Microbubble-mediated ultrasonic brain therapy and treatment monitoring via sparse hemispherical transducer arrays

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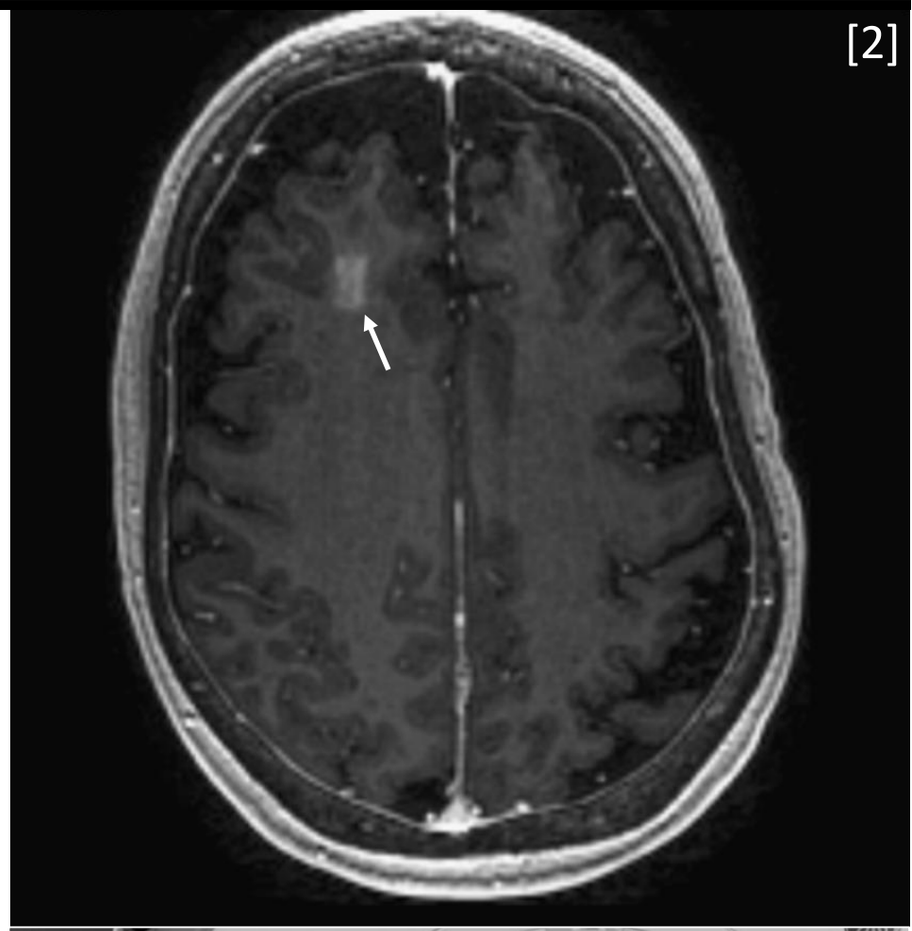
Motivation

- Focused ultrasound (FUS) + microbubbles (MBs): blood-brain barrier (BBB) opening: clinical[1-4]

- Existing FUS arrays: 30 cm diam., 1024-elem. hemispherical; **limited spatial MB information**

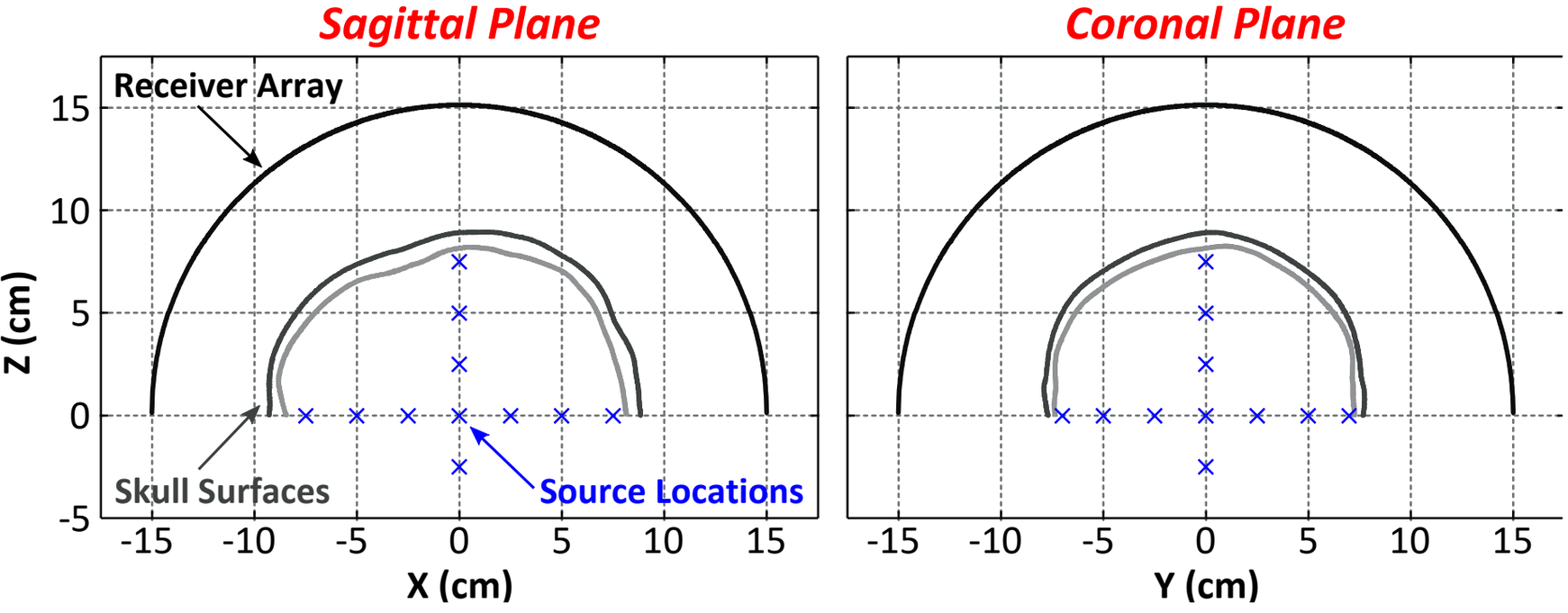
- Multi-element sensor arrays + beamforming: **spatial** & **temporal** source field mapping[5,6]

- Large apertures: resolution, sensitivity, imaging volume; sparsity reduces **complexity** & **cost**

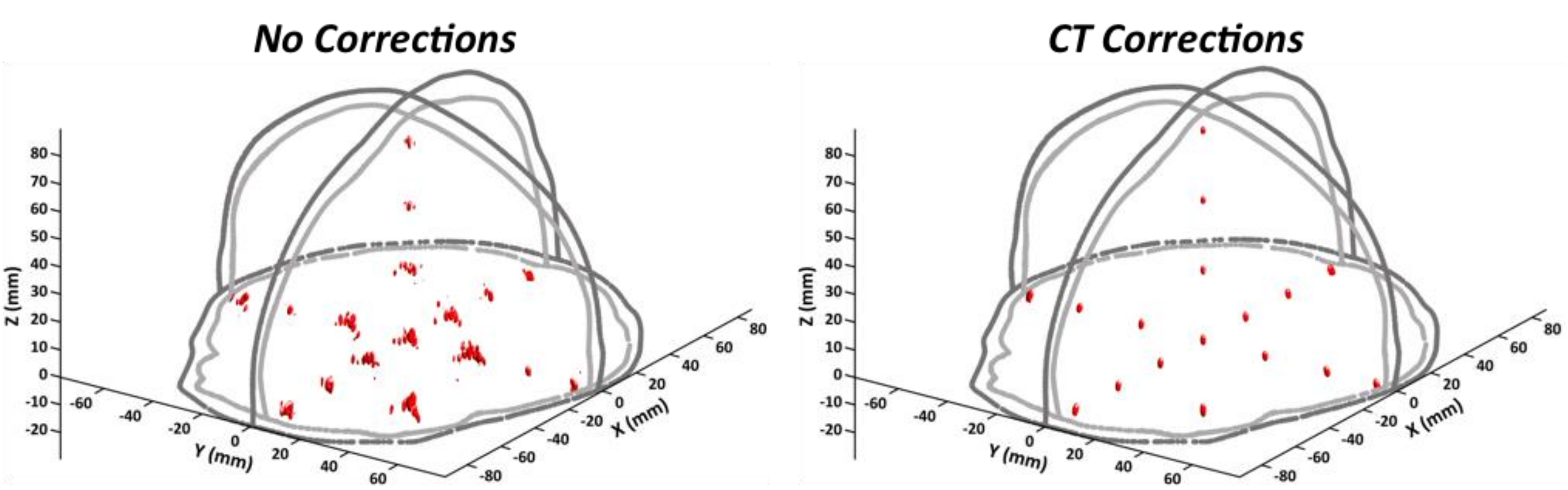

[2]

