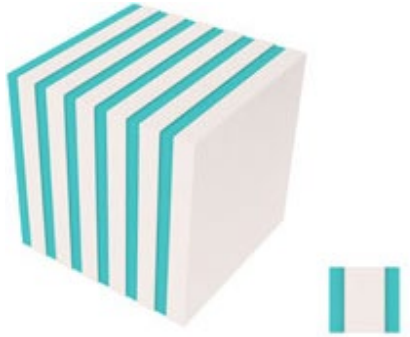
- Full phase and amplitude
- All combinations of phase and amplitude

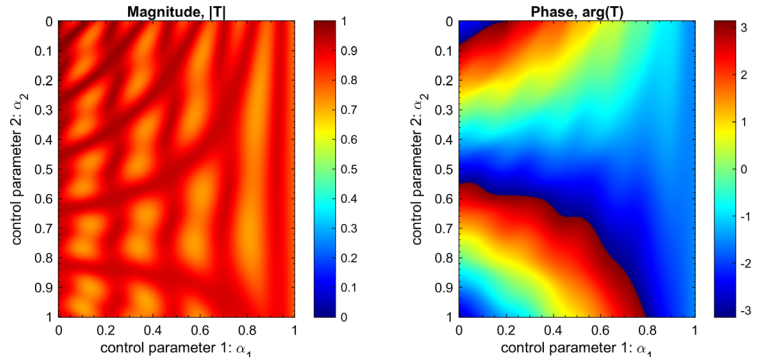


Phononic-crystal holograms

Tune magnitude and phase

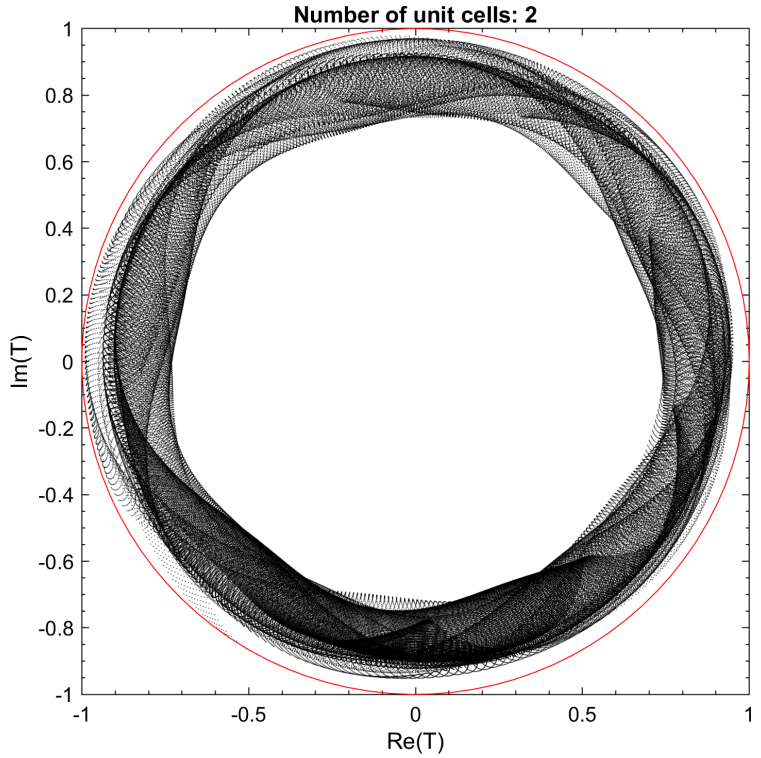
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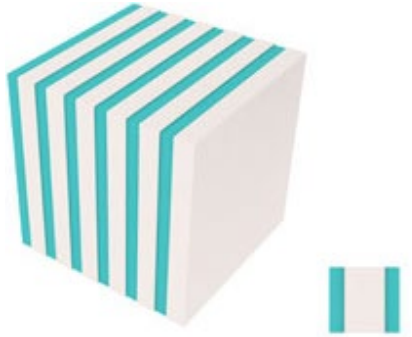
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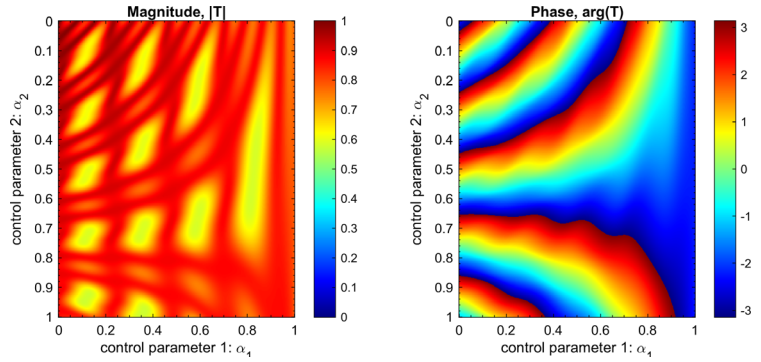


