Measurement and modelling for novel therapeutic applications of ultrasound

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BSc – Integrated Science (Biophysics)

PhD – Medical Biophysics

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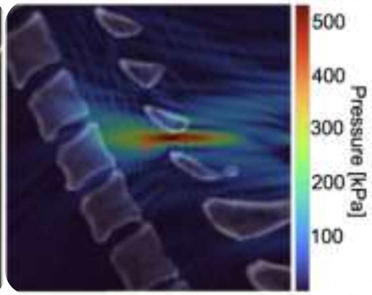
McMaster University (2012 – 2016)

University of Toronto (2016 – 2021)

UCL (2021 – current)

My Projects

Spinal Cord Neuromodulation



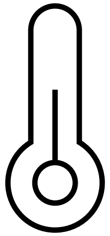
- Device Development & Characterisation
- Safety
- Numerical Modelling

Ultrasound Rewarming

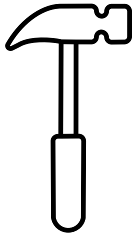
- Device Development & Characterisation
- Numerical Modelling
- Validation with biological samples

“New” therapeutic ultrasound applications

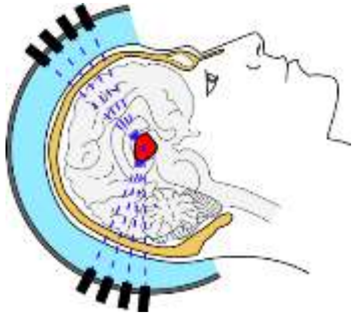
Rely on old mechanisms of action: broadly divided into thermal, mechanical, cavitational

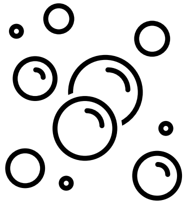


Thermal
Absorption of sound

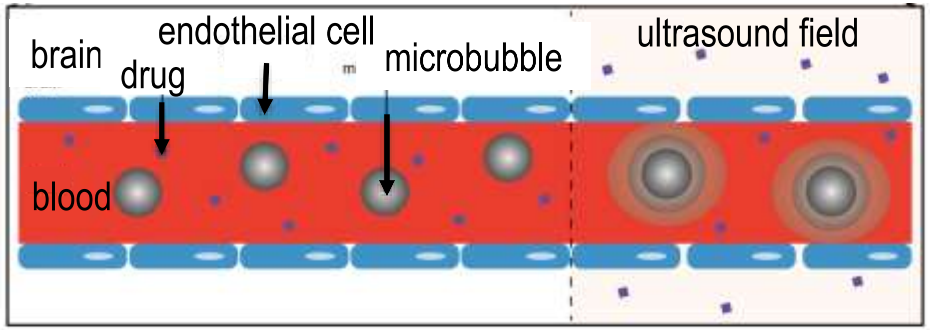


Mechanical
Radiation Force
Shock waves





Bubble activity (cavitation)
Shear forces
Energy release



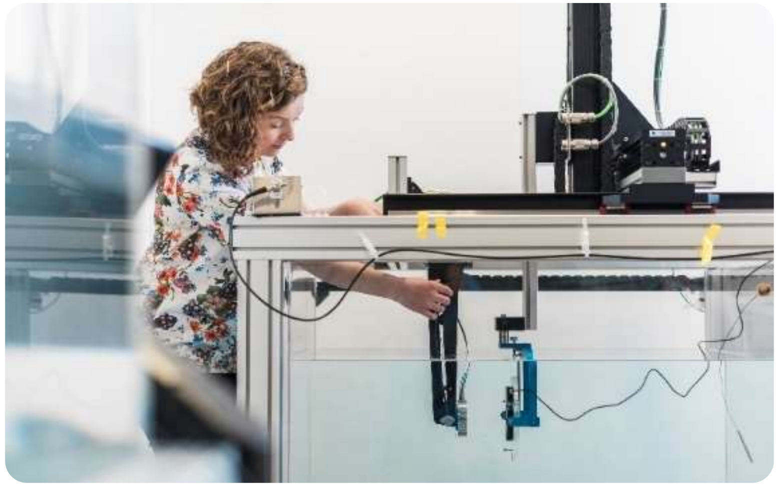
UCL Biomedical Ultrasound Group

Best-known for the k-Wave toolbox
(>15 000 users, >2000 citations)

Validated for:
free field, glycerol wedges

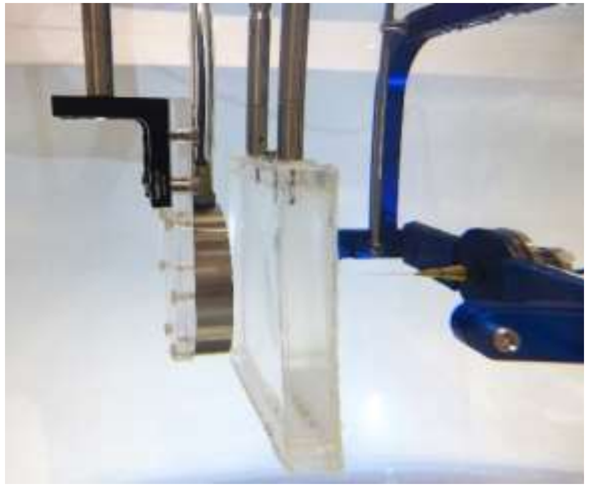
Validation underway for:
Transcranial Ultrasound

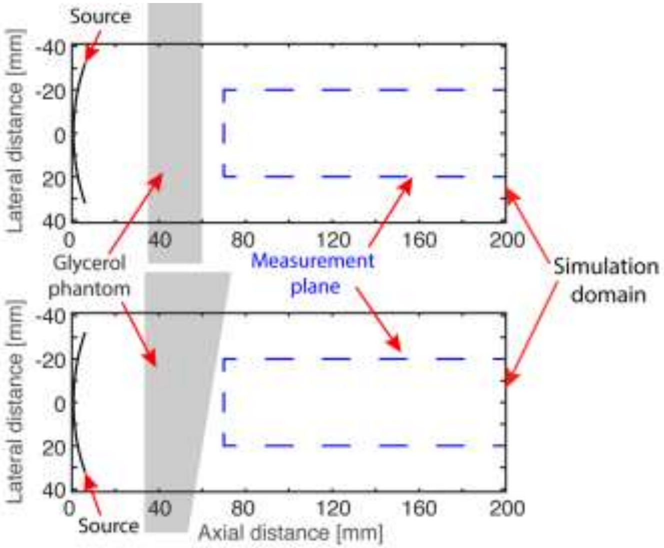
Ultrasound Metrology

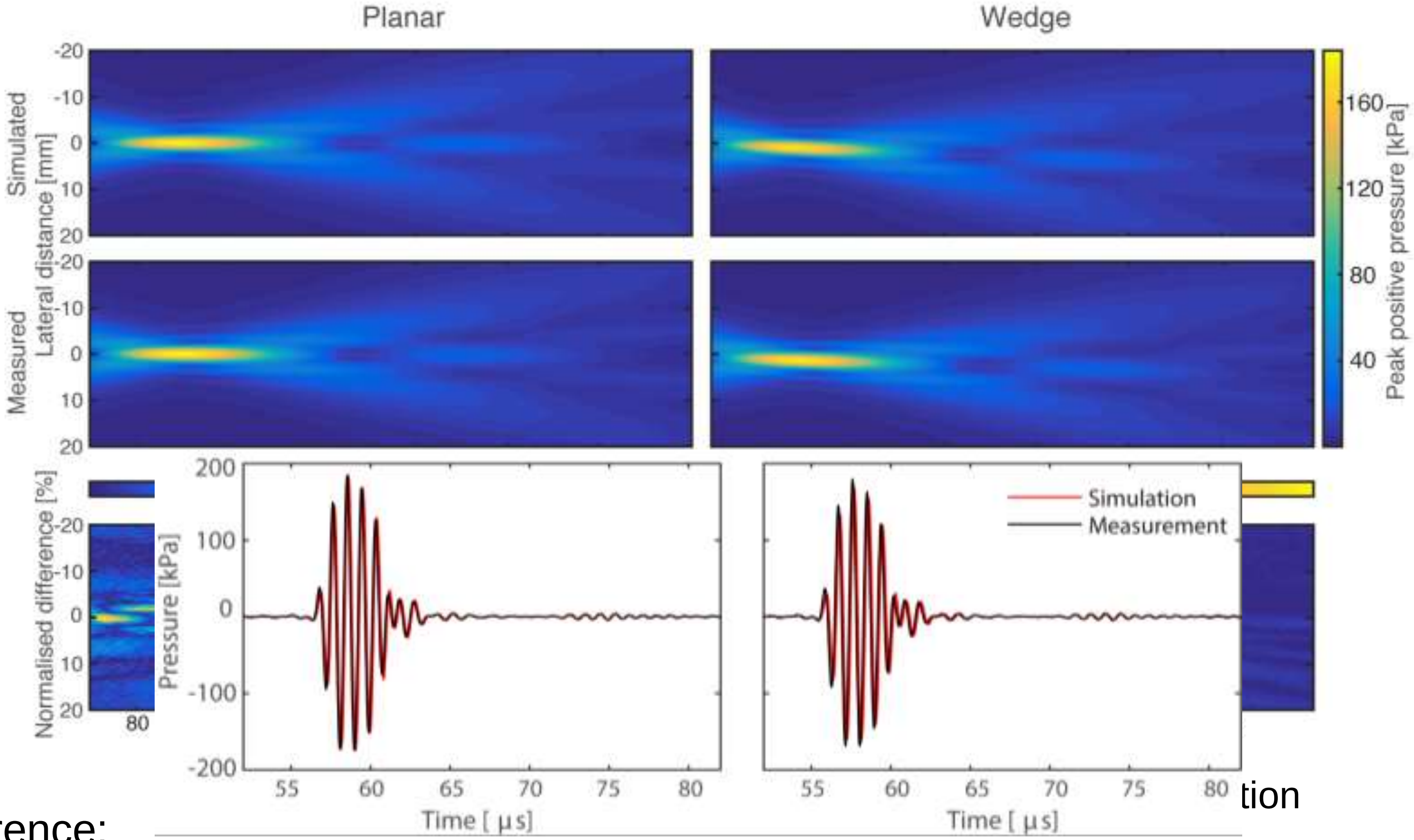


Modelling propagation through fluid phantoms

Fields can be modelled accurately if we know medium properties and geometry





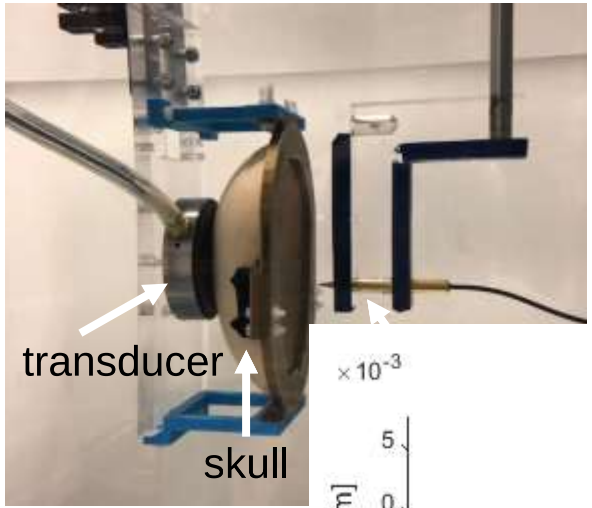


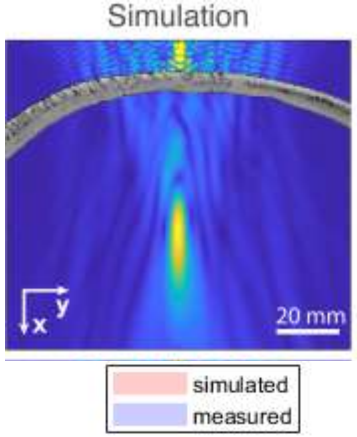
Difference: 0.8% 0.2 mm 1.4% 0.6 mm

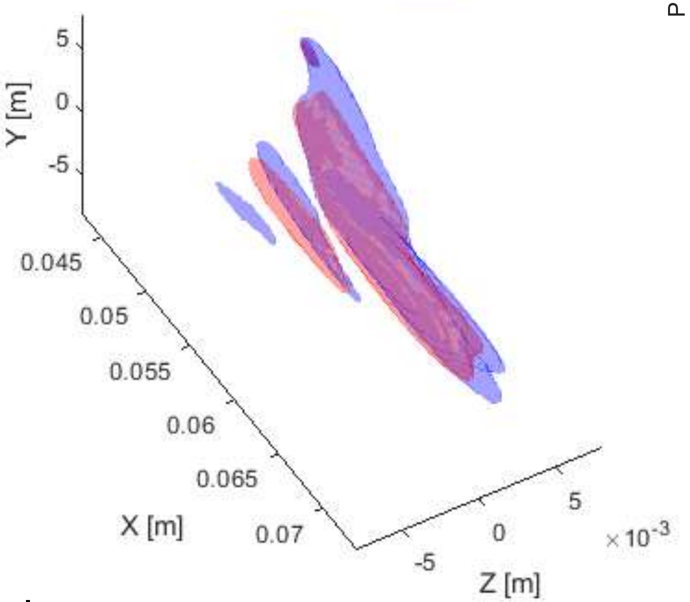
Martin et al, IEEE UFFC, 67(1), 2019

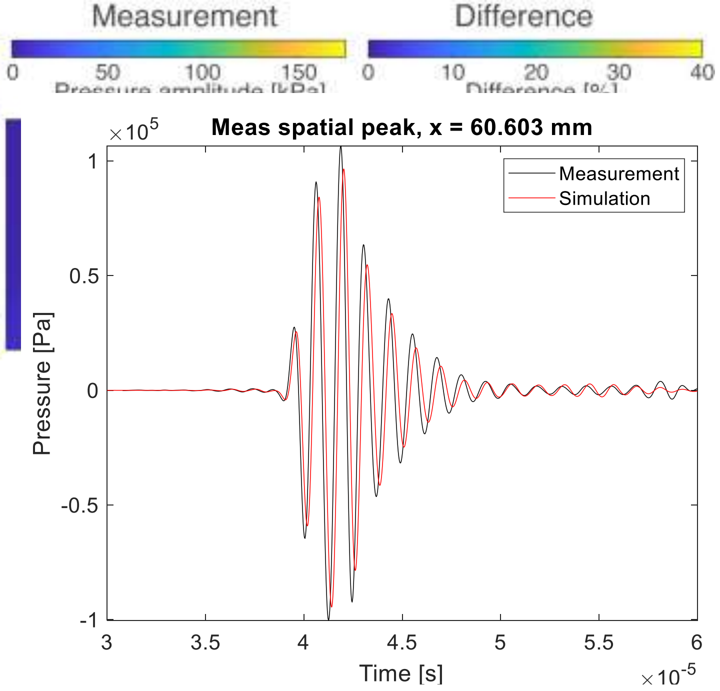
Skull propagation: model – measurement comparison