[1] Mainprize *et al*, *Sci Rep* (2019)
[2] Lipsman *et al*, *Nat Comm* (2018)
[3] Abrahao *et al*, *Nat Comm* (2019)
[4] Carpentier *et al*, *STM* (2016)
[5] Sato *et al*, *JASA* (1980)
[6] Salgaonkar *et al*, *JASA* (2009)

Array Design Simulations



- **Multilayered Ray-Acoustics[1]**
- **Delay, Sum, & Integrate Beamformer[2]**
- **Simulation Variables**
  - Source Location/Frequency
  - Receiver Number/Layout/SNR
  - Skull Morphology (3 CT datasets)

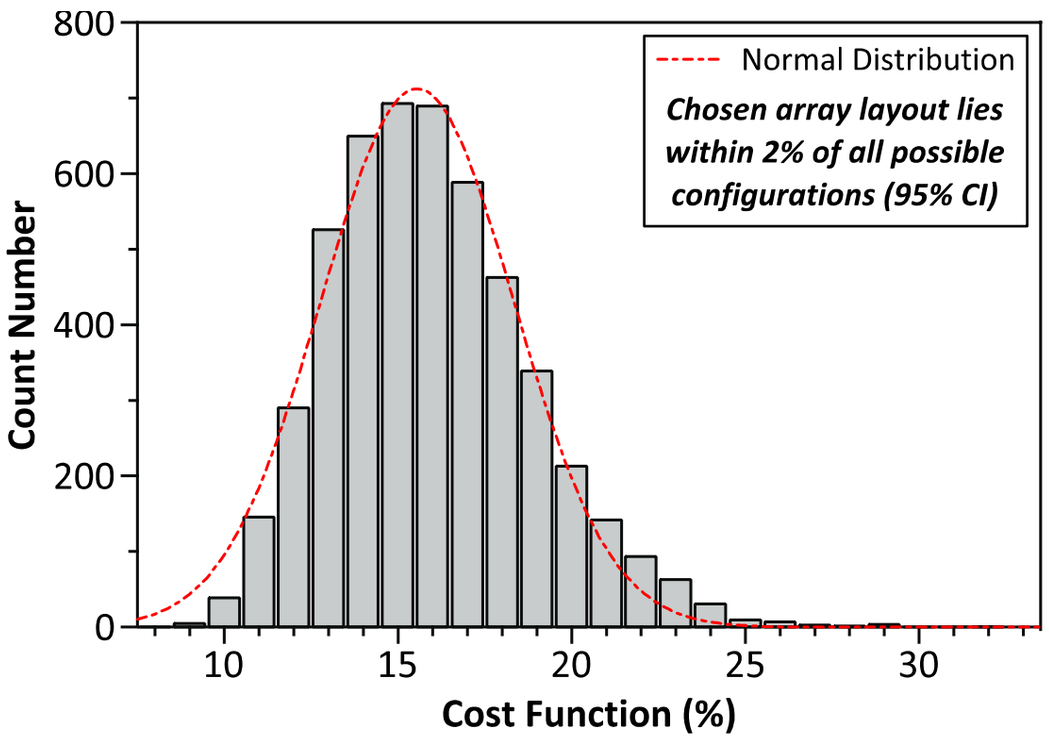


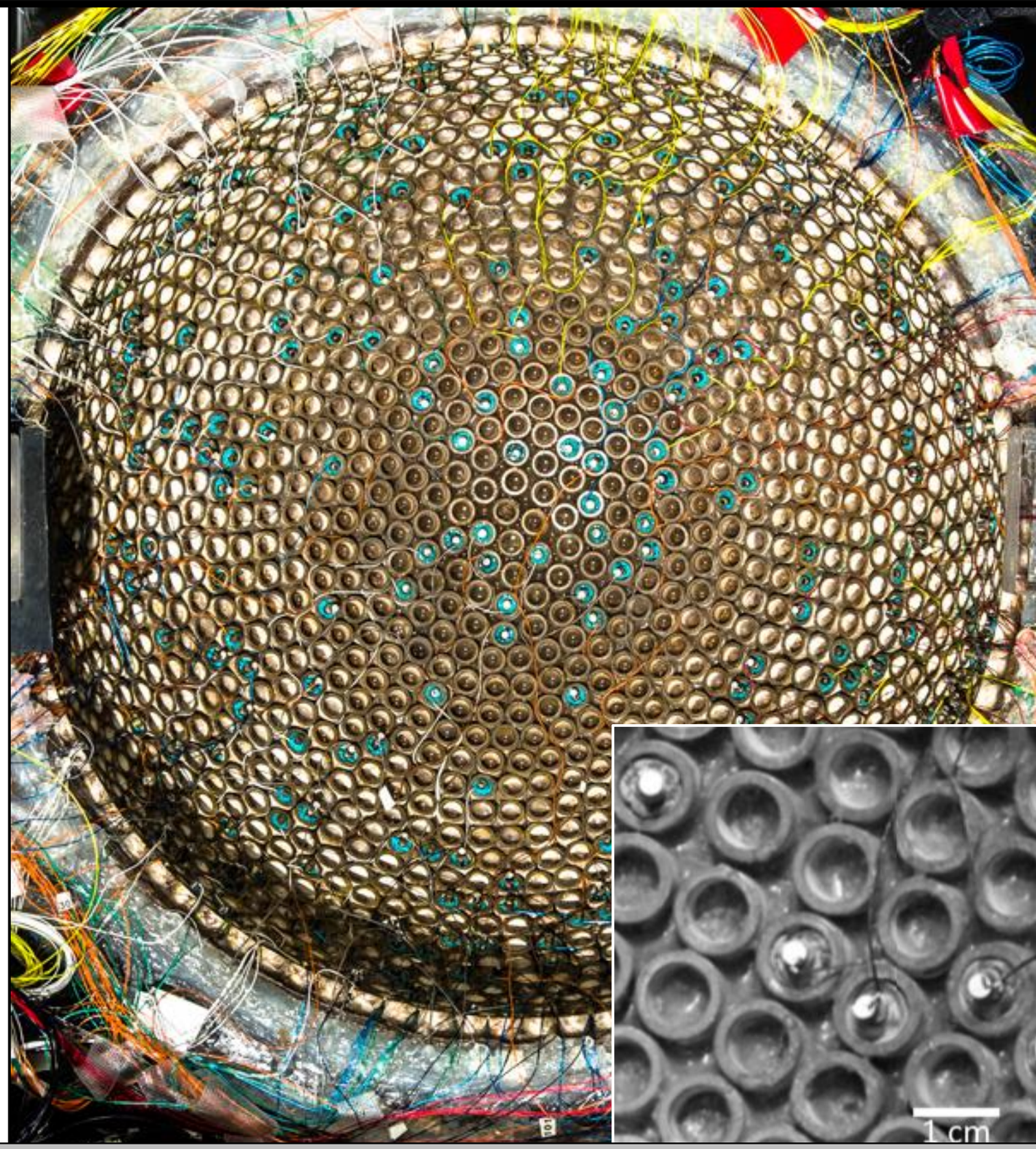
(Bottom) -6 dB source field intensity isosurfaces
N_{RCV} = 128, f = 500 kHz

[1] Jones *et al*, *PMB* (2013)
[2] Norton & Won, *IEEE TGRS* (2000)

First Generation Dual-Mode Brain Array

- 128 x piezo-ceramic disks[1]
  - f_{Rx} = 612 kHz
  - $sparsity_{area}$ = 1.8%
- Integrated w/ transmit array[2]
  - f_{Tx} = 306 kHz
- Simulation-optimized layout
  - 5,000 trial configurations