Phononic-crystal holograms

Tune magnitude and phase

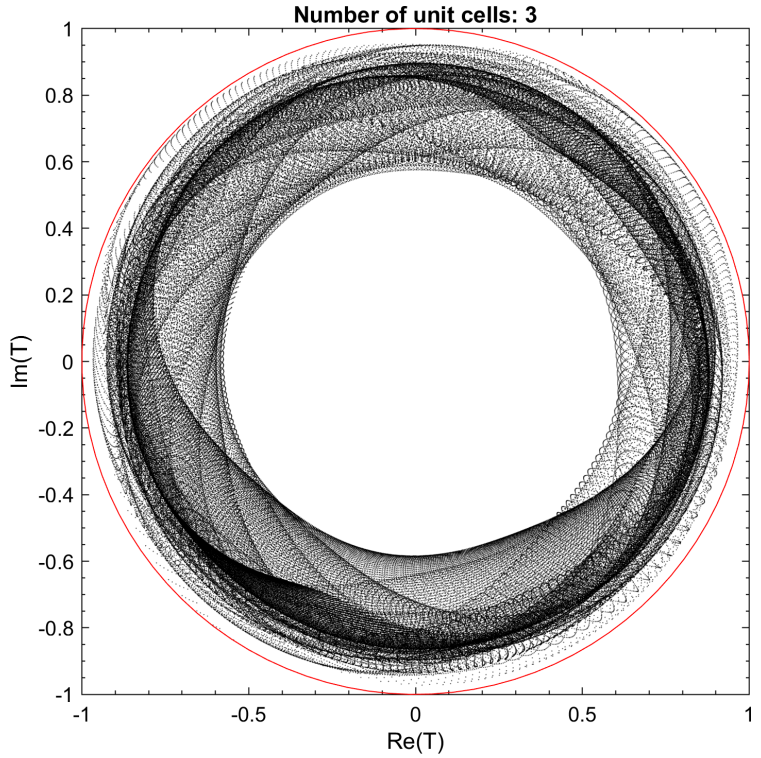
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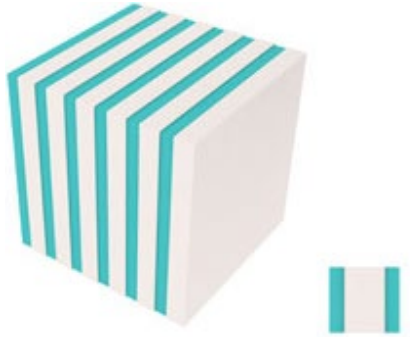
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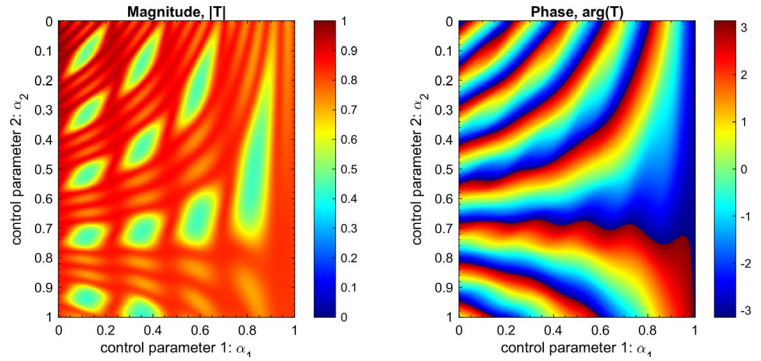