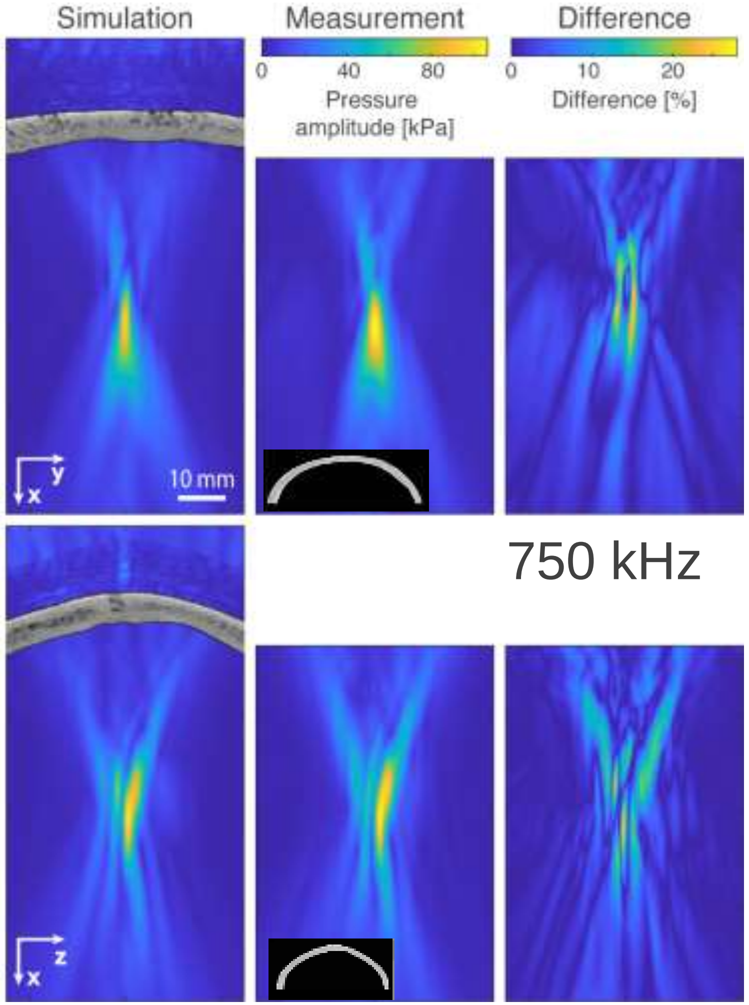
Model can predict field reasonably well given we don't have all the information











750 kHz

f0 = 270, 400,
750, 1000 kHz
64 mm diameter
64 mm ROC
k-Wave fluid model

Differences:

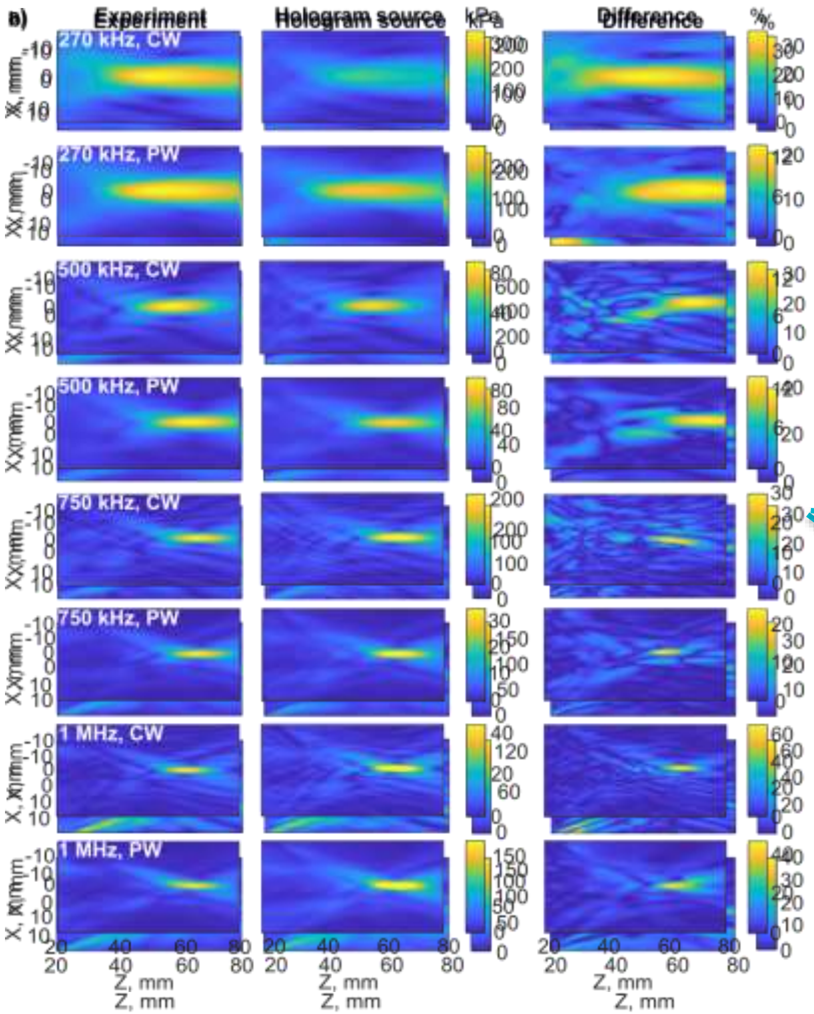
amplitude	5 - 30%
position	0.7 – 5.8 mm
volume overlap	56 - 75%

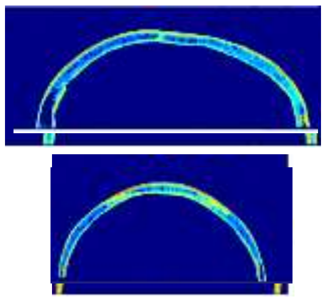
Krokhmal & Martin, in review, 2024

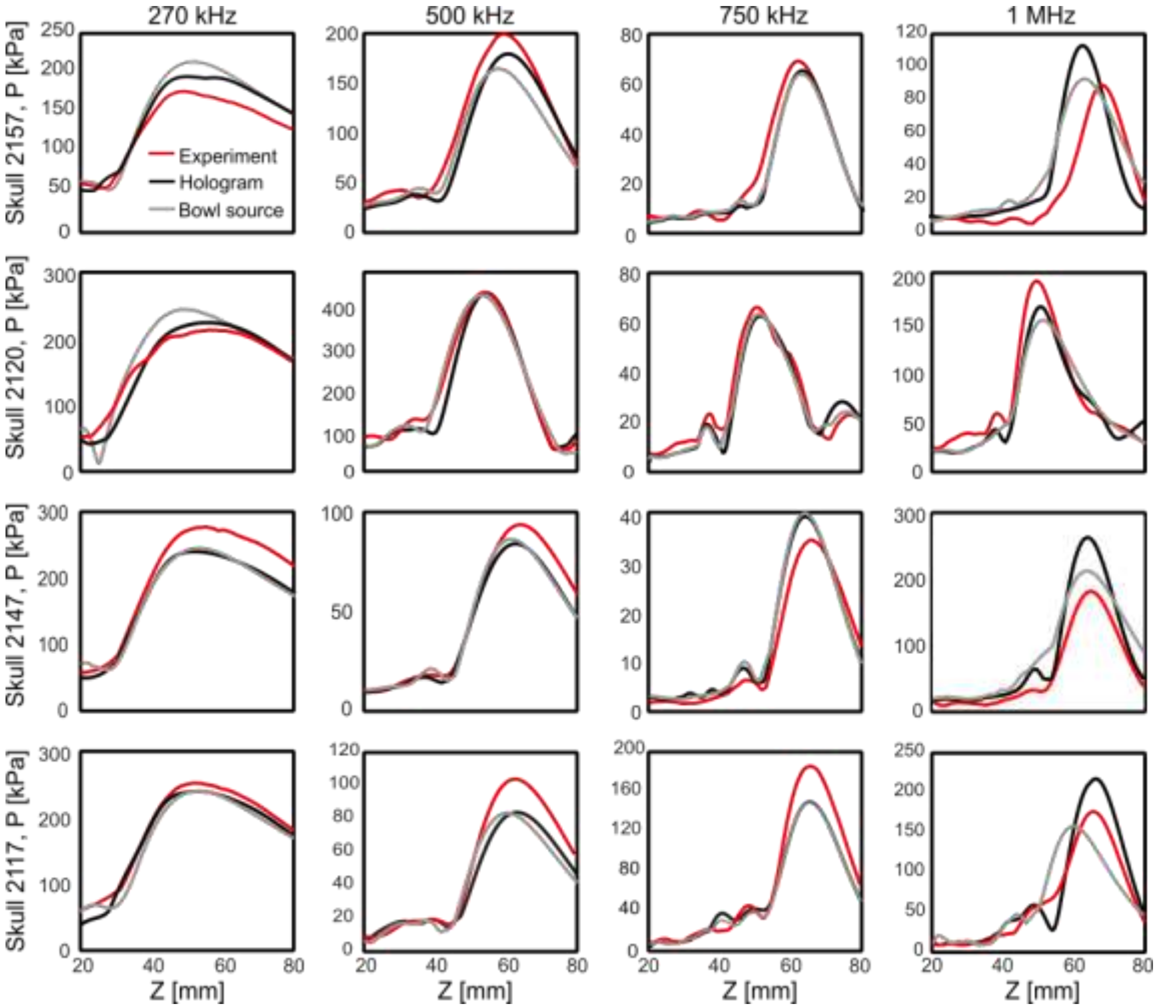
Comparison of peak pressure in simulation and experiment

The skull introduces significant aberration increasing with frequency and well captured in simulation

Skull 2147







Krokhmal & Martin, in review, 2024

Transcranial focused ultrasound neuromodulation

1950s - experiments with craniotomies – too invasive [1]

2002/3 – CT-based transcranial aberration corrections [2,3]

2013 – Insightec system for non-invasive essential tremor treatment [4]

– dose: thermometry, CEM43℃

201X – renewed interest in ultrasonic neuromodulation

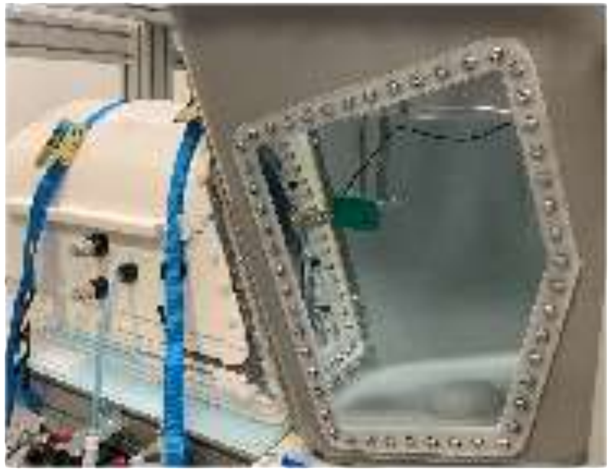
– challenge: exposure parameters to “dose”

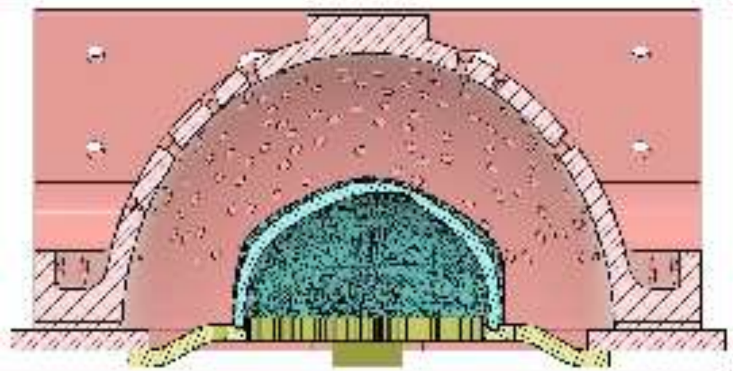
Photo from: Sunnybrook Health Sciences Centre, 2022. 300th patient.

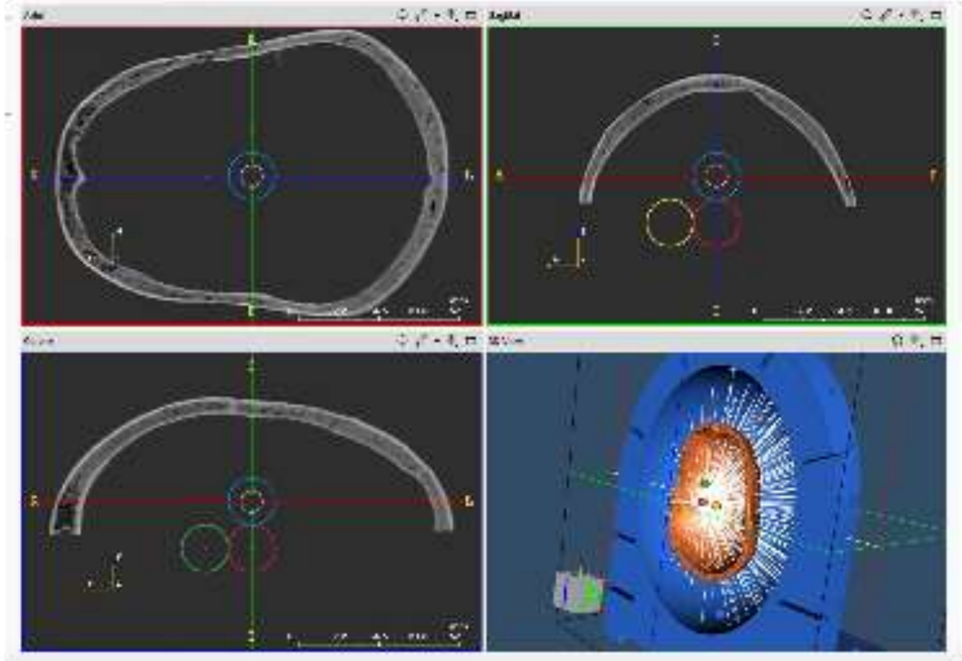
[1] *Fry, Ades & Fry, Science, 1958* [2] *Clement & Hynynen, Physics in Medicine & Biology, 2002* [3] *Aubry et al., JASA, 2003* [4] *Lipsman et al., The Lancet, 2013*

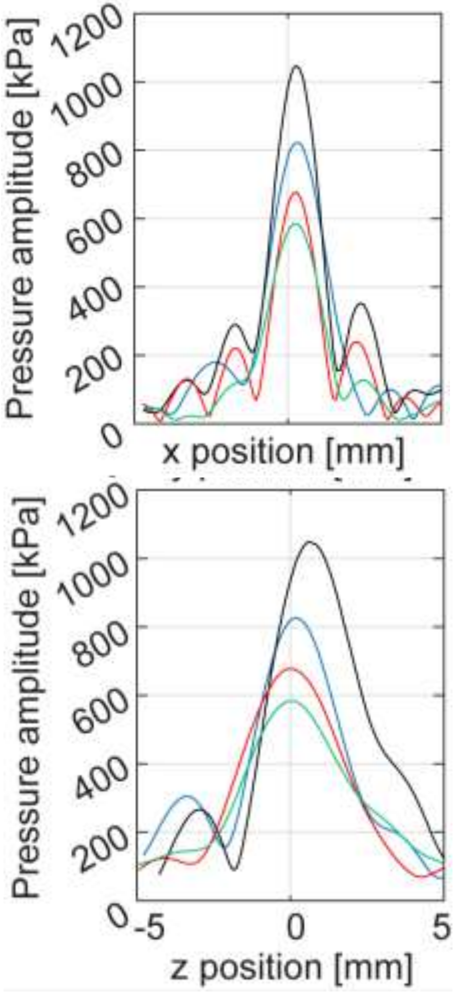
Experimental validation of treatment planning pipeline

Experimental validation of k-Plan fields with skull registered in helmet to test focusing and steering coordinates