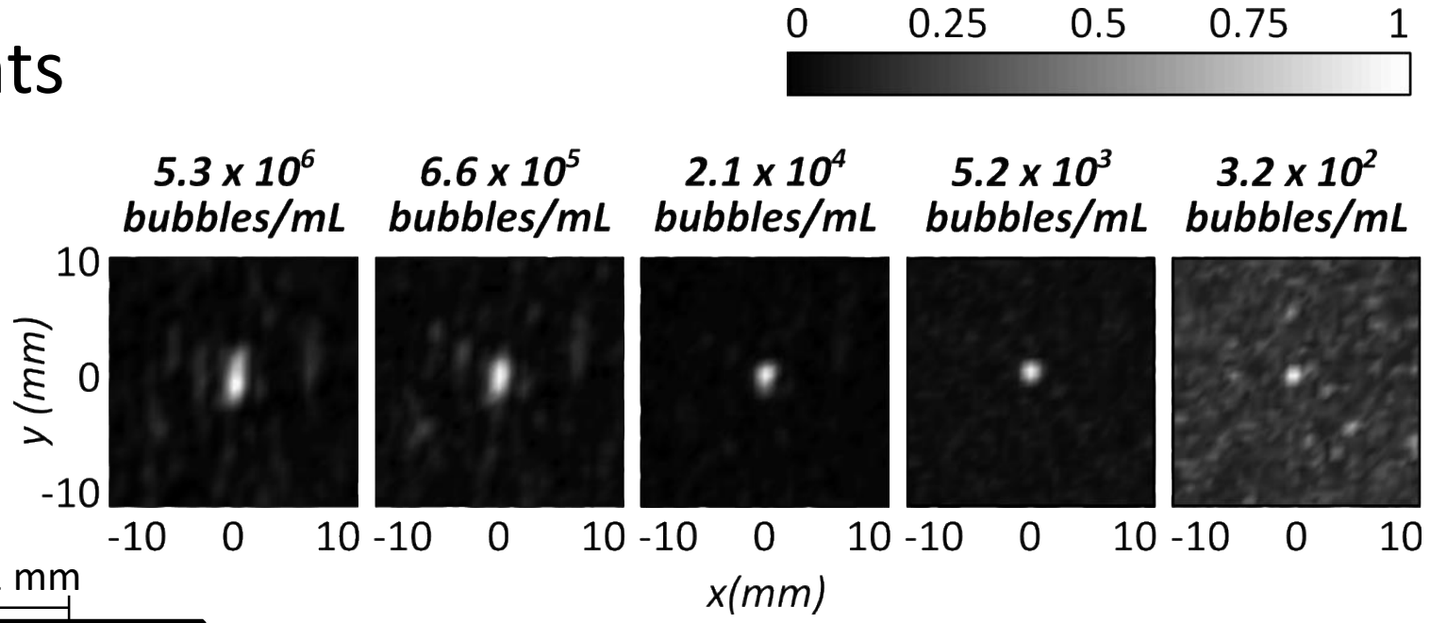


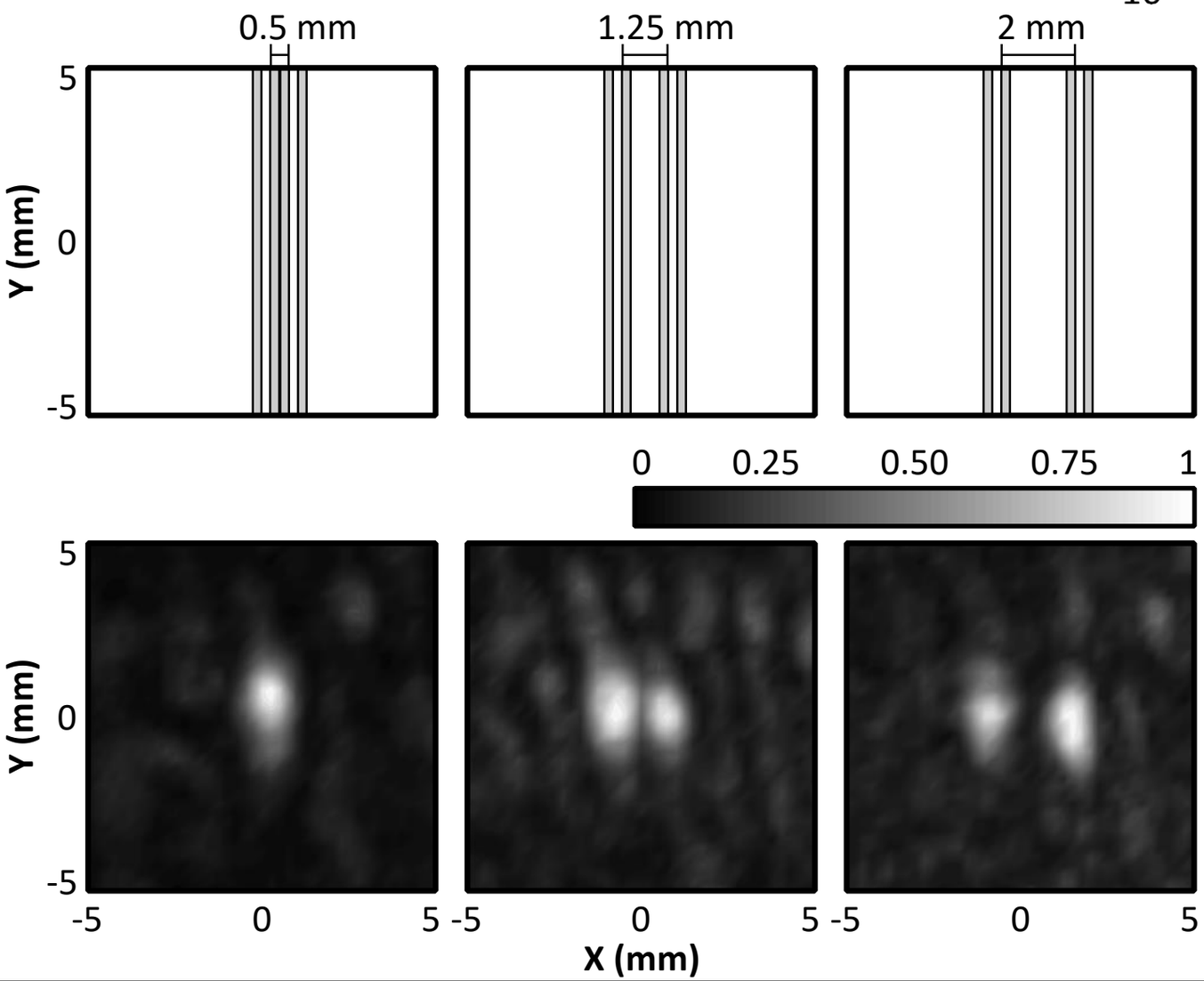
[1] O'Reilly *et al*, *IEEE TBME* (2014)

[2] Song *et al*, *IEEE TBME* (2010)

Array Characterization: Sensitivity & Resolution

- **Right**: imaging single bubble events through *ex-vivo* human skullcap[1]
- **Bottom**: estimating two-source resolution