Phononic-crystal holograms

Tune magnitude and phase

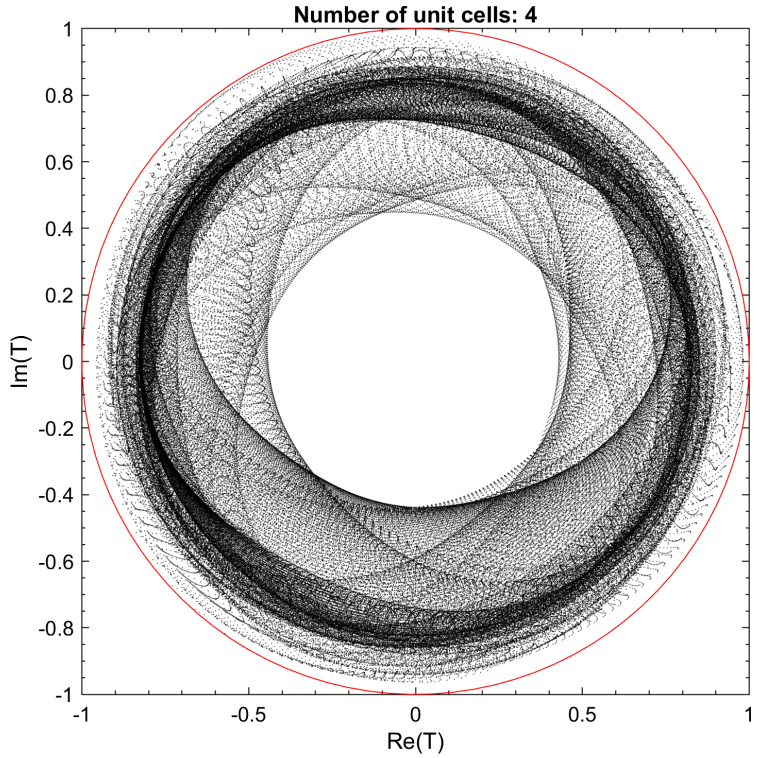
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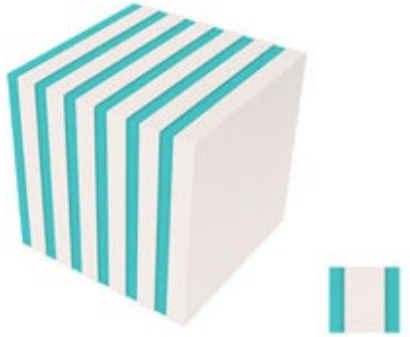
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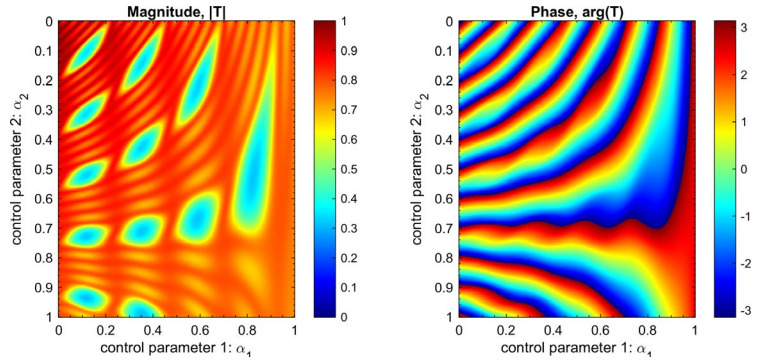