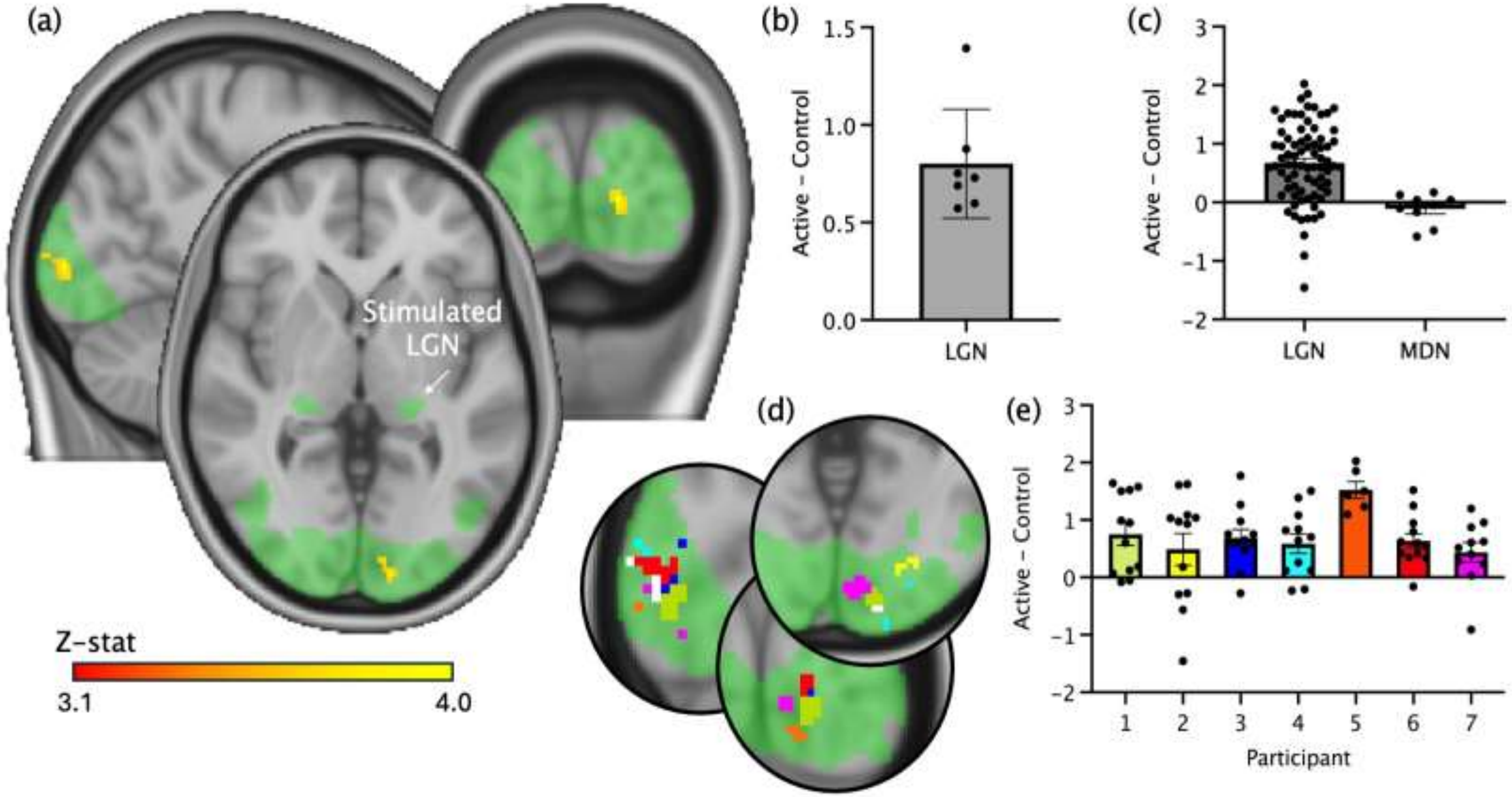




Martin et al., in review, 2024

Online sonication of LGN modulates visual evoked potentials

Significant changes in activity on fMRI in V1 in each participant, no change when stimulating control region



Martin et al., in review, 2024

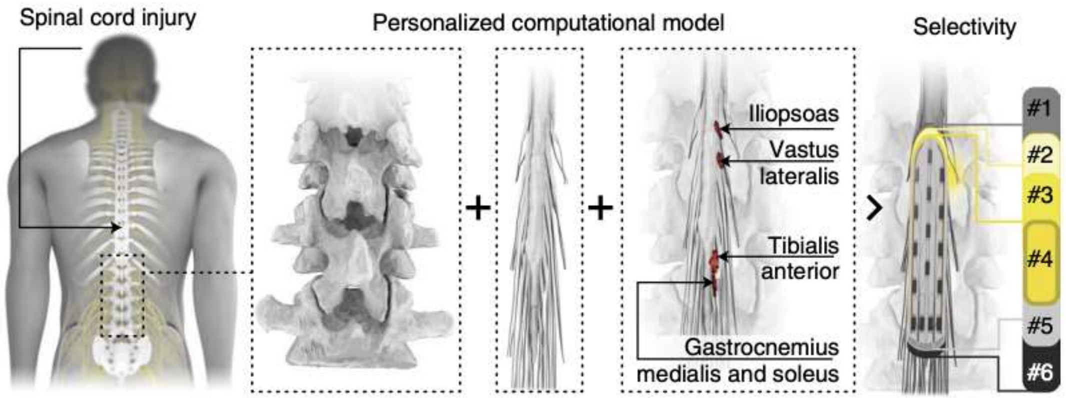
Opportunities for focused ultrasound spinal cord neuromodulation

Small animal studies have shown:

- spontaneous discharges in *ex vivo* spinal cord (toad)
- increases or decreases in reflex amplitude
- increases or decreases in muscle recruitment
- increases in grasping strength
- decreases in spasticity

Xu et. al., Ultrasound in Medicine & Biology, 2024

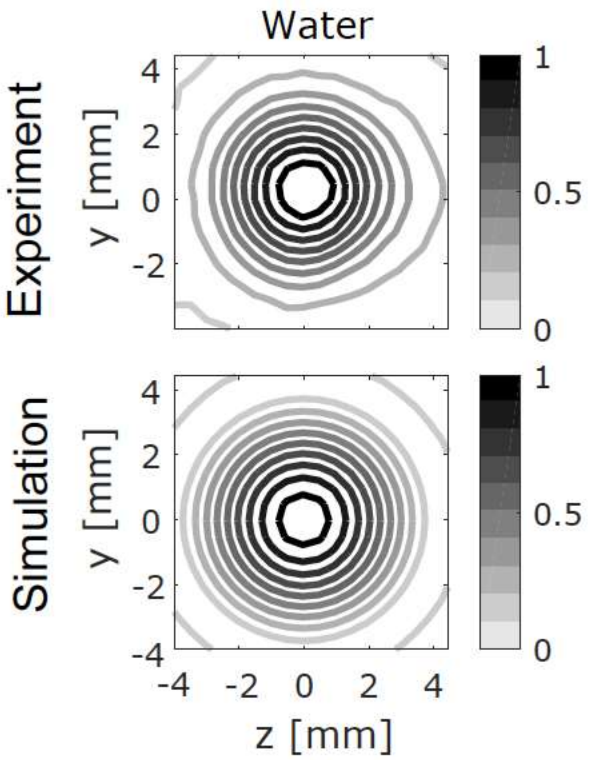
Motivation: advances in electrical stimulation

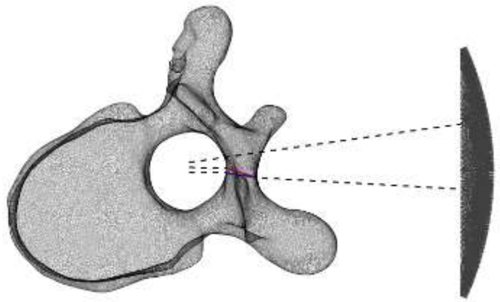


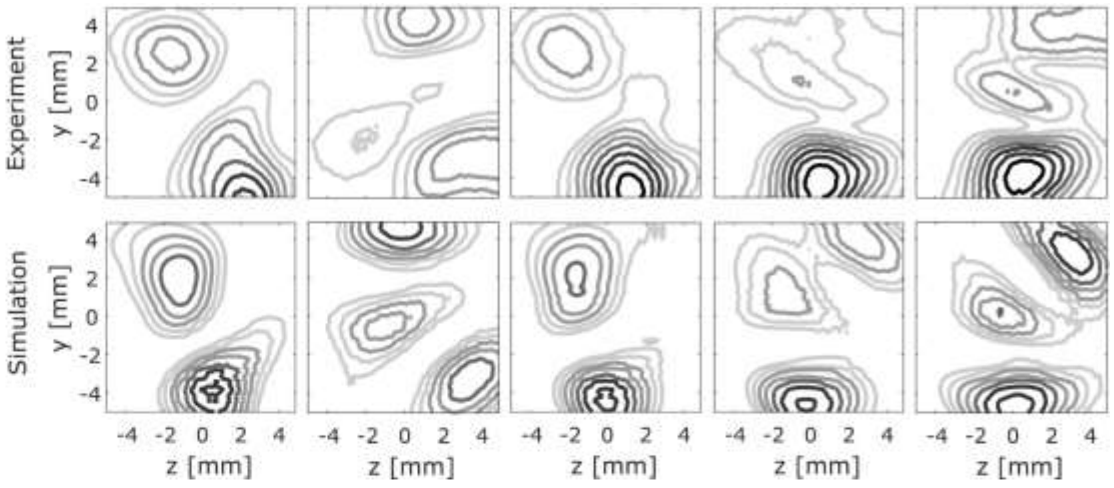
Rowald et al., Nature Medicine, 2022

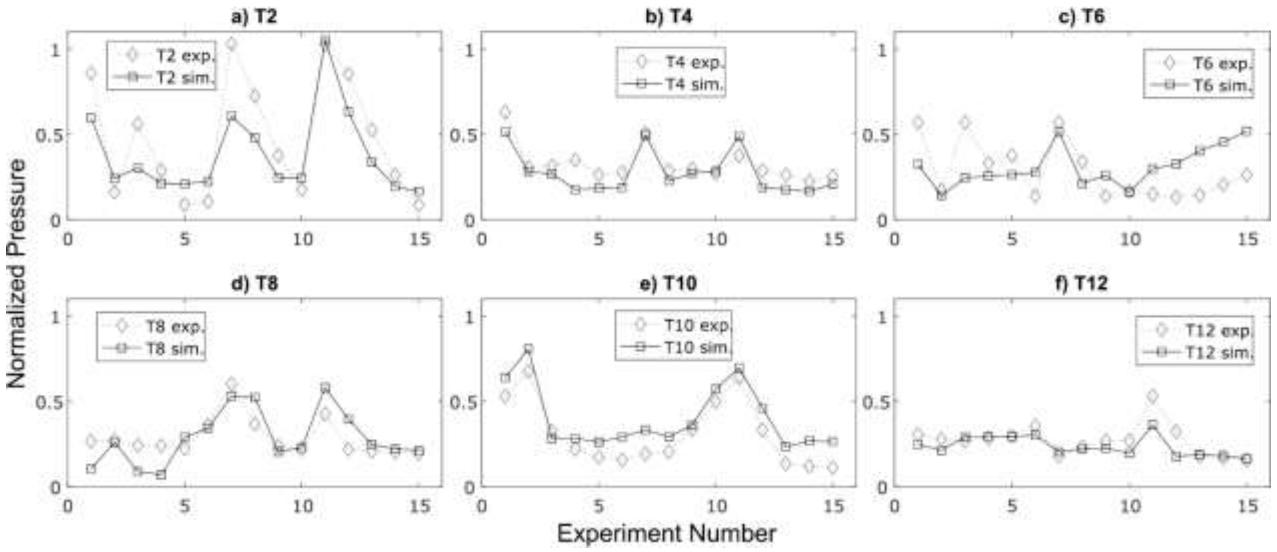
Potential for treating movement disorders?