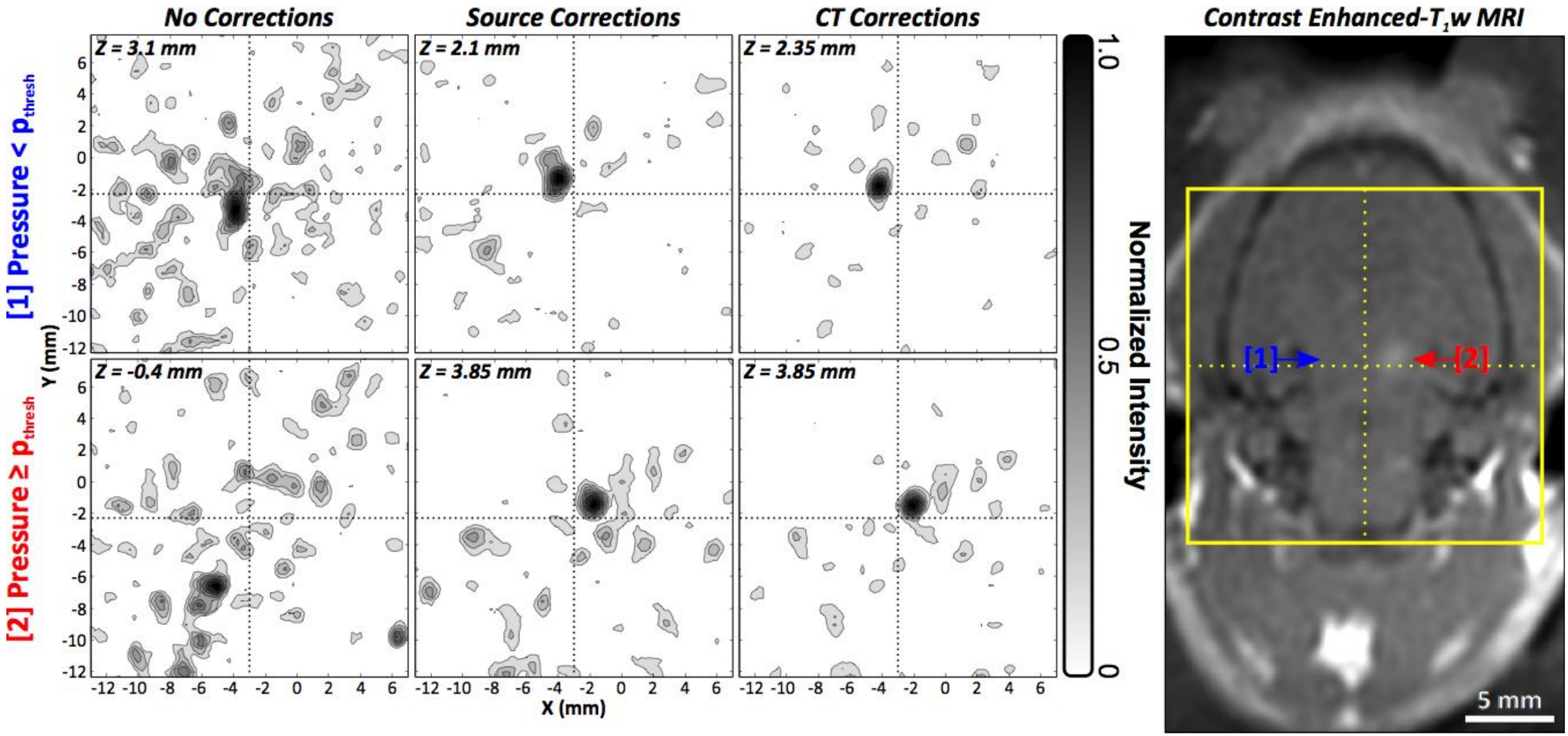


- **Lateral** resolution[1]: 1.25-2 mm (simulations[2]: 1.8 ± 0.1 mm)
- **Axial** resolution[1]: 2-3.5 mm (simulations[2]: 2.9 ± 0.2 mm)

[1] O'Reilly *et al, IEEE TBME* (2014)

[2] Jones *et al*, *PMB* (2013)

Transcranial Imaging *In Vivo*: CT Corrections



- CT corrs: reduced positional error (deviation from source corrs) from **2.3 ± 2.0 mm** (no corrs) to **0.8 ± 0.5 mm** [12 sonications, 3 rats]

Planes of max. intensity, linear contours: 10% intervals **Jones *et al, Med Phys* (2015)**

Multi-Frequency Dual-Mode Brain Arrays

- **128 & 256 Module Arrays[1,2]**

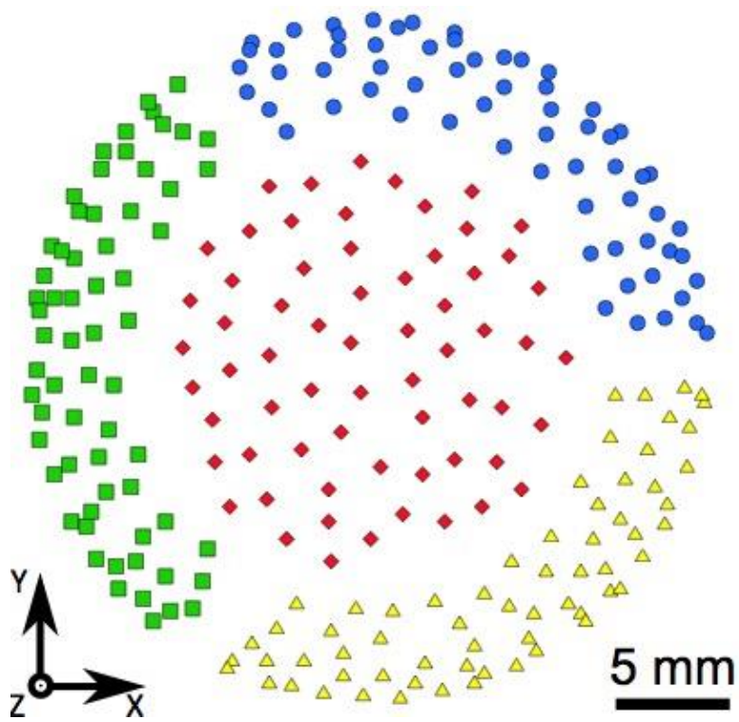
  - 3 x PZT4 tubes; lateral mode

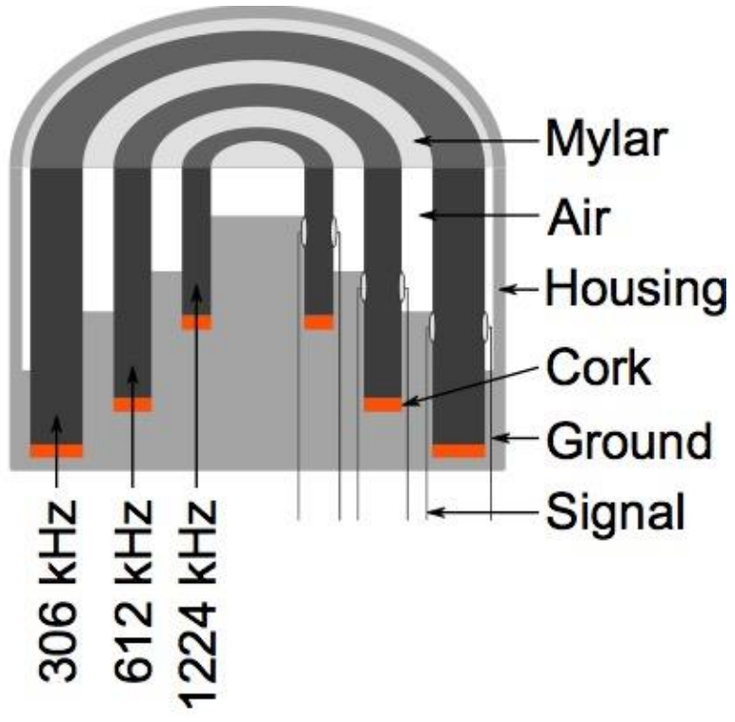
  - $f_{Tx/Rx}$ = 306/612/1224 kHz

  - OD = 2.0 λ; ID = 1.4 λ

  - $sparsity_{area}$ = 6.4/1.6/0.4%

  - simulation-optimized layout[3]