Phononic-crystal holograms

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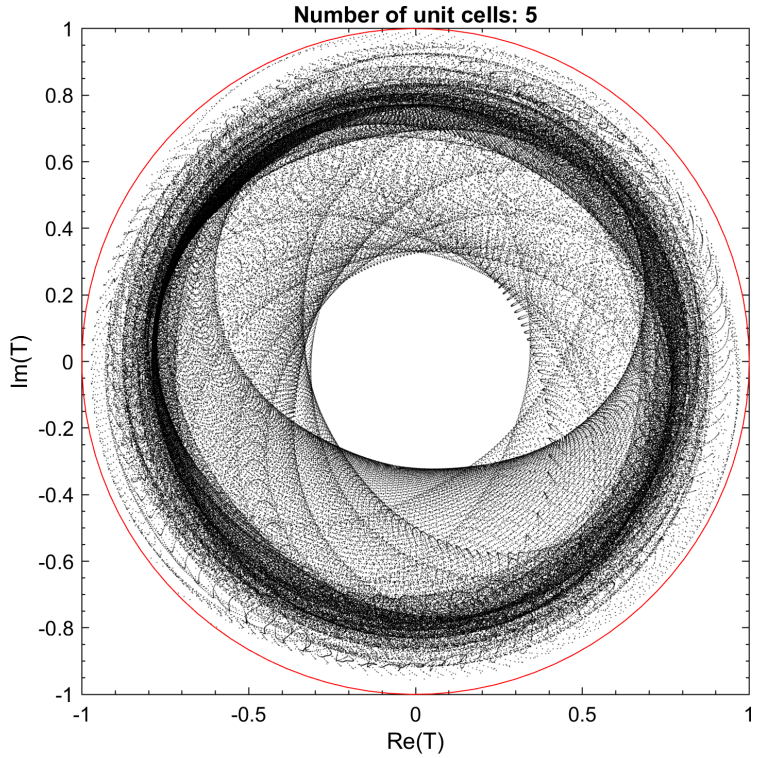
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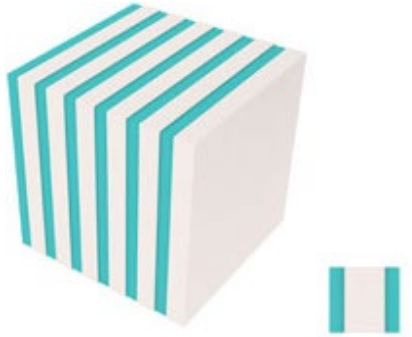
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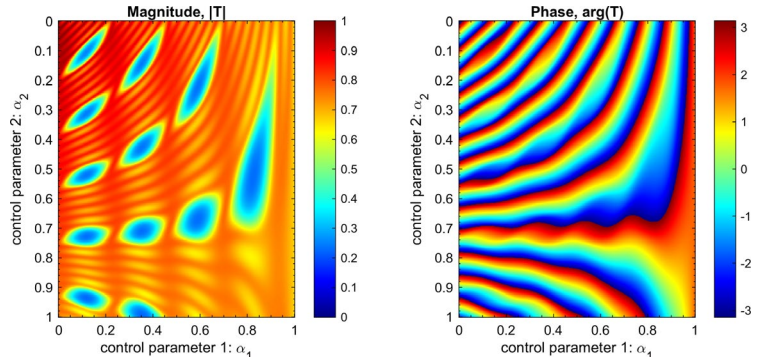