Challenge: Focusing ultrasound through the spine



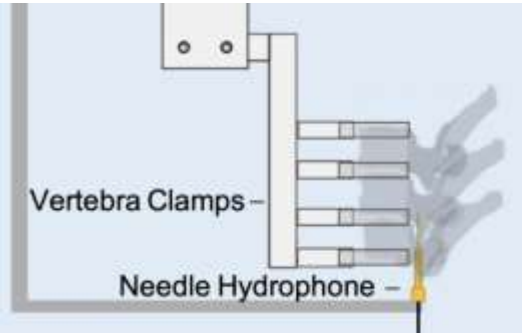


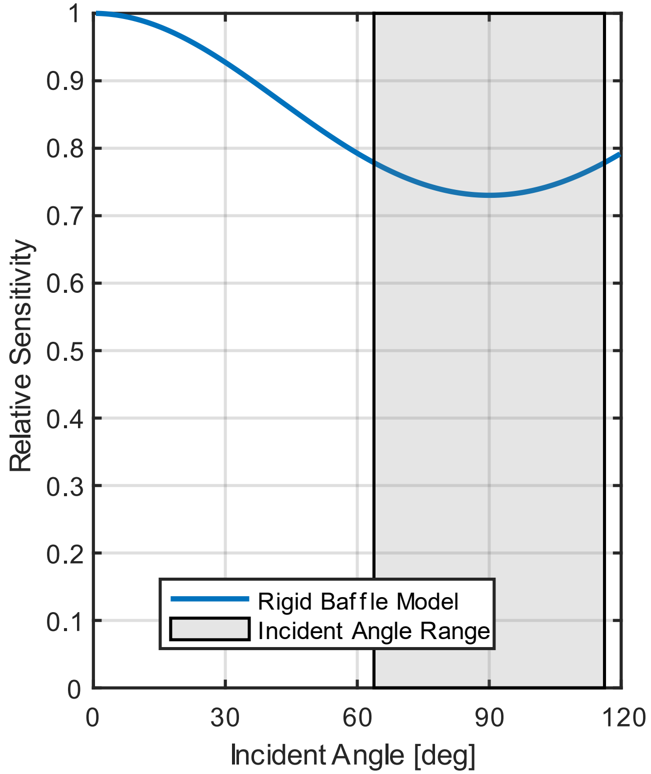


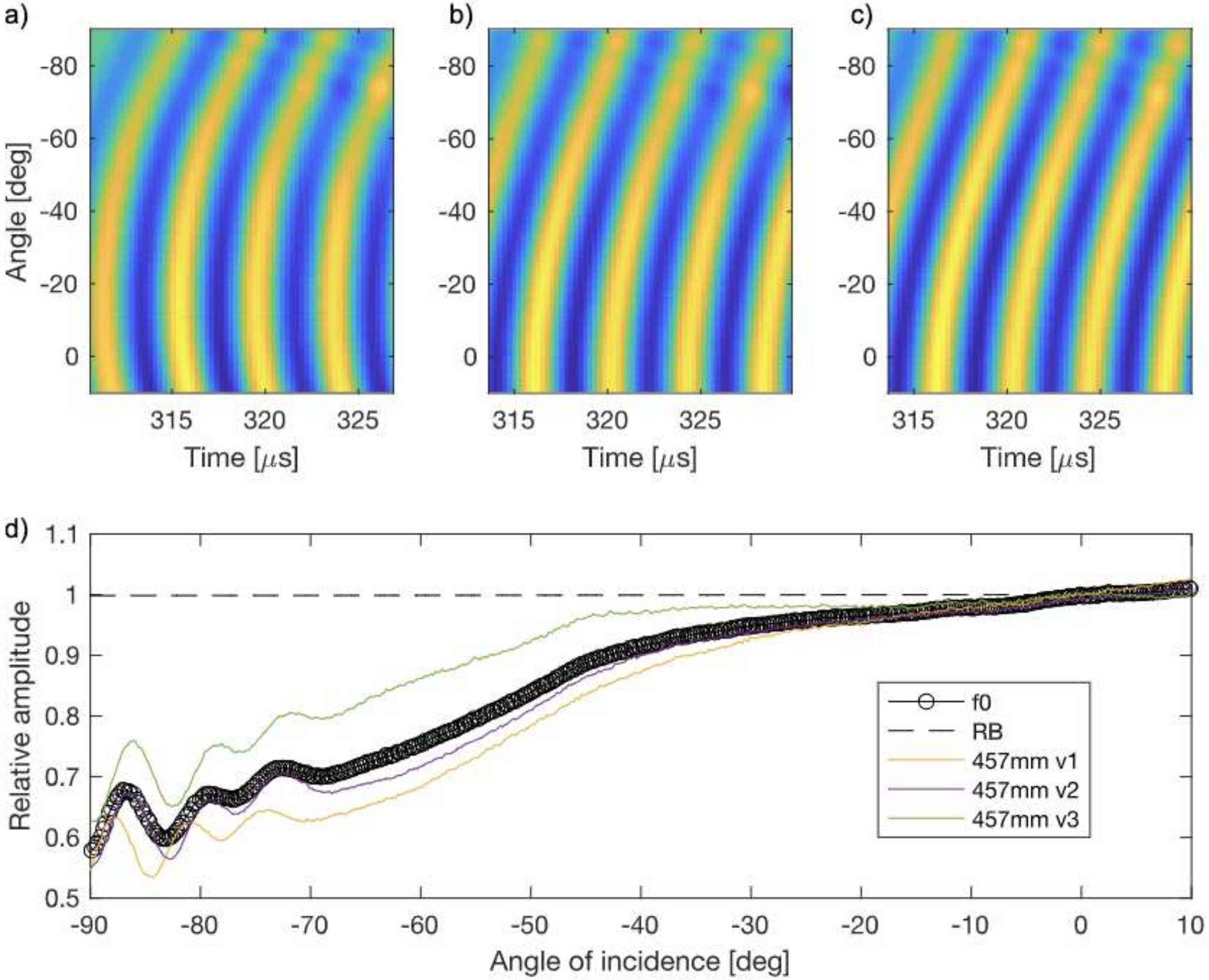


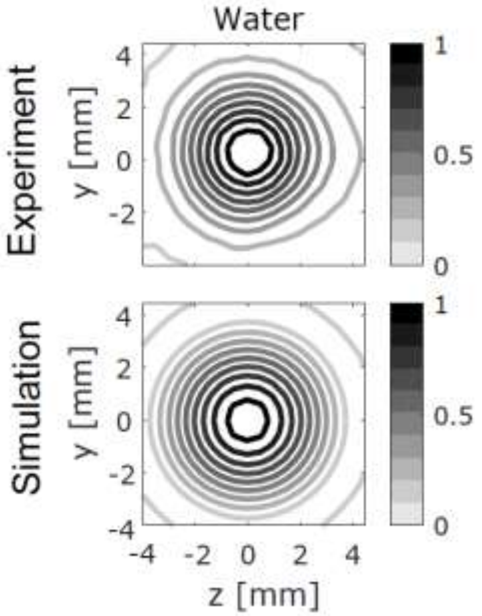
Xu & O'Reilly, *Physics in Medicine & Biology, (2018)*

Source of error: hydrophone directivity

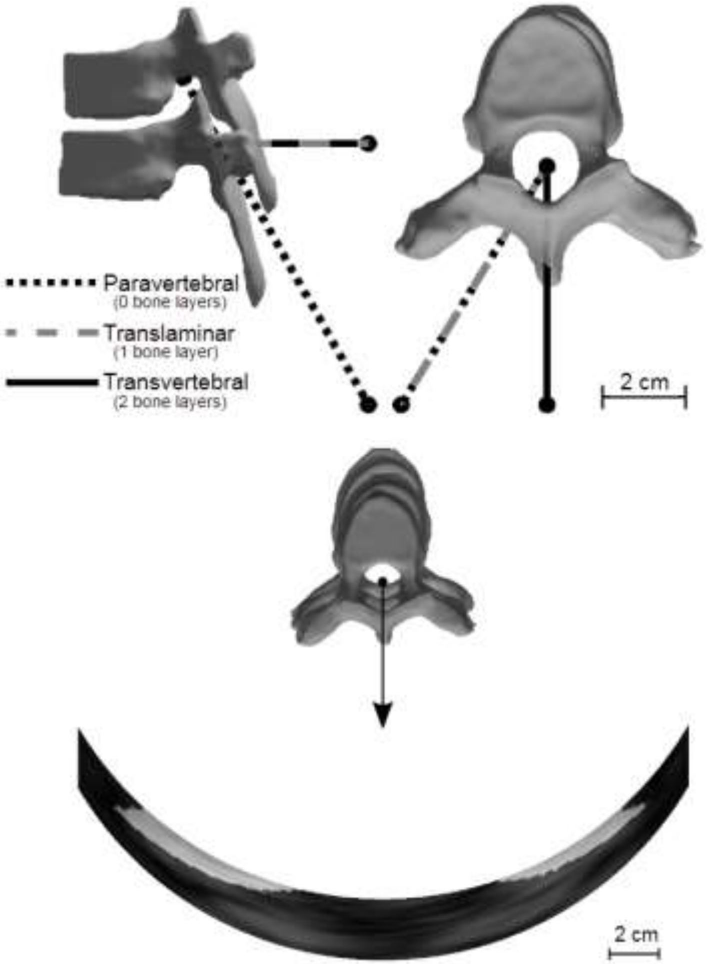


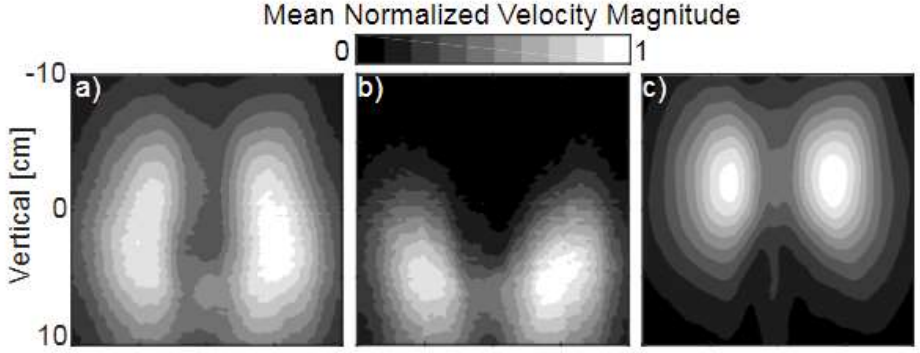


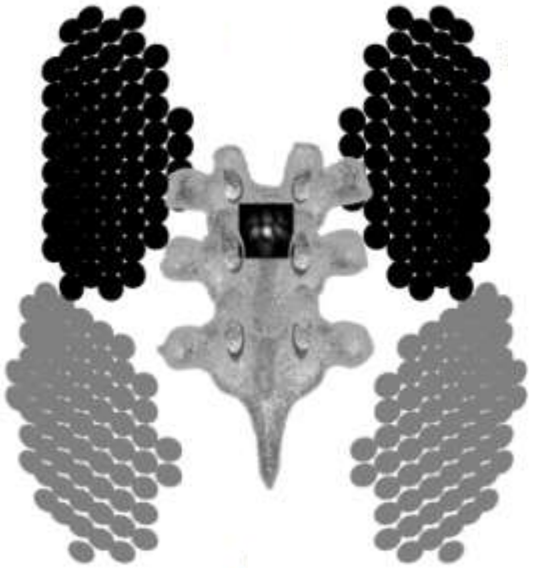


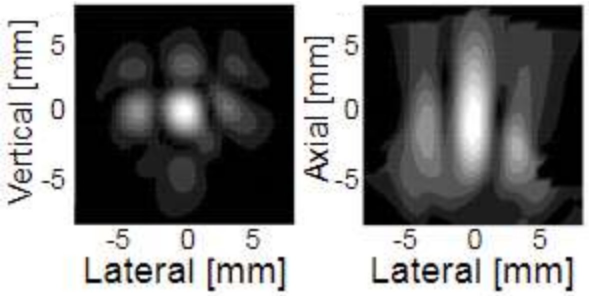


Approach: array + image-based aberration correction





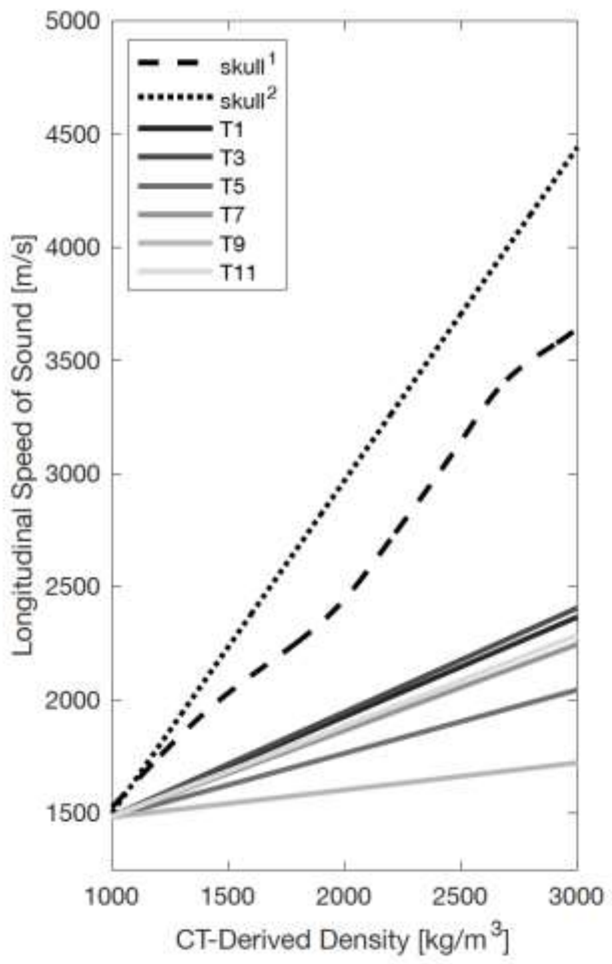




Xu & O'Reilly, *IEEE Transactions on Biomedical Engineering, (2019)*

Further challenges and opportunities in trans-spine focusing

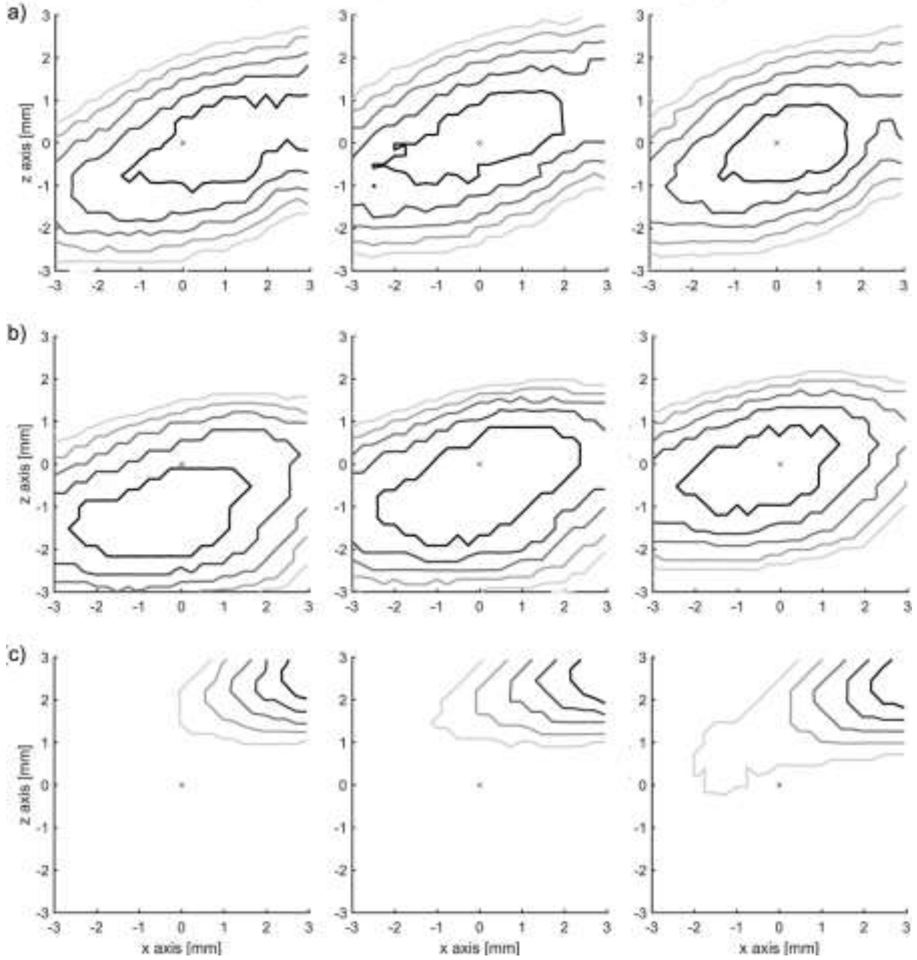
Sound speed across multiple vertebrae/spines