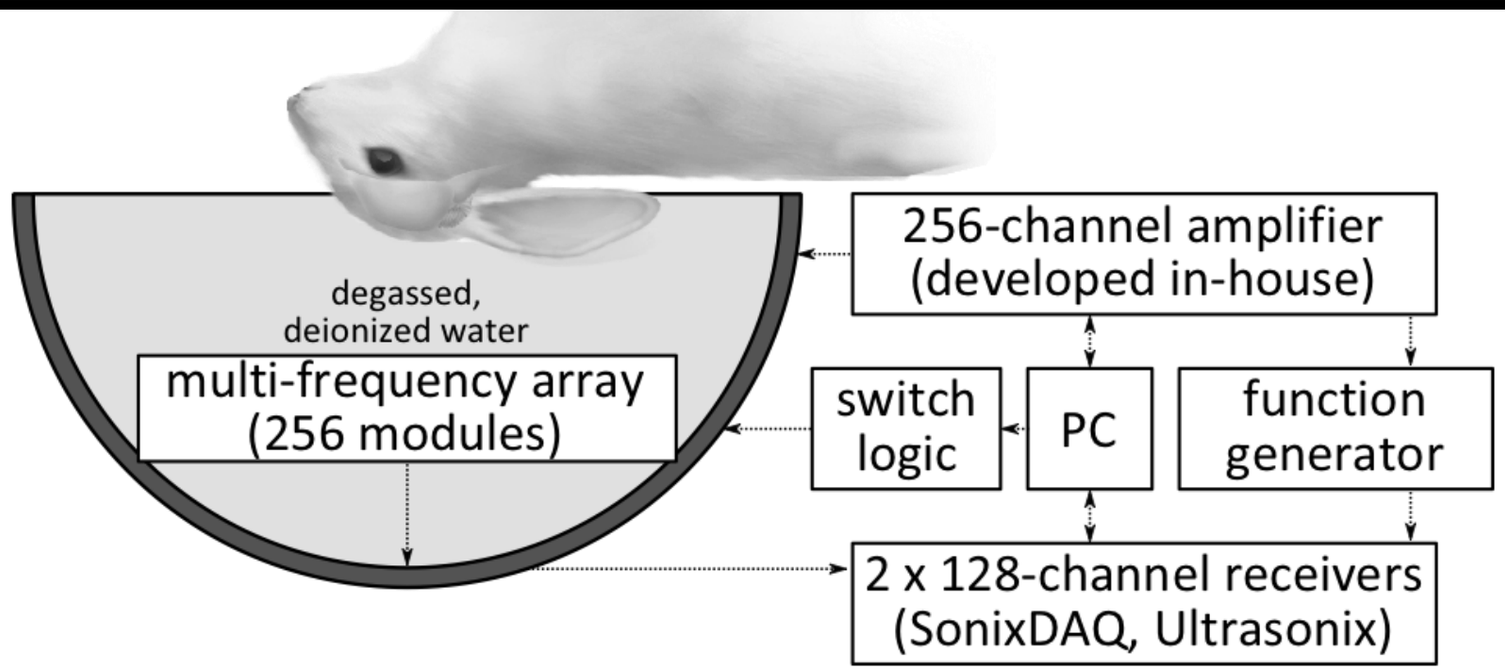




[1] Deng *et al*, *PMB* (2016) [2] Jones *et al*, *Theranostics* (2018) [3] Jones *et al*, *PMB* (2013)