Phononic-crystal holograms

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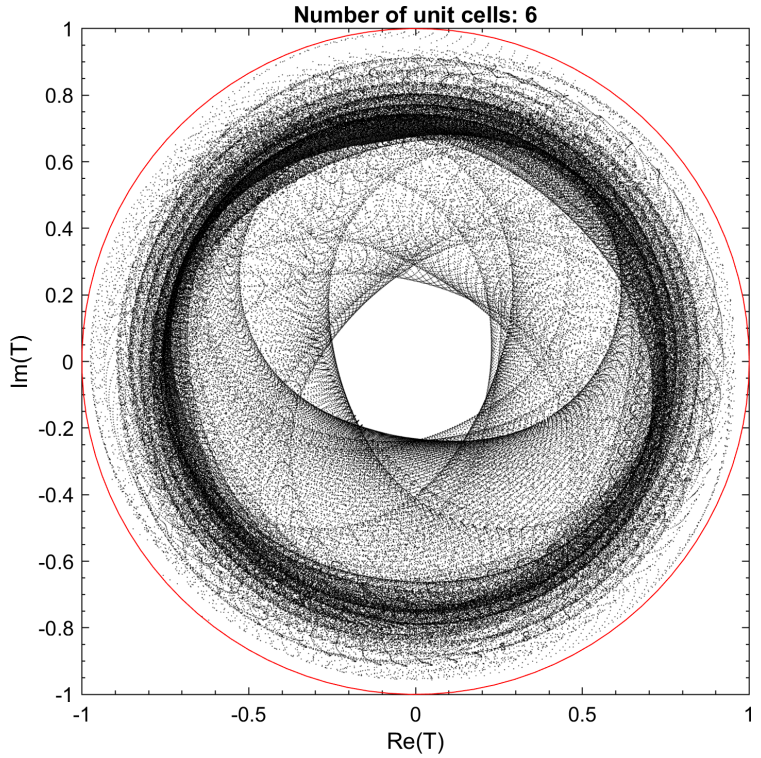
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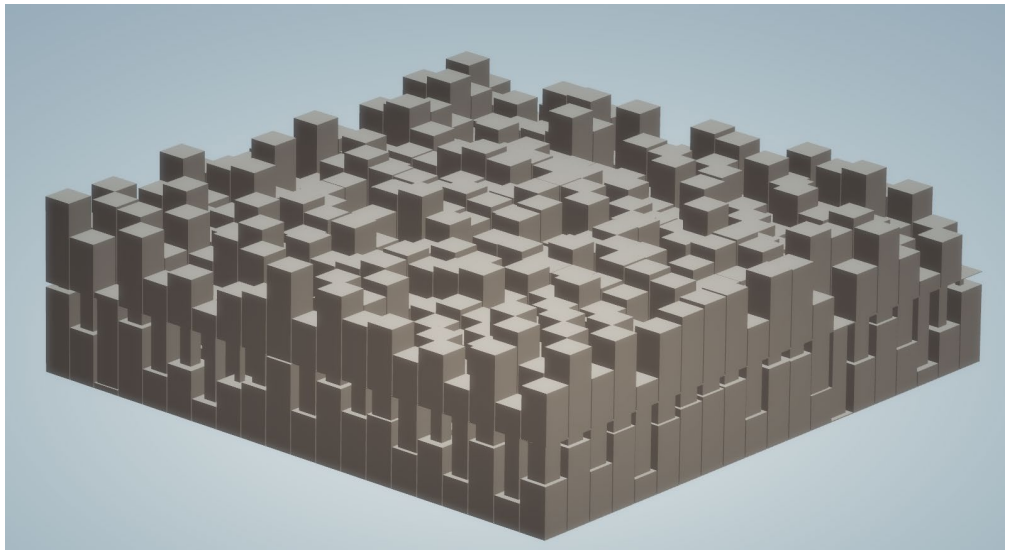
Metamaterial holograms

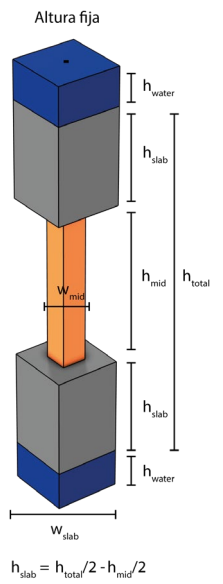
Tune magnitude and phase

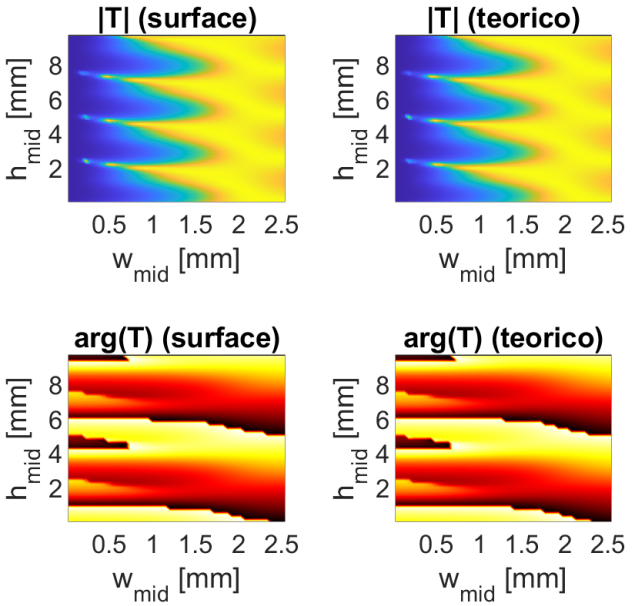
- Topology: structure with at least 2 degrees of freedom
- Single resonator (plastic + air)
- Unit cell (~ 1 mm), air voids (~50 um)
- Analytical TMM unit cell model.
- Numerical FEM validation for transmission