Xu & O'Reilly, JASA, 2022

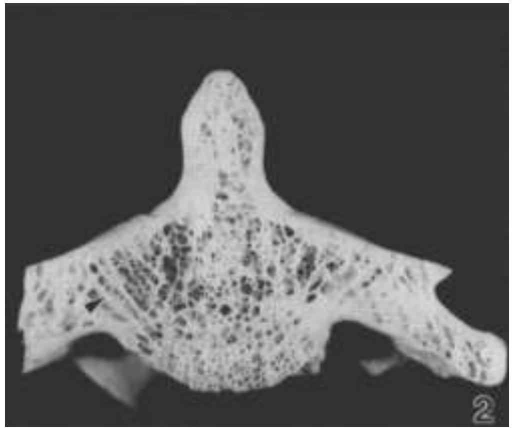
Improved Aberration Correction

Geometric Delays | Ray Acoustics | Hydrophone

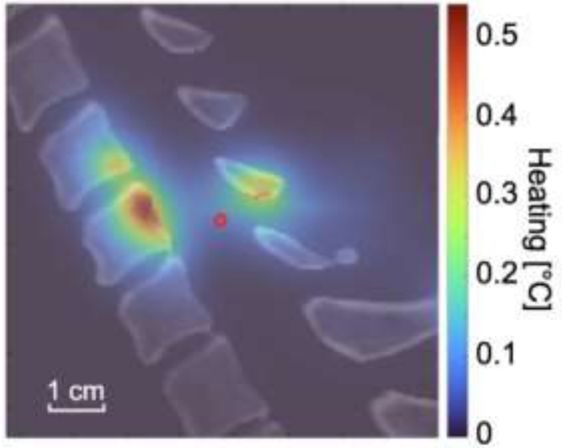


Martin et al., Physics in Medicine & Biology, 2024

Anisotropy

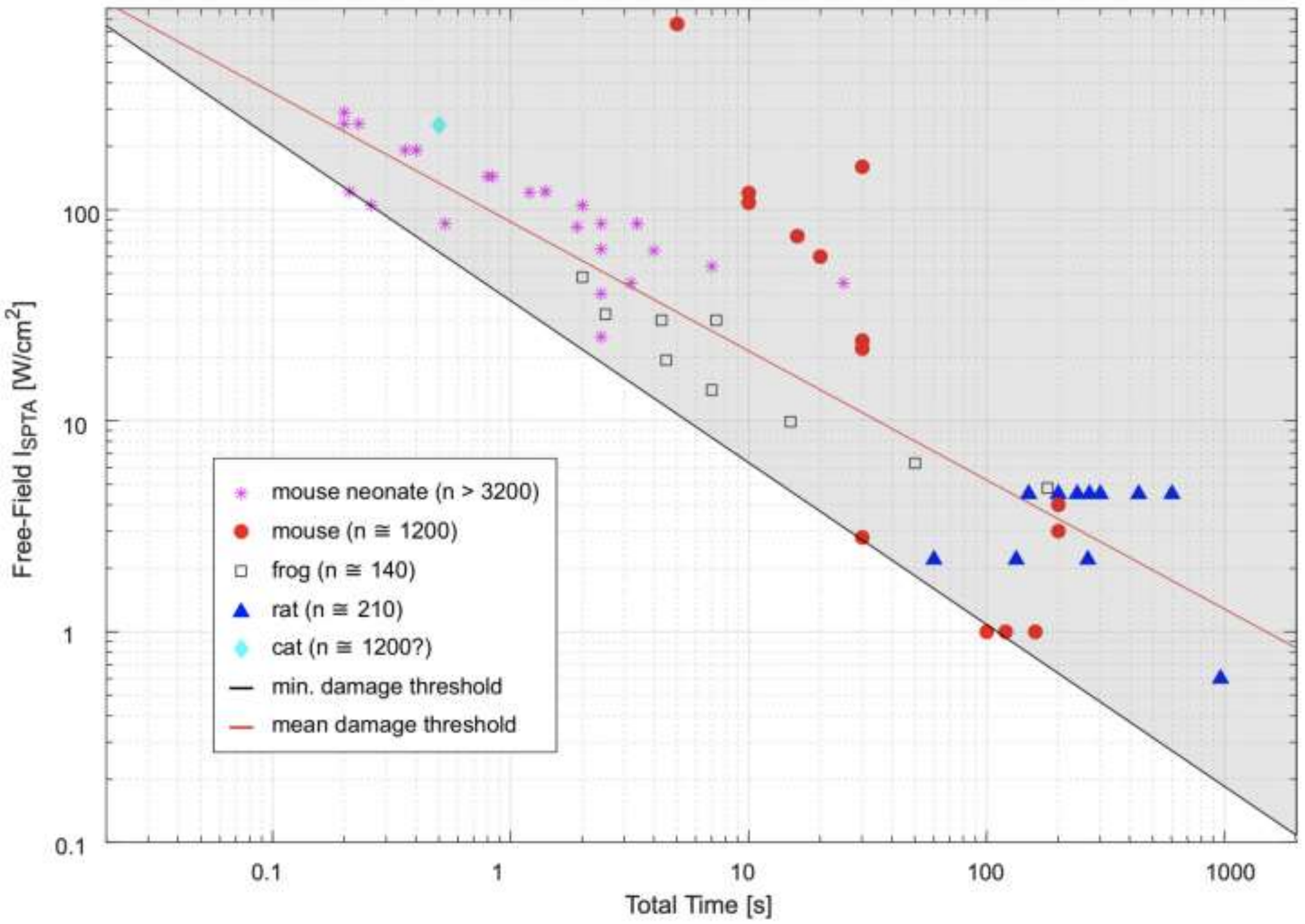


Heating

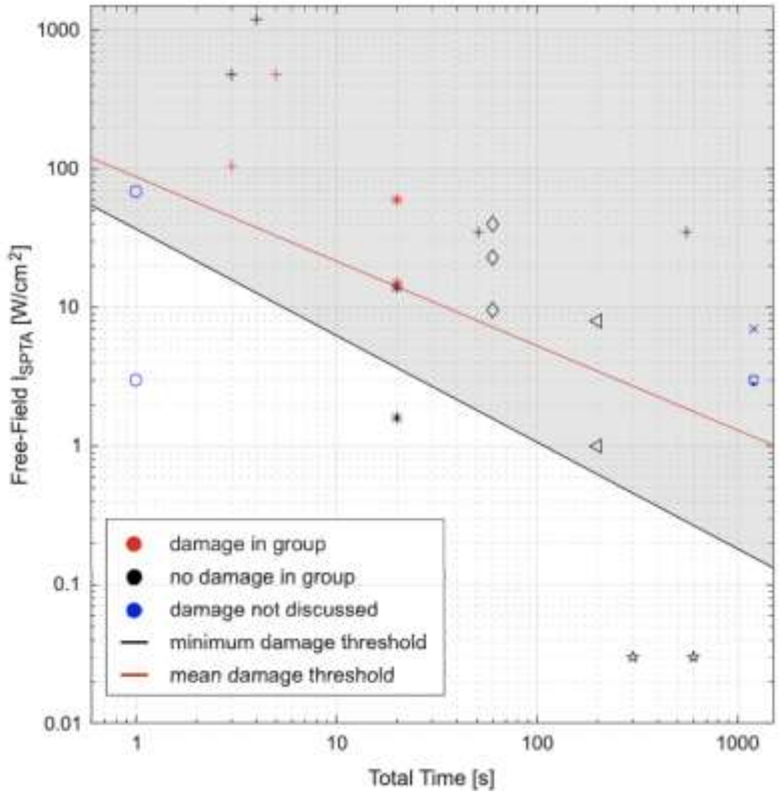


Xu et al., Physics in Medicine & Biology, 2024

Challenge: spinal cord safety

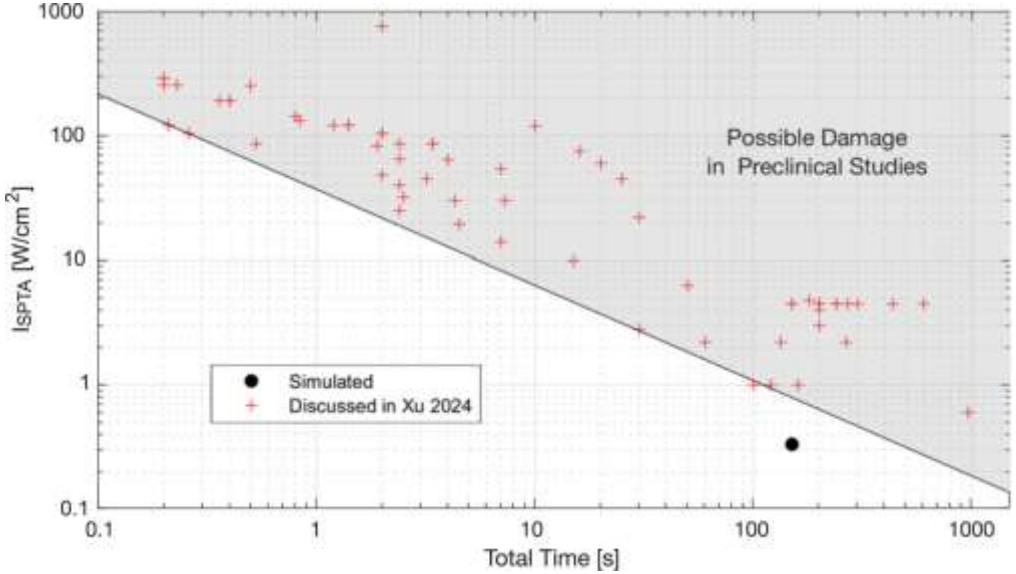


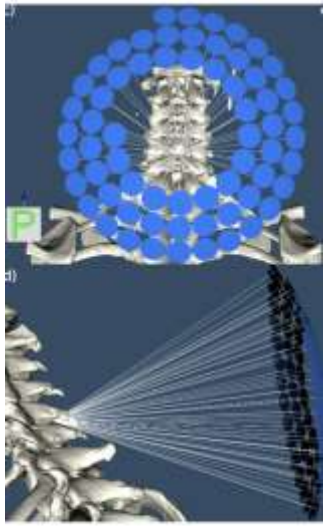
Currently no human or human-scale experiments

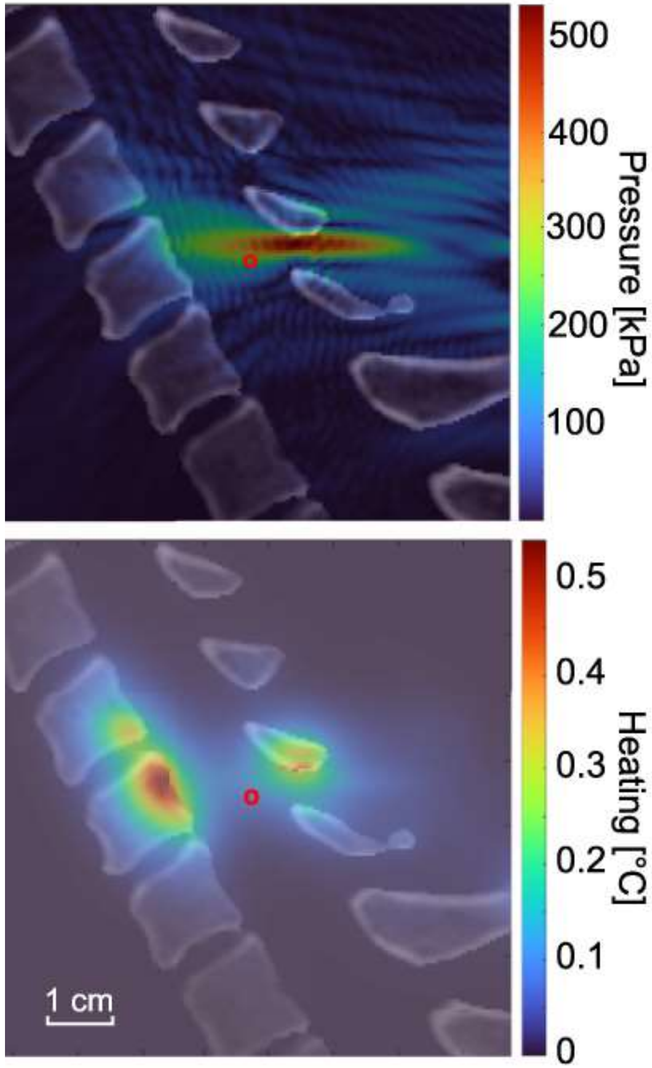


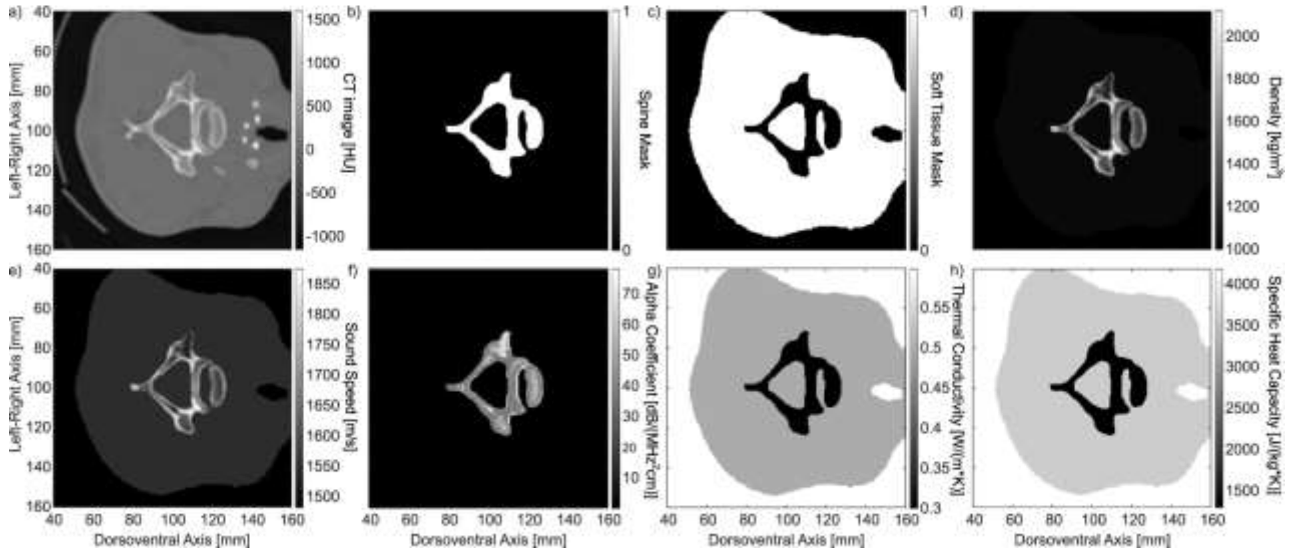
Xu et. al., Ultrasound in Medicine & Biology, 2024

Approach:





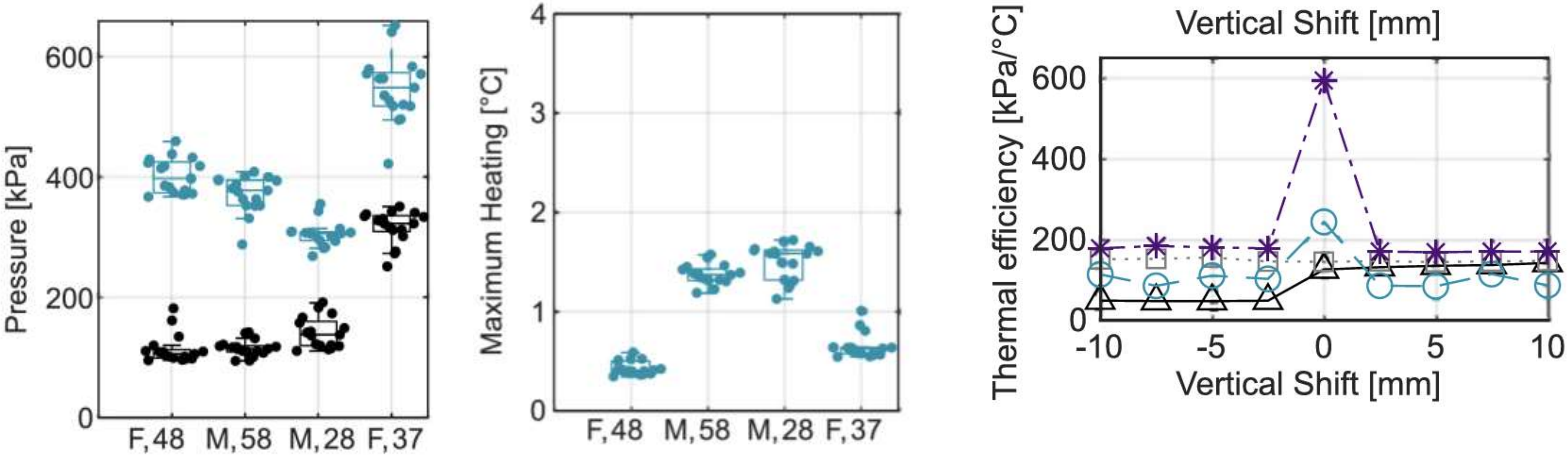




Xu et al., Physics in Medicine & Biology, 2024

Human scale simulations show high variance in sonication ‘efficiency’