3D Subharmonic Imaging: Exposure Calibration

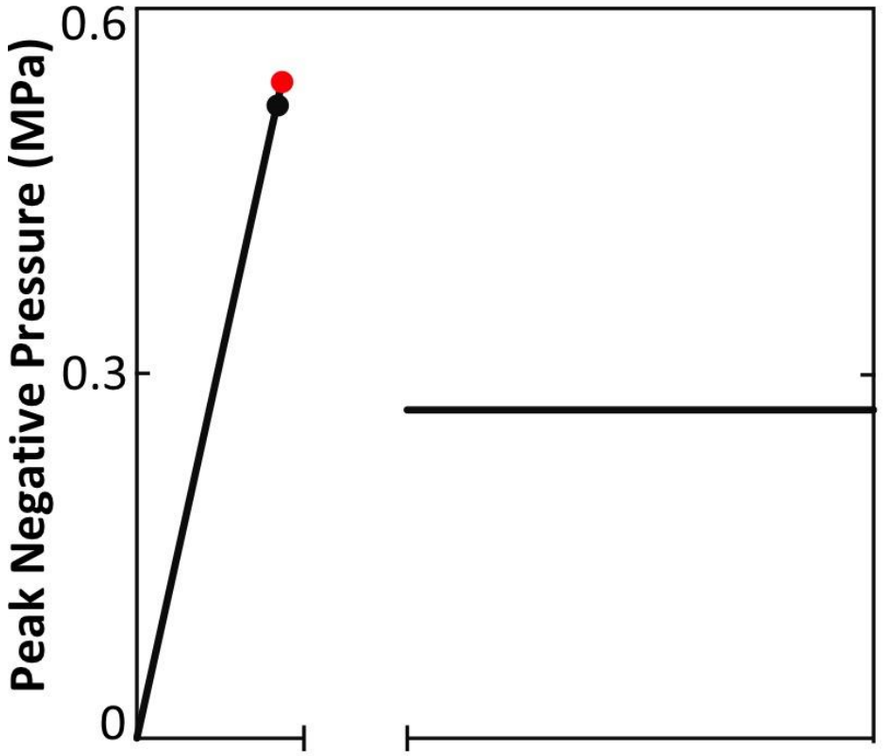
f_{Tx} = 612 kHz
f_{Rx} = 306 kHz

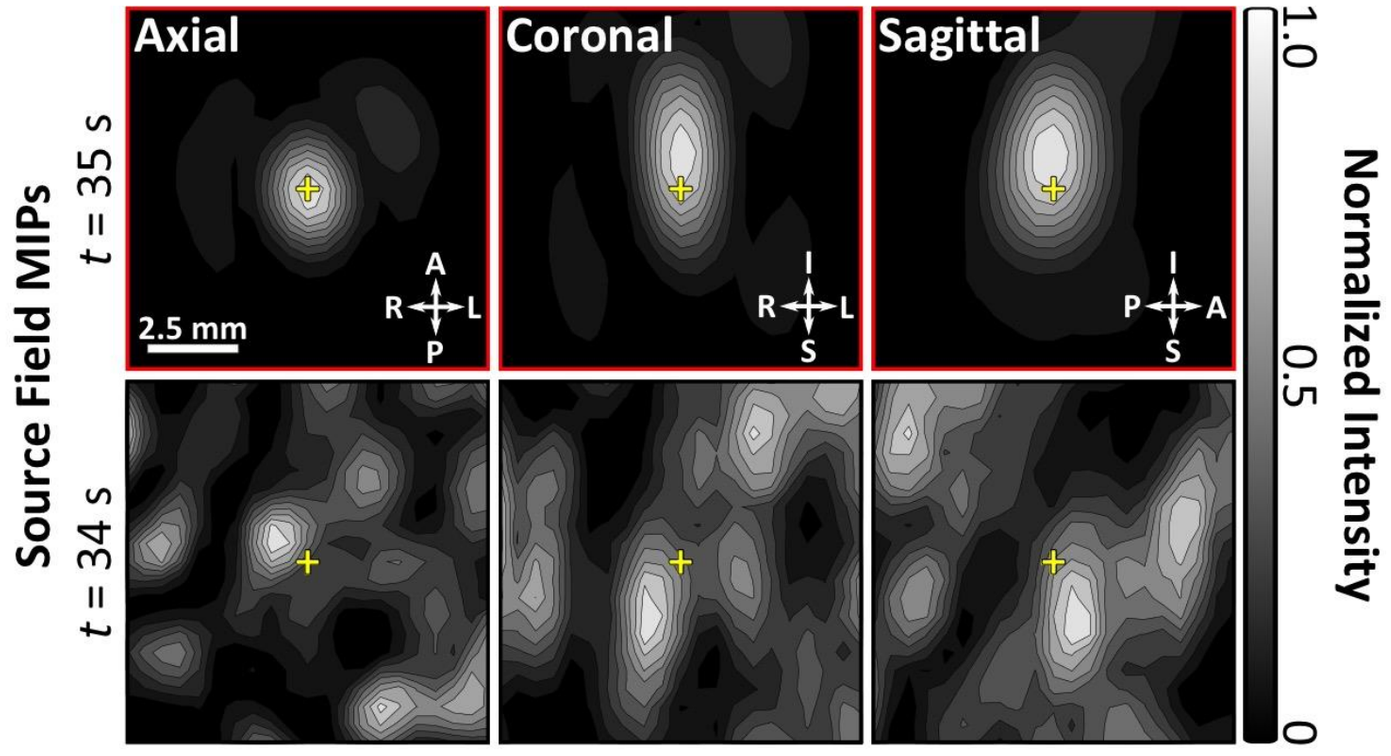


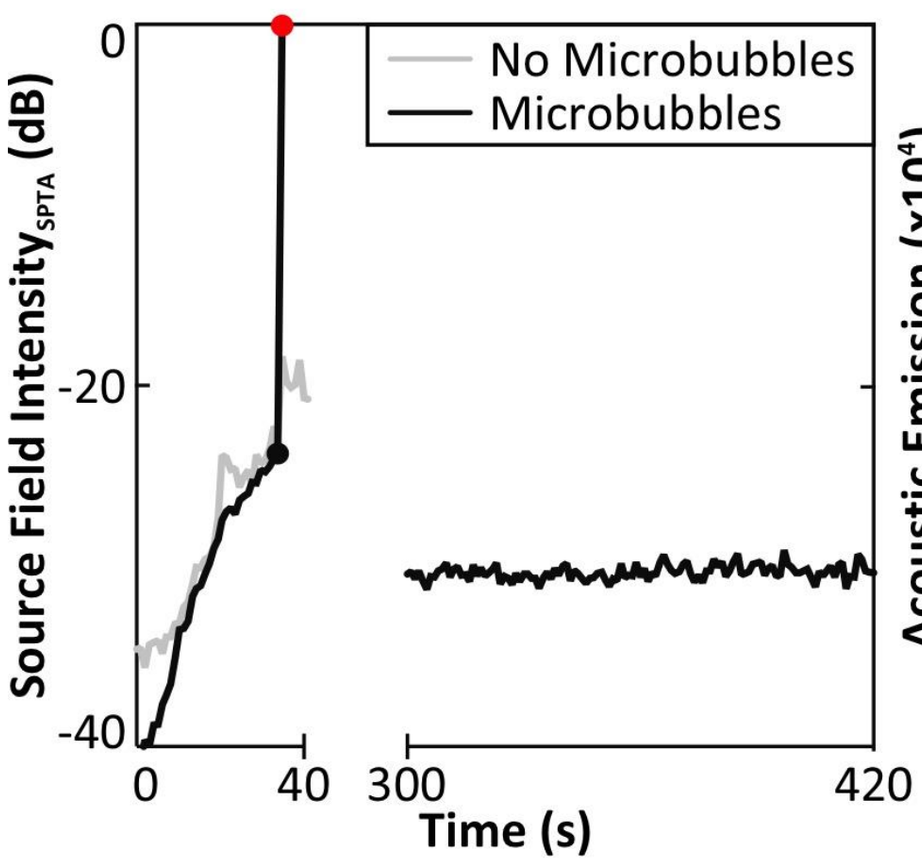
Pre-Calibration (T_2w MRI) **Post-Calibration (CE-T_1w MRI)** **Post-Volumetric (CE-T_1w MRI)**

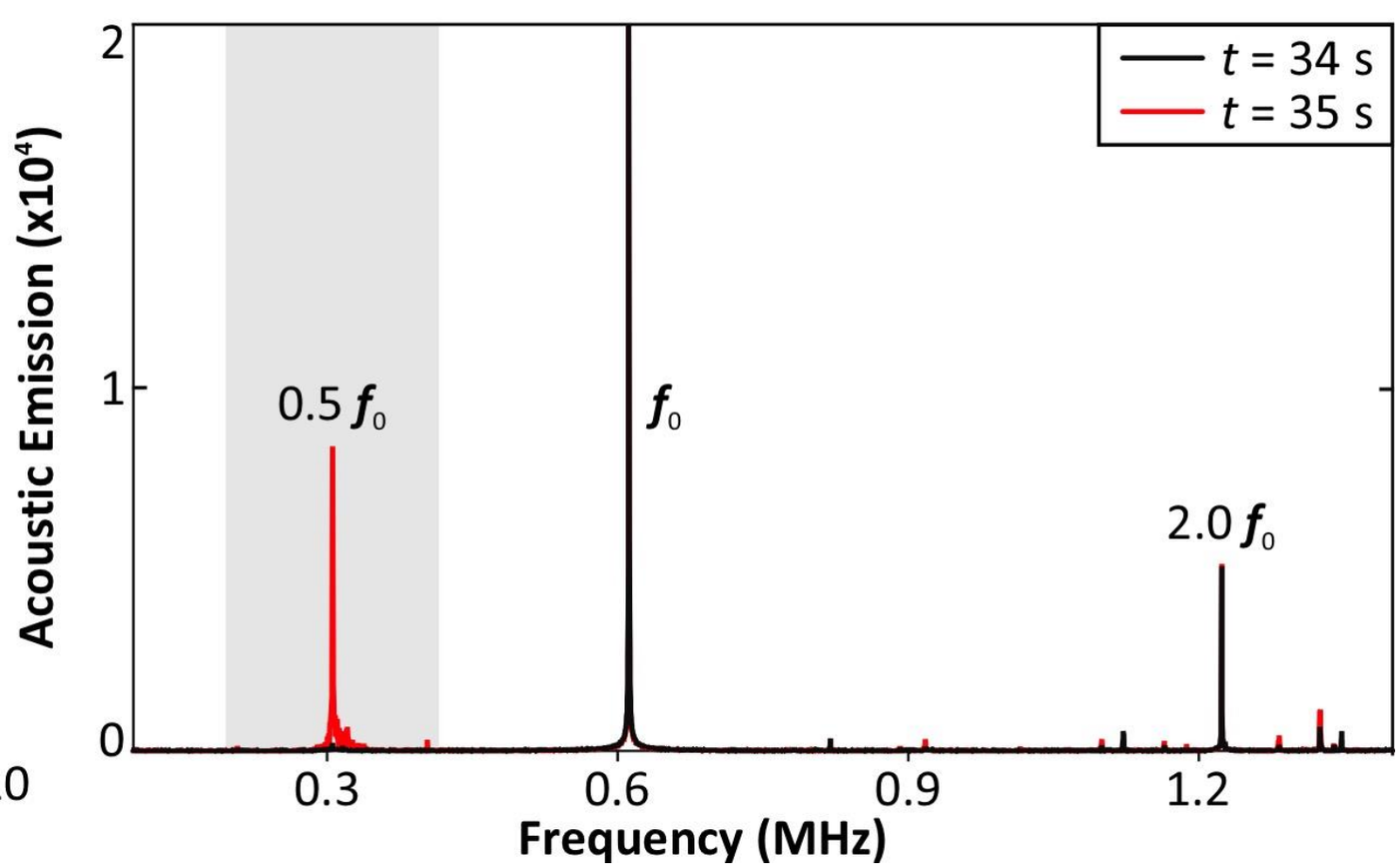
- **Calibration**: single-point pressure ramp ➔ subharmonic threshold (p_{sub})
- **Volumetric**: fixed pressure (50% p_{sub}) multi-point (electronic steering)

3D Subharmonic Imaging Calibration: Example









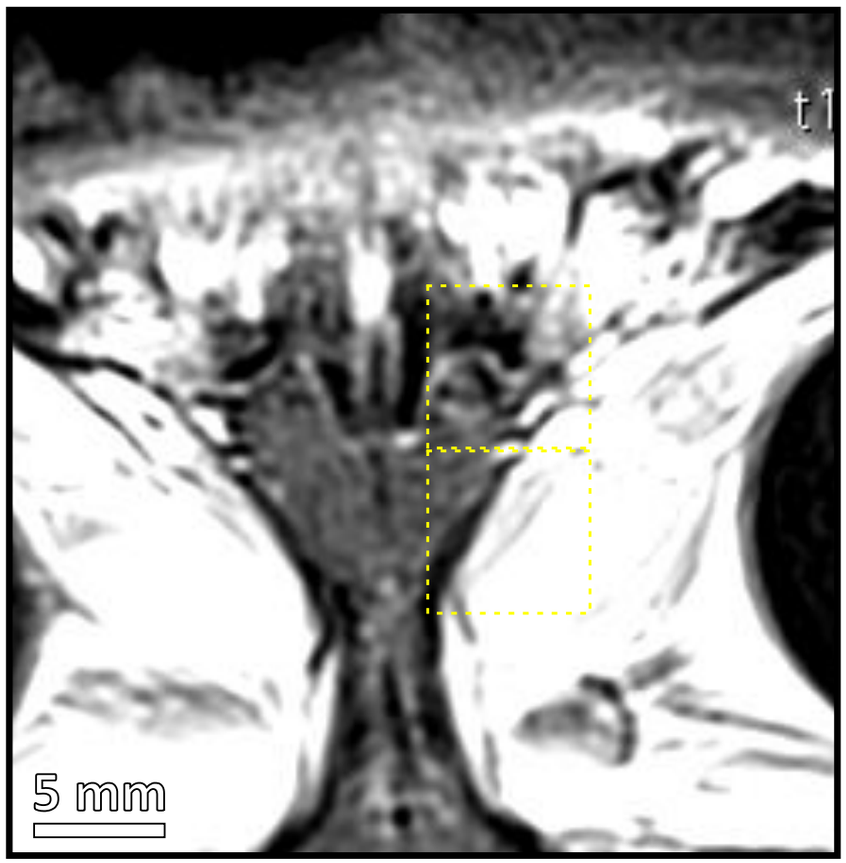
(Top Right) Linear contours: 10% intervals, target: + symbols

Jones *et al, Theranostics* (2018)