Argand diagram

- Full phase and amplitude
- All combinations of phase and amplitude



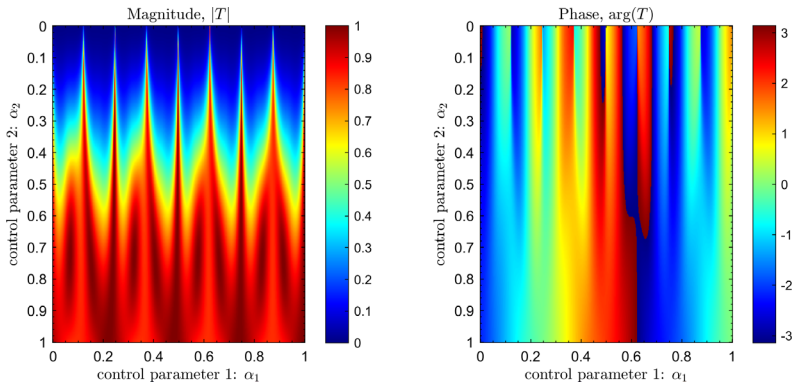




Metamaterial holograms

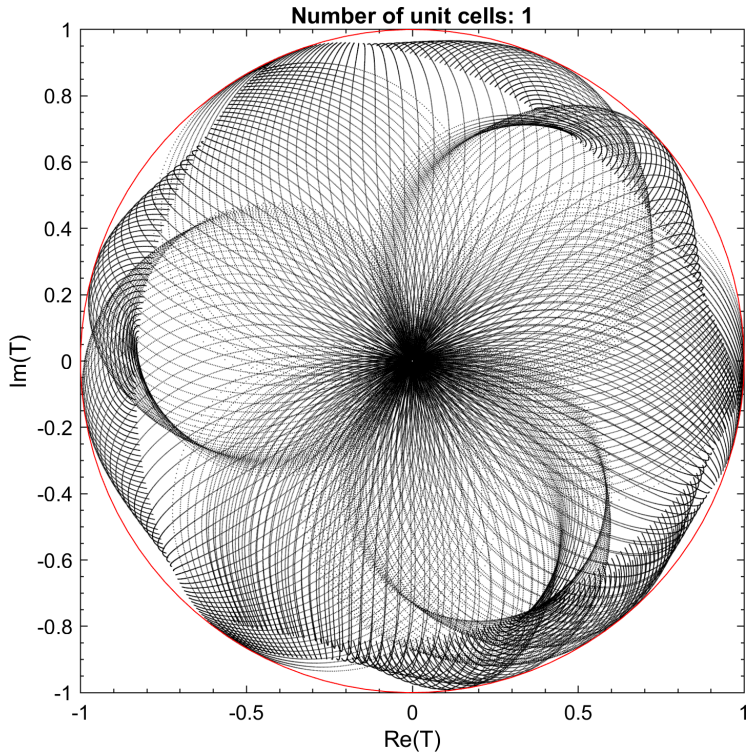
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Argand diagram

- Full phase and amplitude
- All combinations of phase and amplitude



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. Holographic Focused Ultrasound Hyperthermia System for Uniform Simultaneous Thermal Exposure of Multiple Tumor Spheroids. *Cancers*, *15*(9), 2540. (2023).
- 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

Coworkers

- Sergio Jimenez-Gambín (I3M, Valencia) (Now PostDoc at Columbia University)
- Diana Andrés (PhD Student) (I3M, Valencia)
- Nathalie Lamothe (PhD Student) (I3M, Valencia)
- Alicia Carrión-García (Post Doc) (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)
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- Ian Rivens, Institute of Cancer Research (London, UK)



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- Generalitat Valenciana: ACIF/2017/045.
- European Union: IDIFEDER/2018/022

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MINISTERIO DE CIENCIA, INNOVACIÓN Y UNIVERSIDADES
AGENCIA ESTATAL DE INVESTIGACIÓN
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FONDO EUROPEO DE DESARROLLO REGIONAL
"Una manera de hacer Europa"
GENERALITAT VALENCIANA
AVI AGÈNCIA VALENCIANA DE LA INNOVACIÓ