Currently no human or human-scale experiments



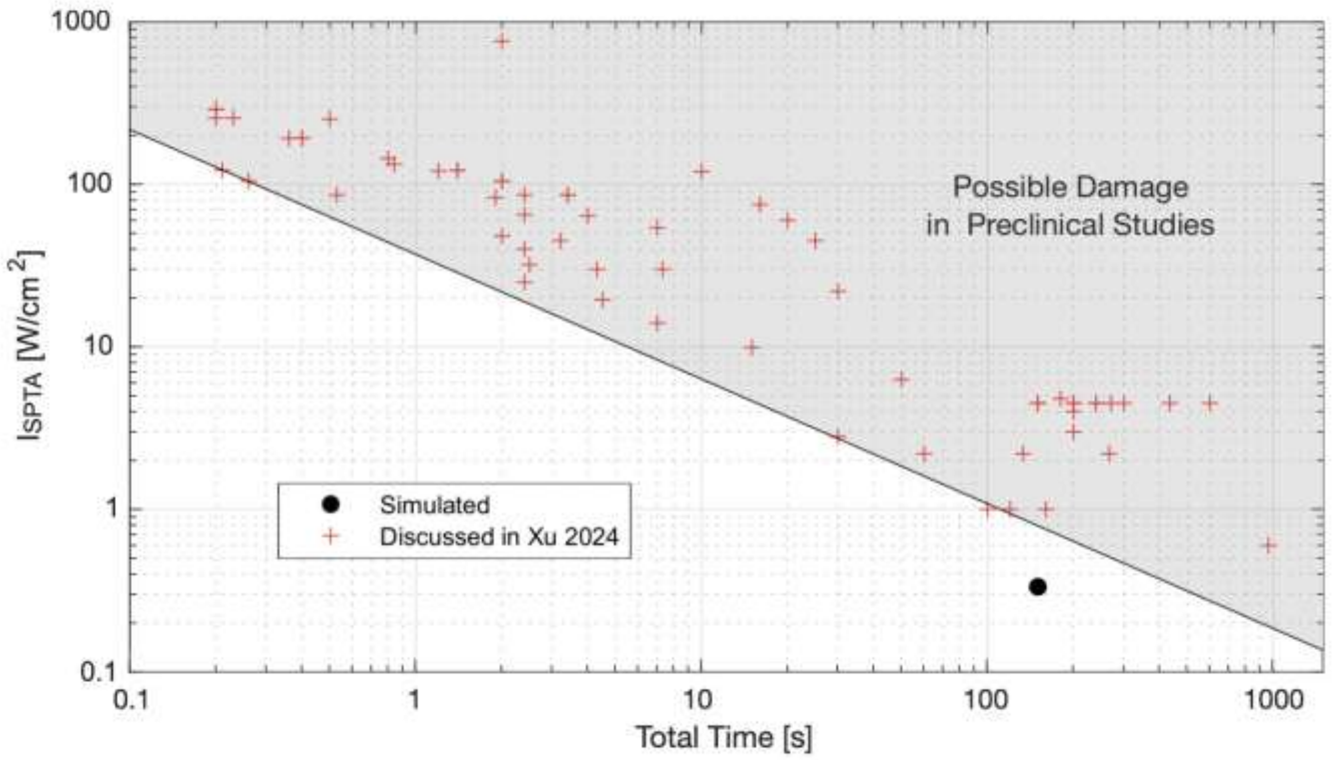
Xu et al., Physics in Medicine & Biology, 2024

Future work

Establish damage threshold in large animal model(s)

Establish accurate array-spine registration

Improve methods for trans-spine aberration correction – k-Wave



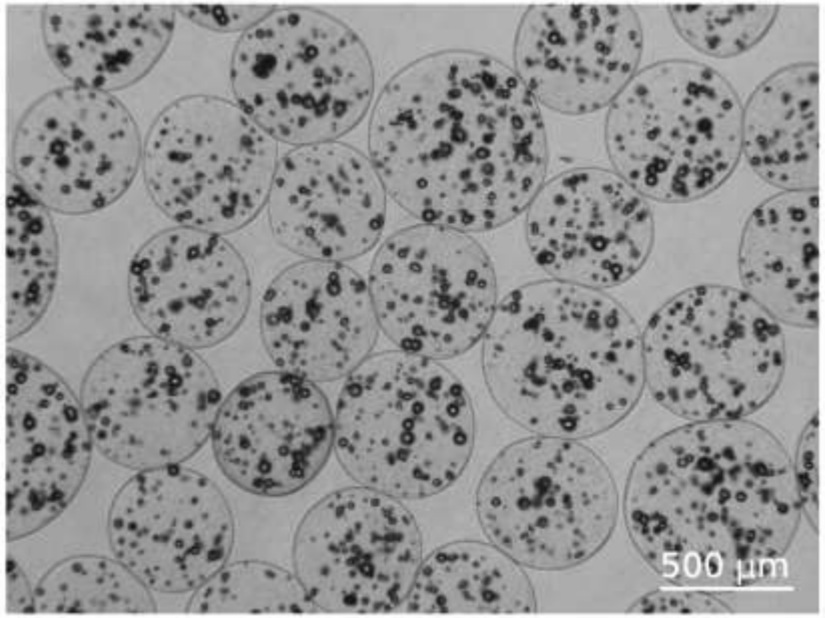
Ultrasonic Rewarming

Cell & organ cryopreservation is limited by slow rewarming

Ice crystal growth at higher sub-zero temperatures (-60 to -20°C) damages cells

The current gold-standard rewarming method is the 37°C water bath, but is unsuited to large volumes

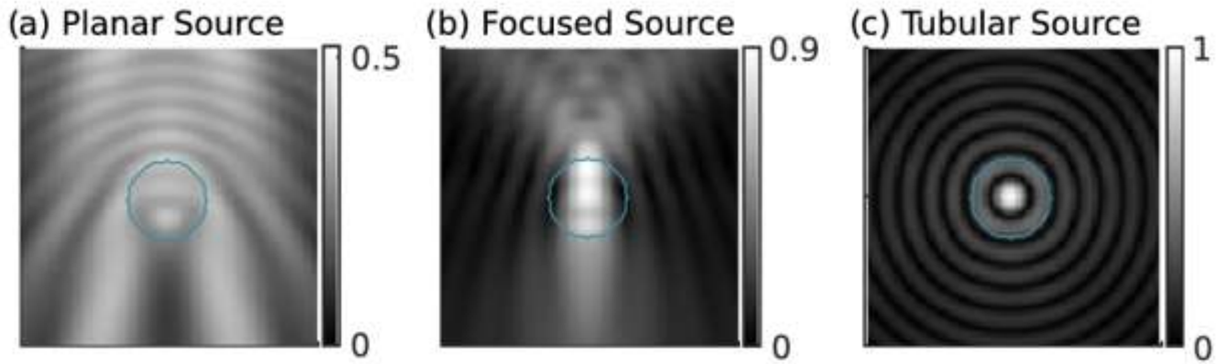
Ultrasound may be suited to volumetric rewarming[1,2]

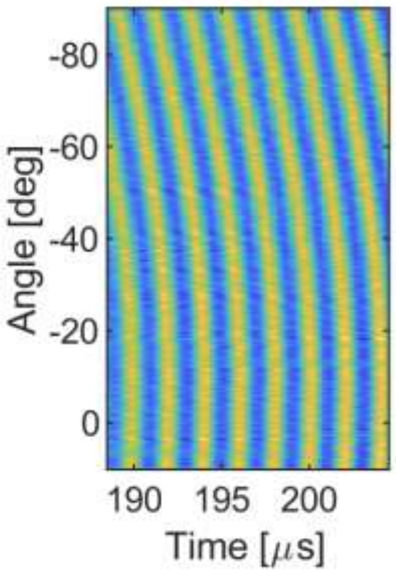


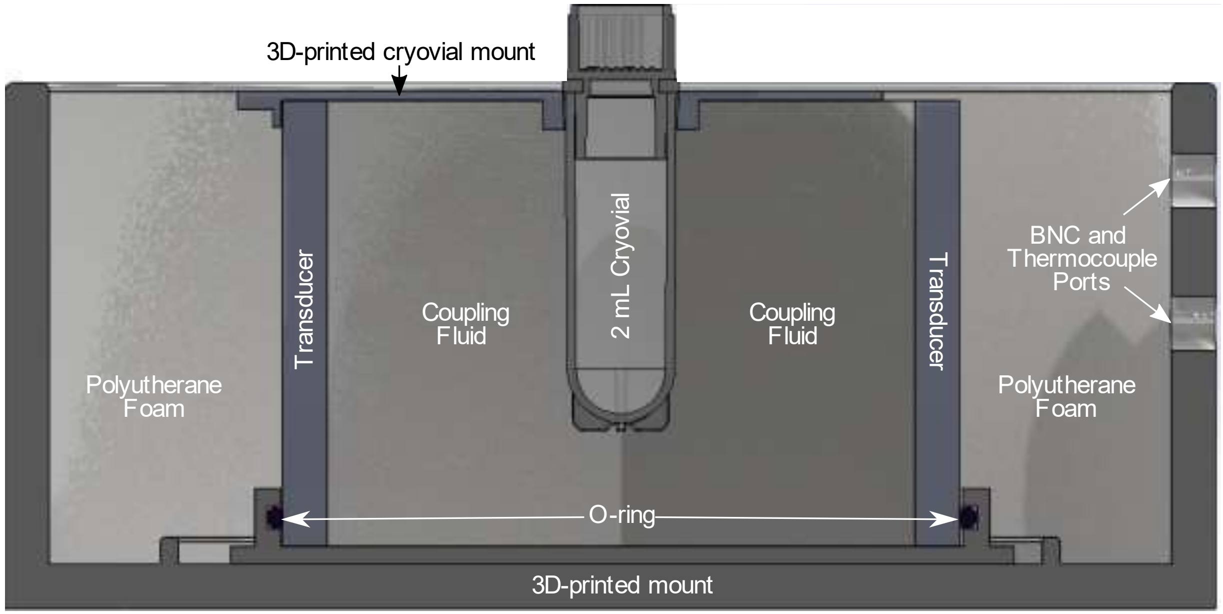
Alginate beads and cryoprotectant solution are used to improve cell cryopreservation.

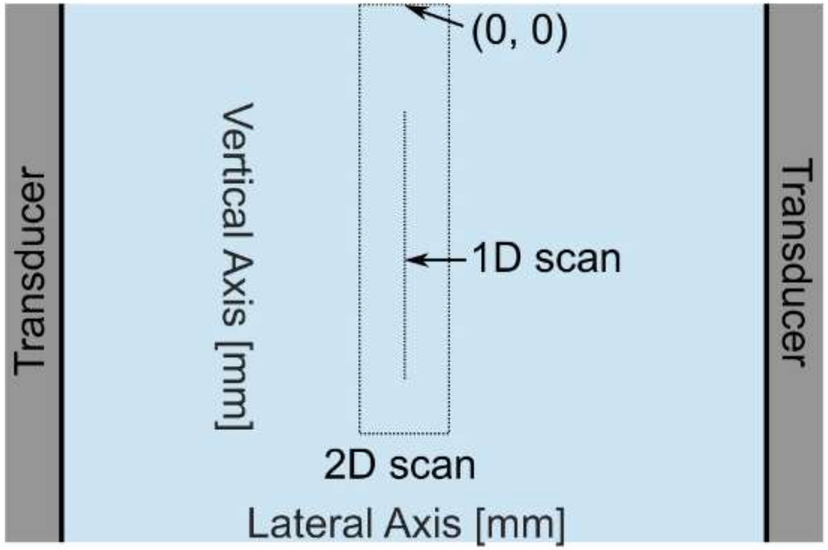
[1] *Xu, Treeby, & Martin, JASA, 2023* [2] *Alcalá et al., Scientific Reports, 2023*