Treatment Group: MRI Example

- Four unilateral grids (6x6, 1mm spacing, 50% $\boldsymbol{p}_{sub}$[1]) per animal (n = 5)
- **1w:** MRI follow-up, sacrificed (H&E)
- BBB opening (T_1w), edema (T_2w), extravasations (T_2*w): **0d & 1w**

Axial CE-T_1w MRI



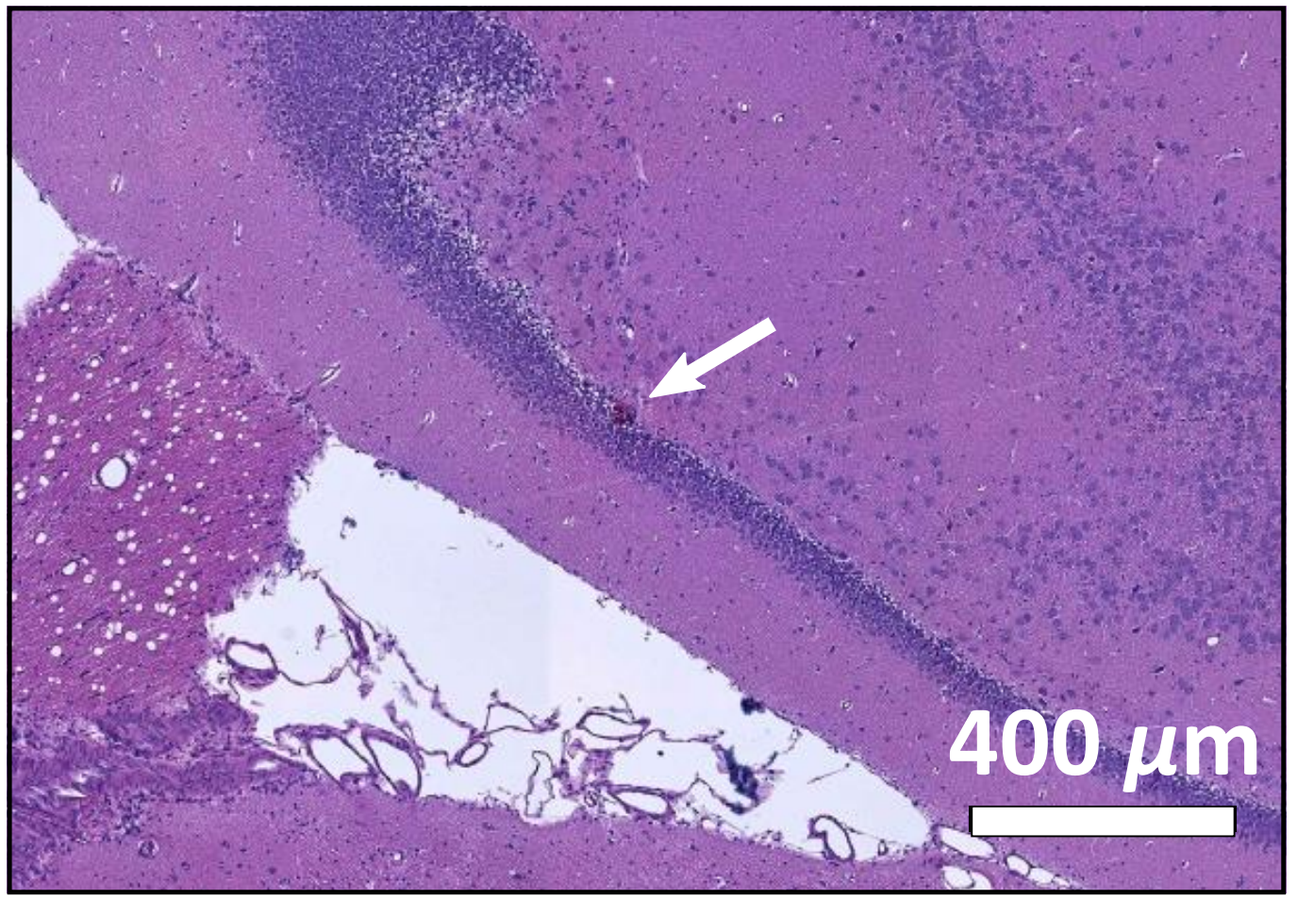
Coronal CE-T_1w MRI

Axial T_2*w MRI

[1] O'Reilly & Hynynen, *Radiology* (2012)

Treatment Group: Summary

- **Worst case:** small region (< 50 μm) of RBCs in perivascular space of single focal spot 1w post-FUS on H&E (arrow)



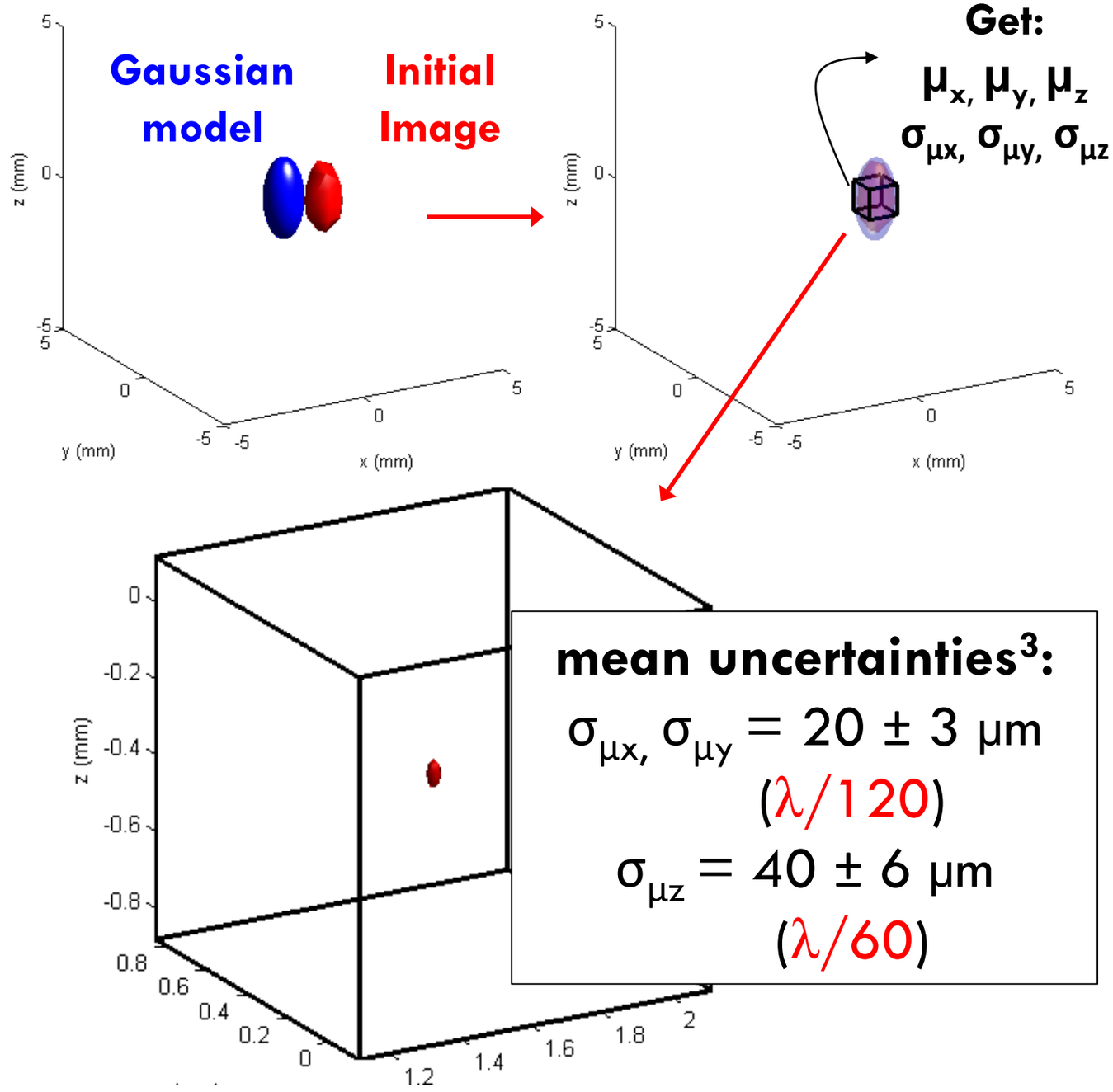
	Time Point	CE-T_1w Hyper	T_2w Hyper	T_2*w Hypo	H&E Extravs
All Focal Spots (n = 720)	Immediate	336 (46.6%)	12 (1.6%)	0	N/A
	1 Week	0	0	0	1 (0.1%)
Calibration Points (n = 20)	**Immediate**	**20 (100%)**	**0**	**0**	**N/A**
	1 Week	**0**	**0**	**0**	**0**