Ultrasonic cryovial rewarming

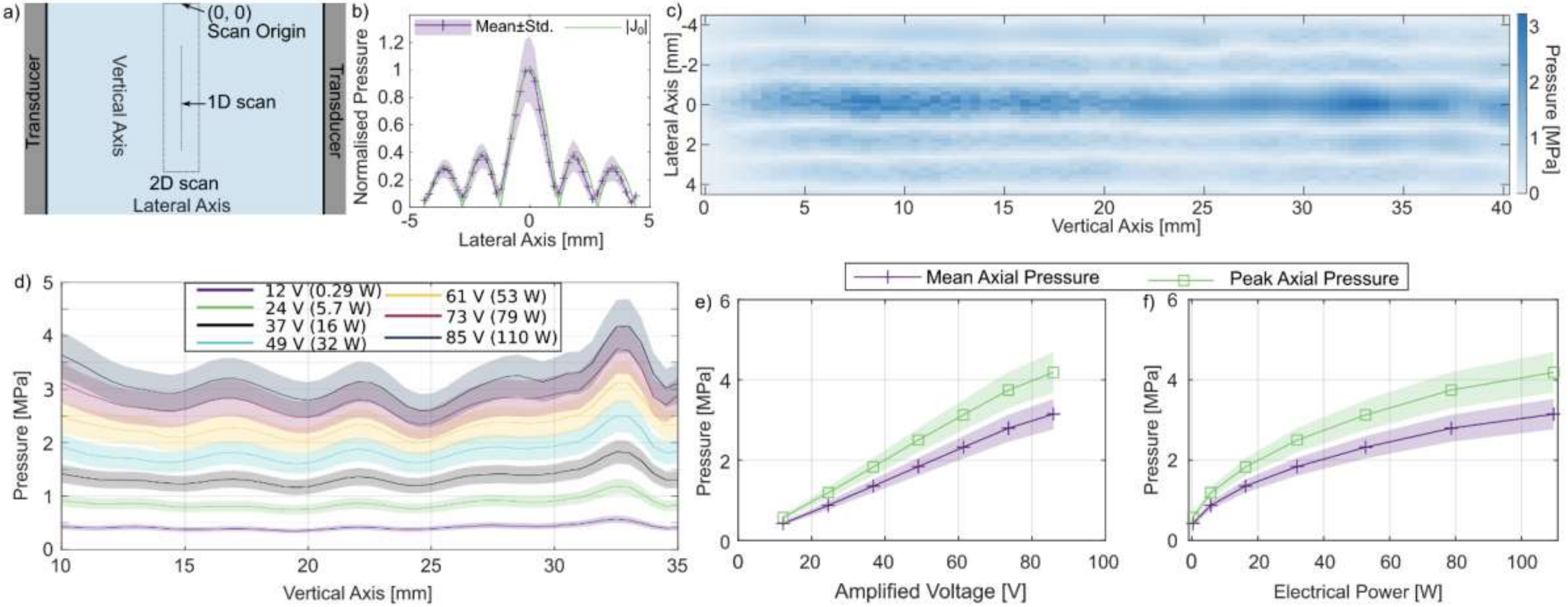






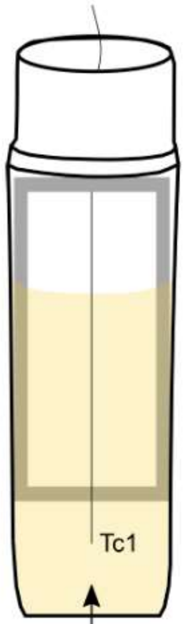


Acoustic characterisation with FOH

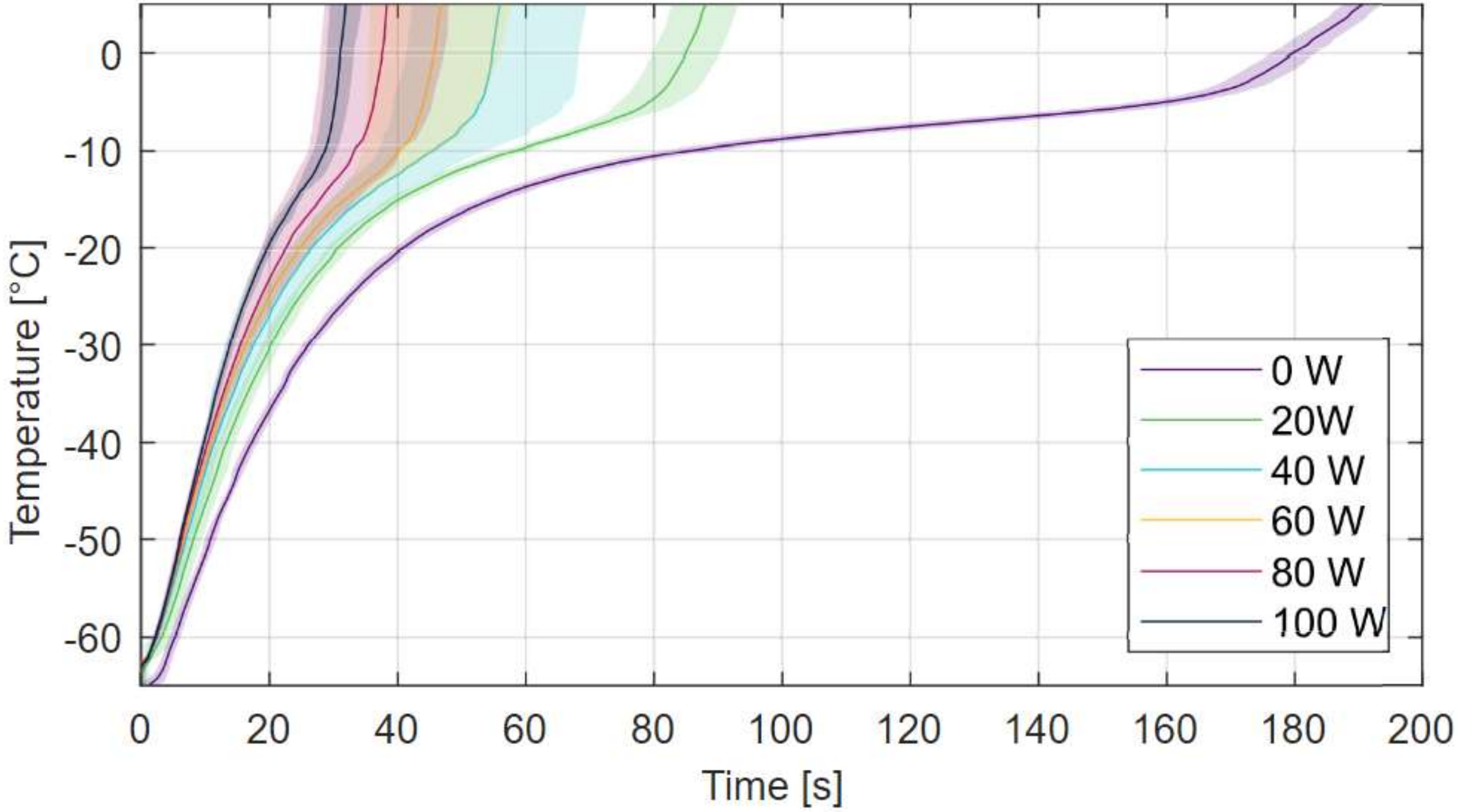


Xu et al., in preparation, 2024

Ultrasound accelerates rewarming



Alginate beads &
Cryoprotectant
Solution

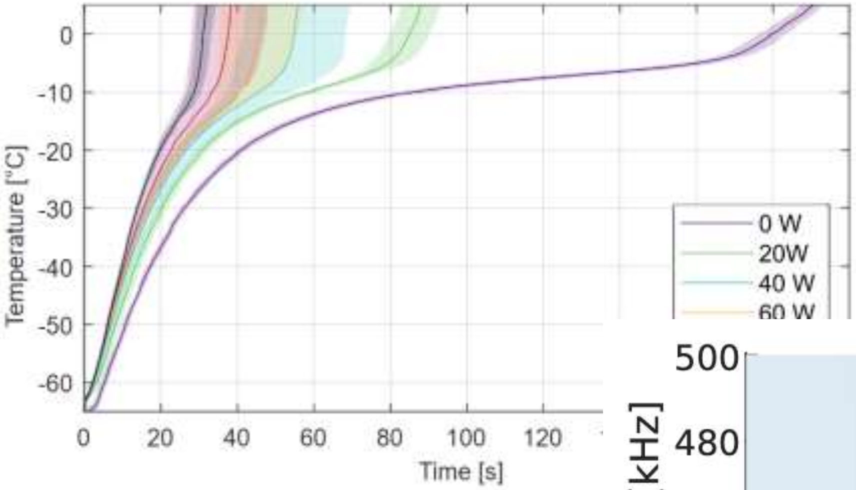


Free-field mean axial pressures and time-averaged intensities:

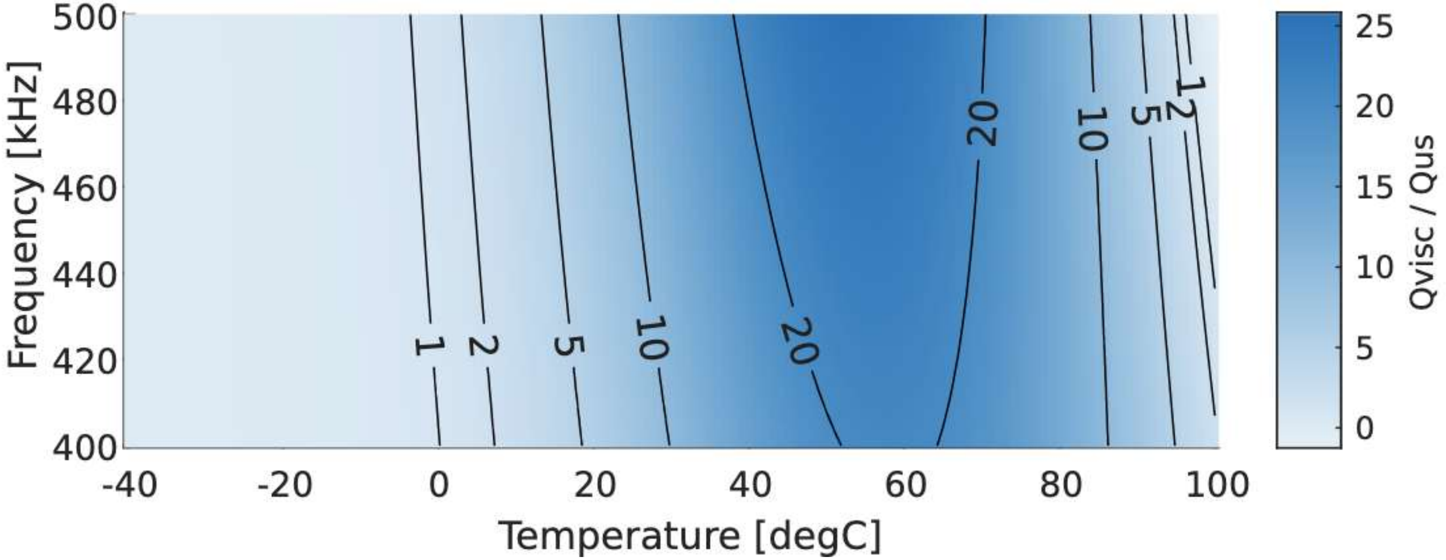
0 W – 0 MPa, 0 W/cm^2
20 W – 1.5 MPa, 75 W/cm^2
40 W – 2.0 MPa, 133 W/cm^2
60 W – 2.4 MPa, 192 W/cm^2
100 W – 2.8 MPa, 260 W/cm^2

Beware the thermocouple viscous heating artifact

Alginate beads & Cryoprotectant Solution

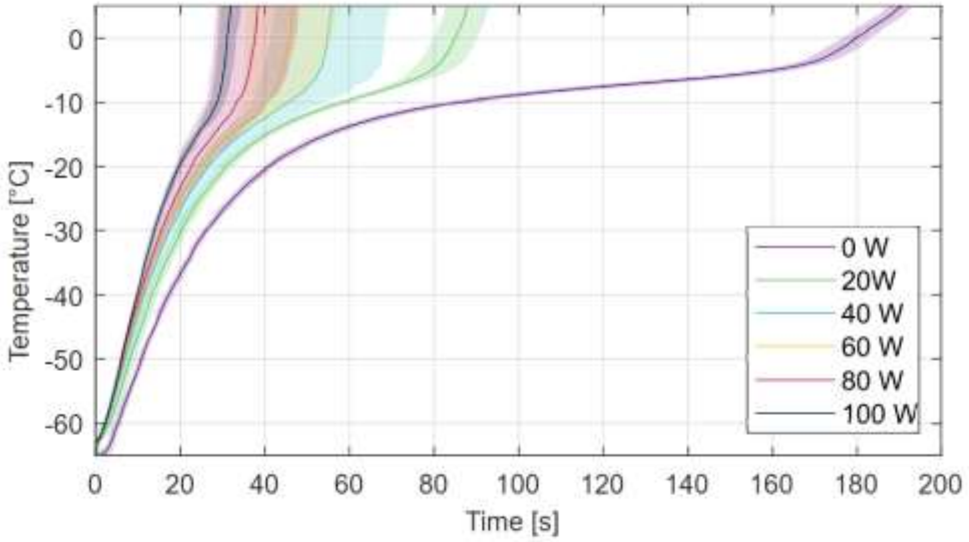


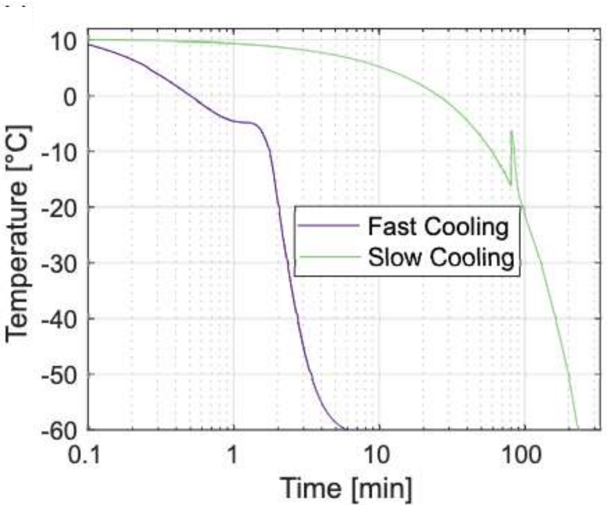
Viscous heating artifact in glycerol

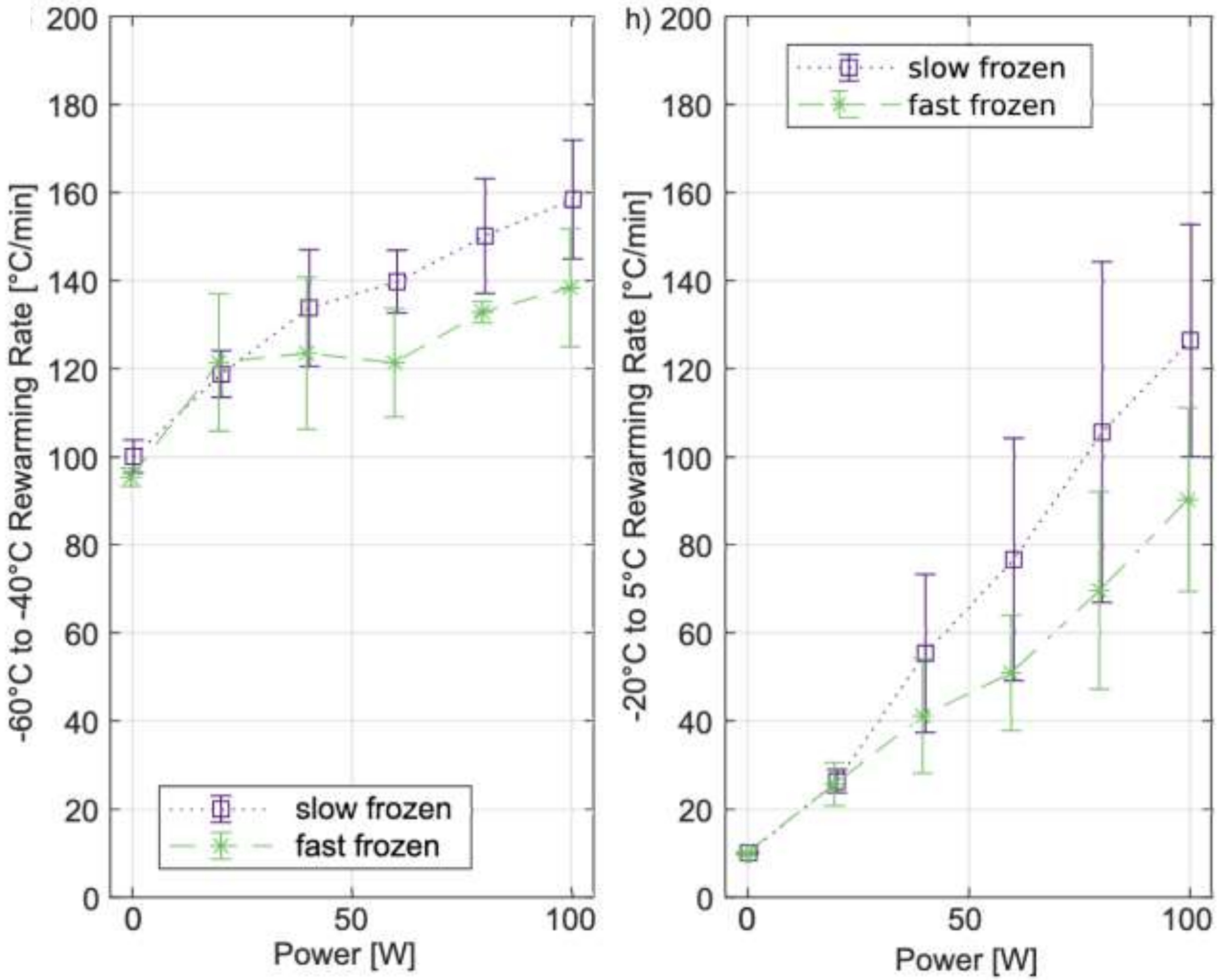


Xu et al., Proceedings of IEEE-JS, 2024

Freezing rate affects ultrasonic rewarming rate

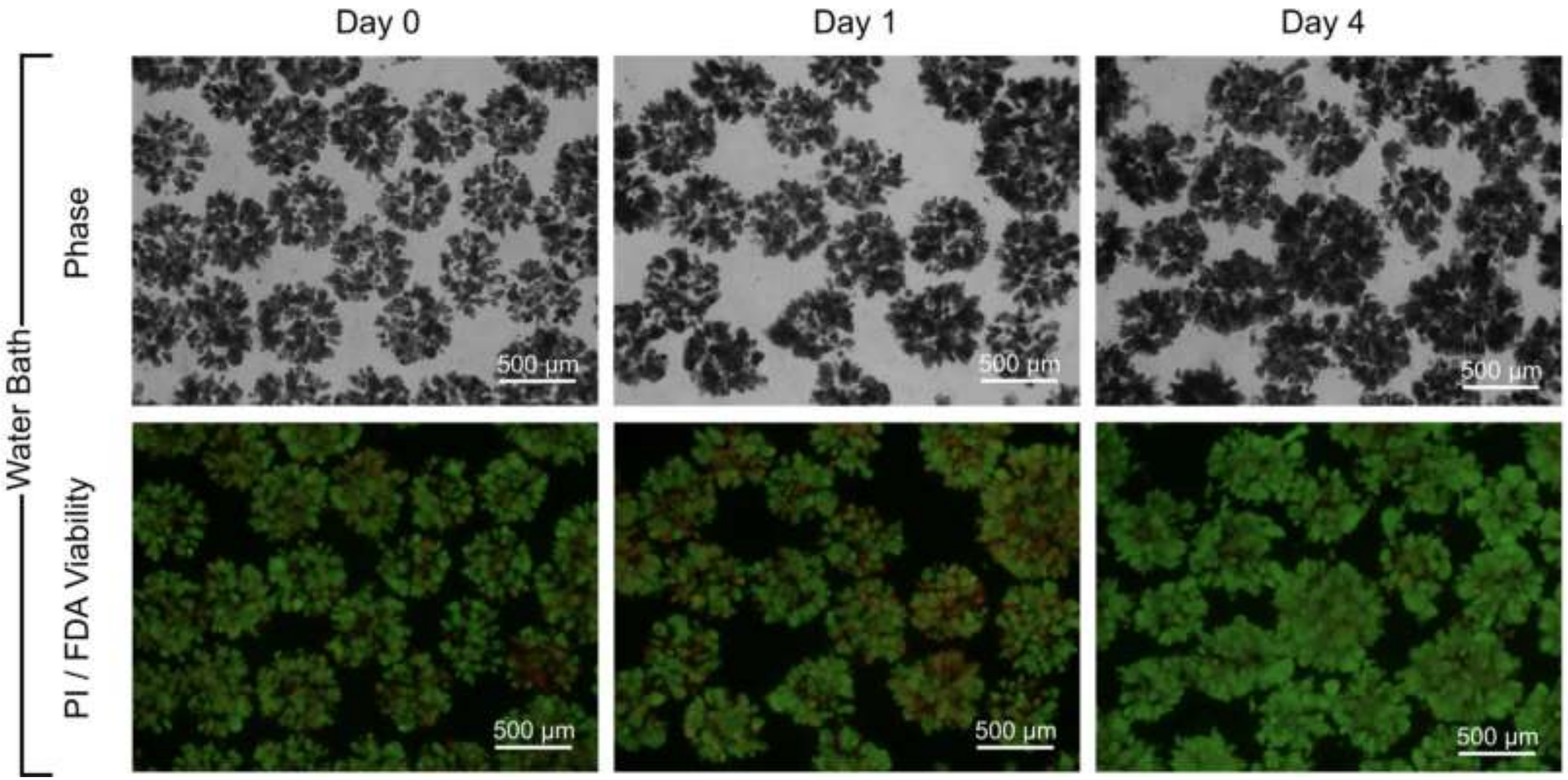




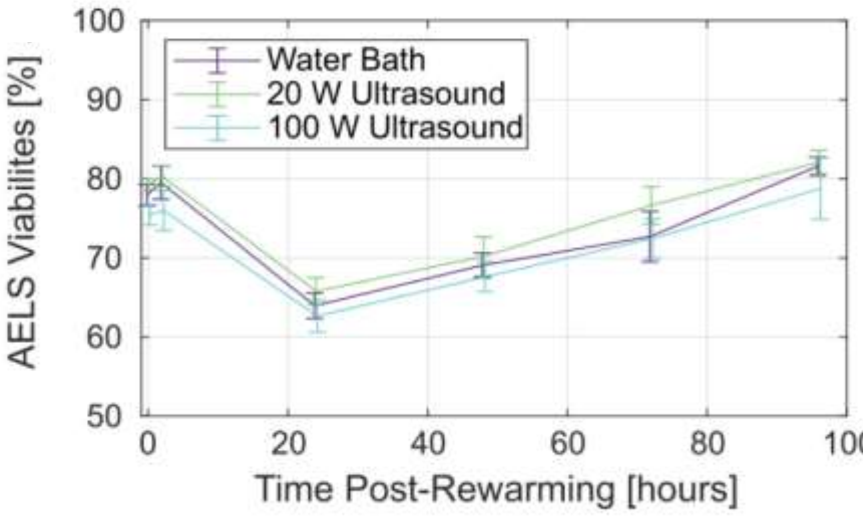


Xu et al., in preparation, 2024

Alginate-encapsulated liver spheroid viability



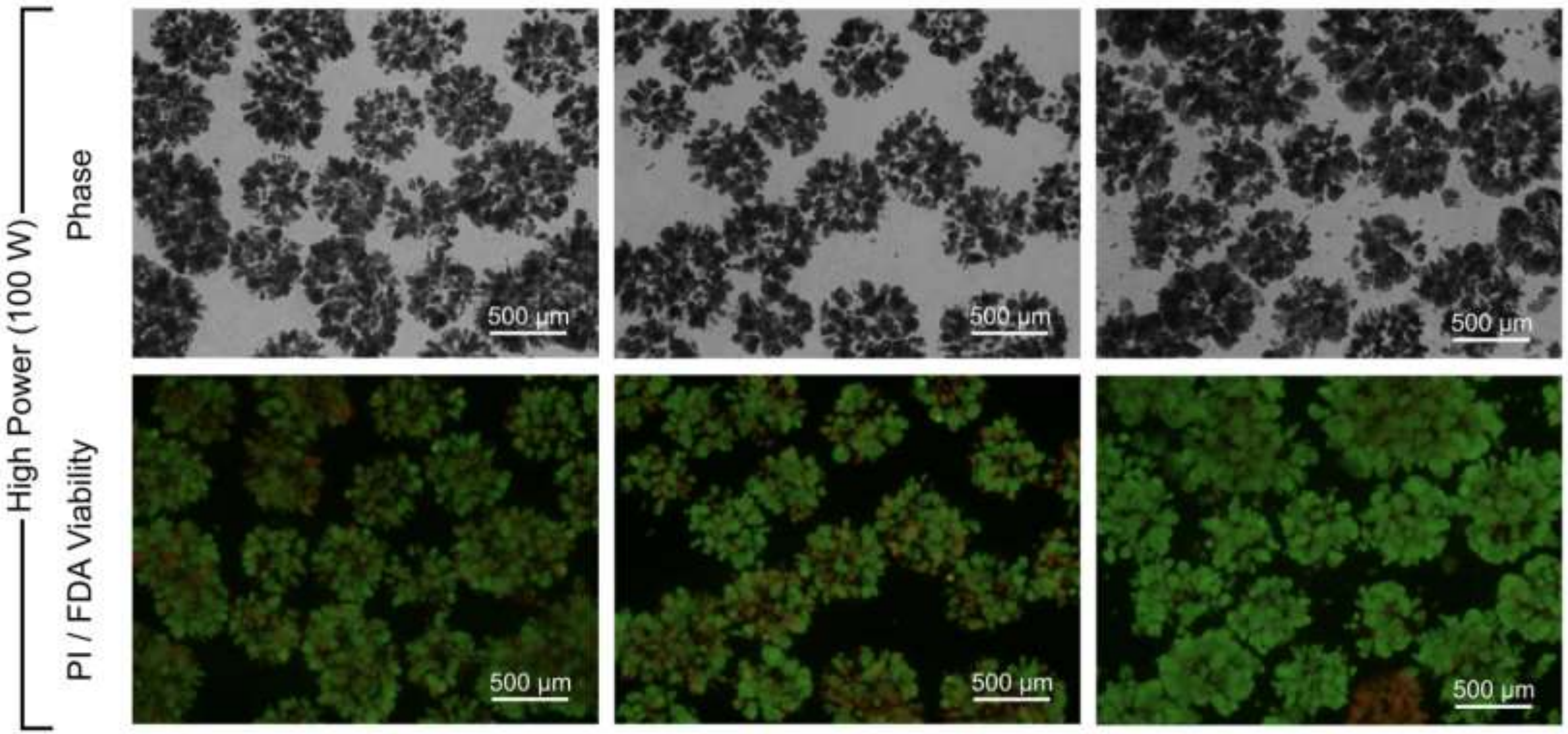
Rewarming exposure time selected to rewarm to 5℃

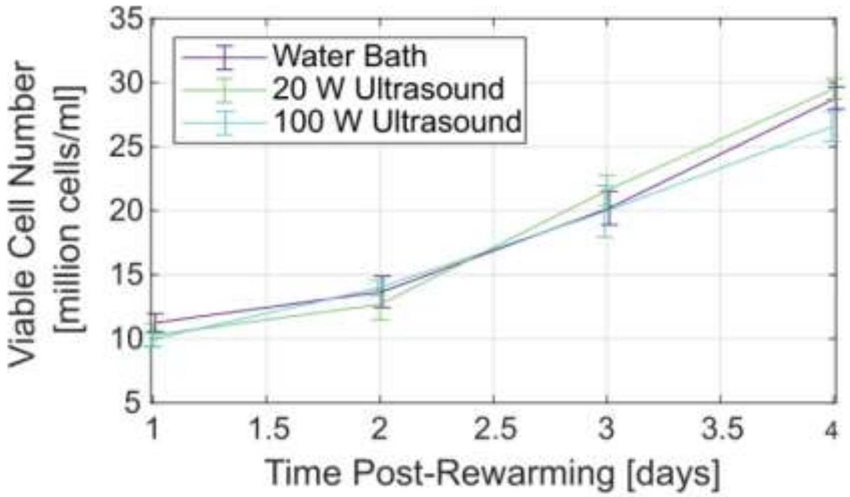


Rewarming at 20 W: 36% increase in rewarming rate over the gold standard 37℃ water bath
Rewarming at 100 W: 360% increase in rewarming rate

Xu et al., in preparation, 2024

Ultrasound improves rewarming rate and maintains cell number





Further optimization of ultrasonic rewarming protocols may broadly improve cryovial rewarming

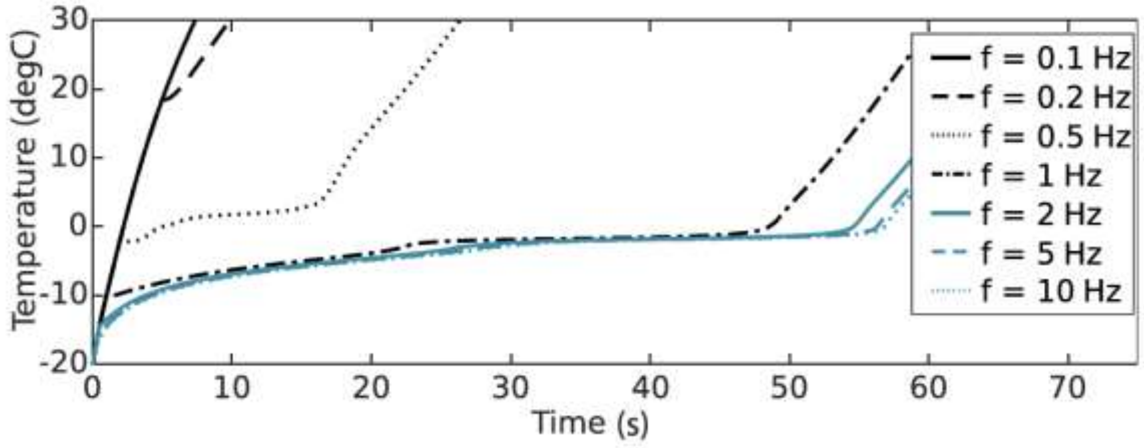
Xu et al., in preparation, 2024

Future work in ultrasonic rewarming

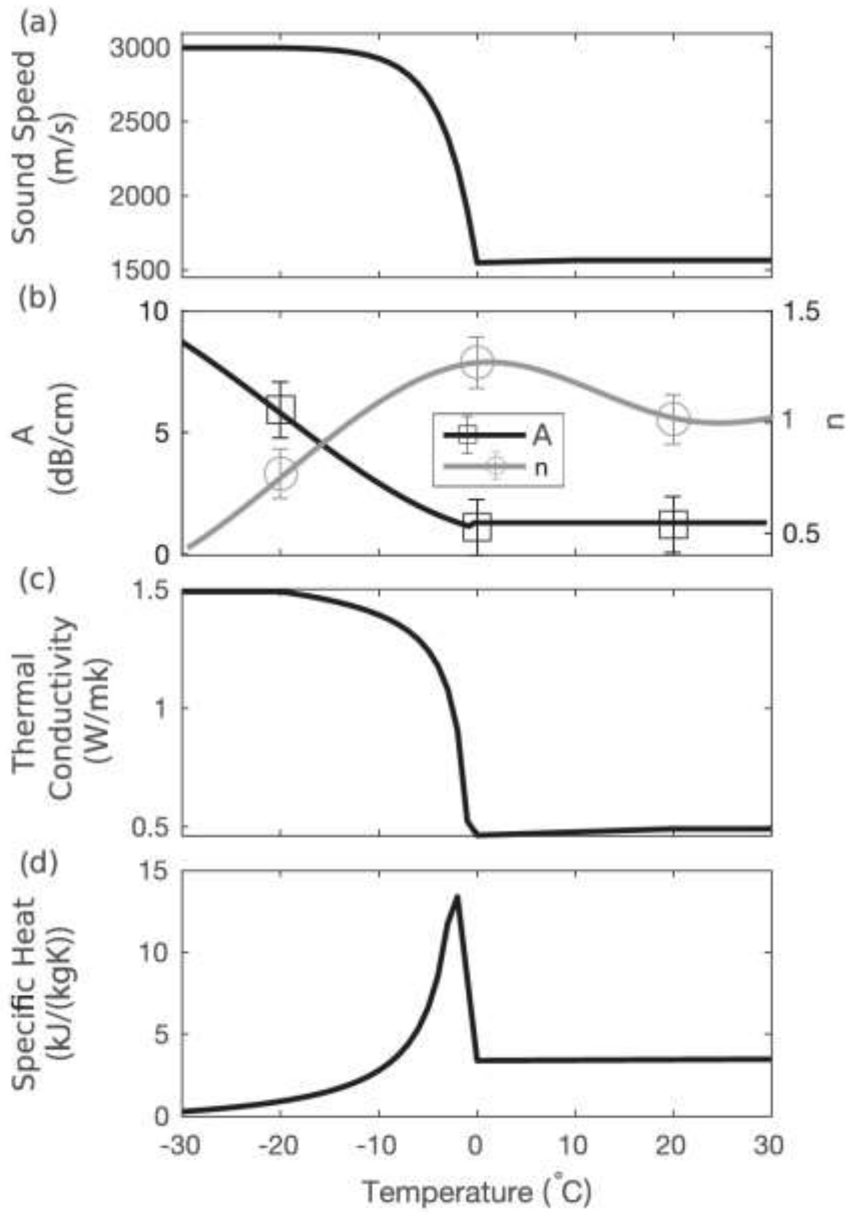
Return to simulation roots

Requires accurate characterisation of temperature-dependence of acoustic and thermal properties

Array development for large-volume rewarming



Xu, Treeby & Martin, JASA, 2023



Conclusions

Simulations are a useful tool throughout the development & implementation of ultrasound applications

Careful metrological validation is needed for confidence in simulations

Plenty of ‘new’ applications and approaches

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