Jones *et al*, *Theranostics* (2018)

Super Resolution Imaging

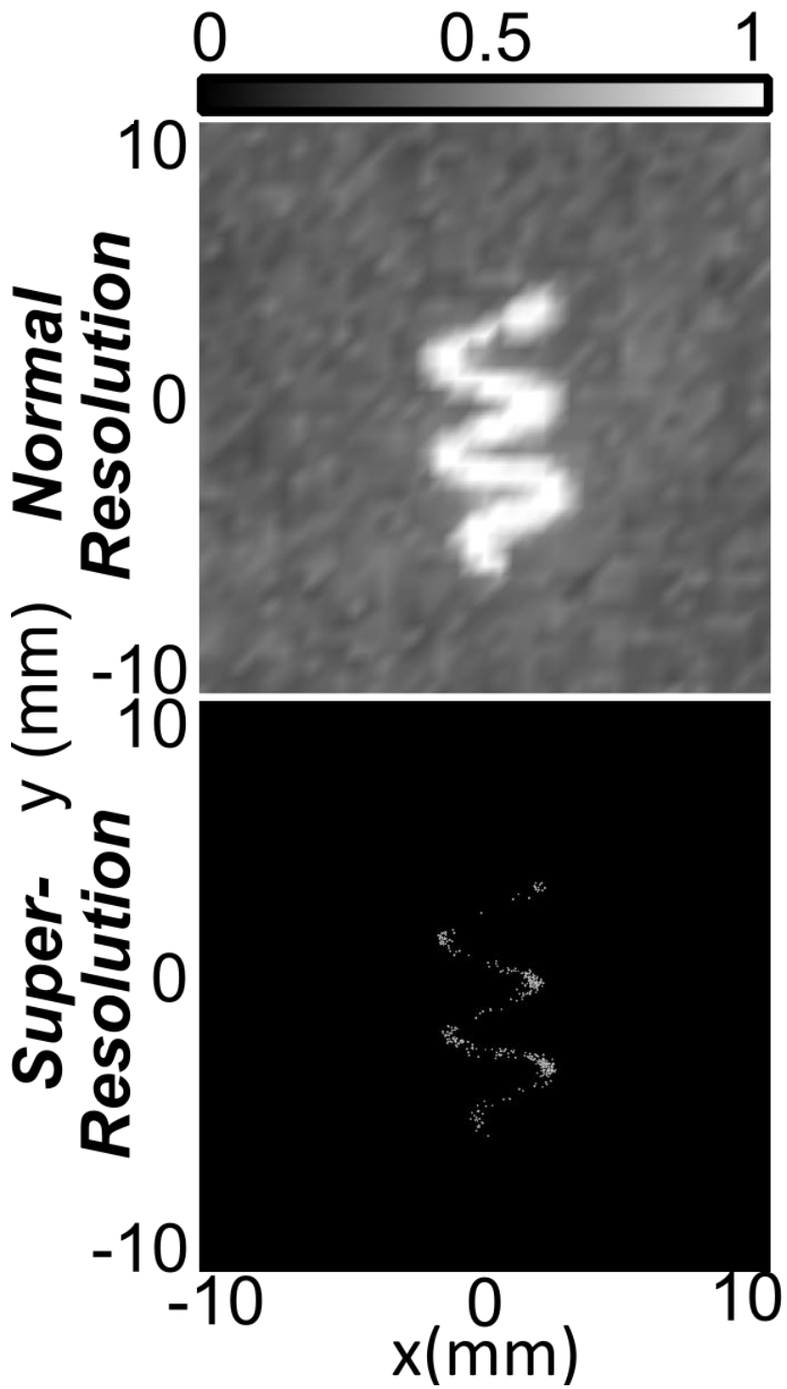
- Position of sources can be estimated beyond the diffraction limit[1]

- Re-plot images of single bubble at higher resolution (PALM[2])
  - Estimate source position
  - Re-plot with widths determined by uncertainties on fit



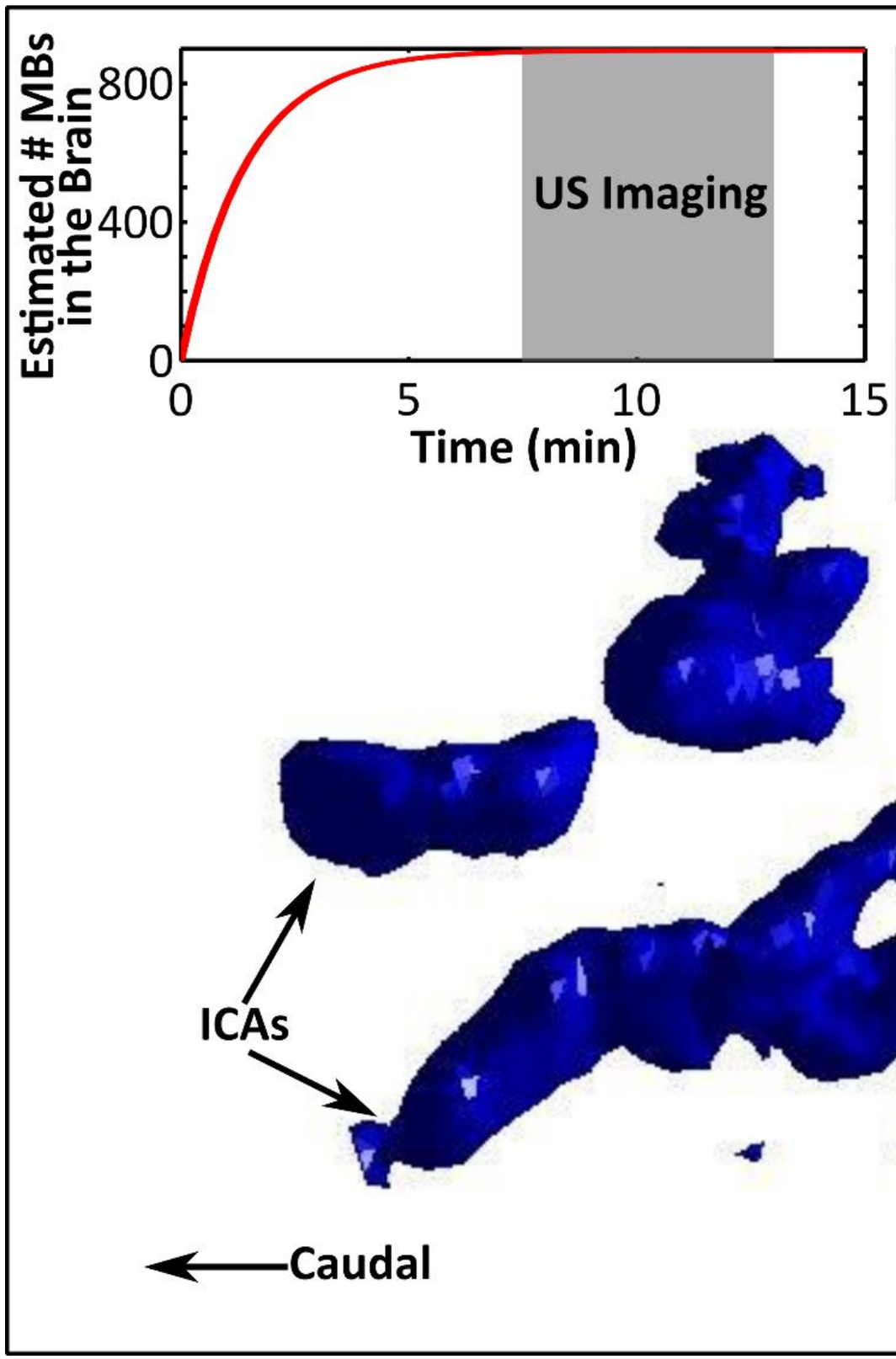
[1] Bobroff, *RSI* (1986) [2] Betzig *et al*, *Science* (2006) [3] O'Reilly *et al*, *Med Phys* (2013)

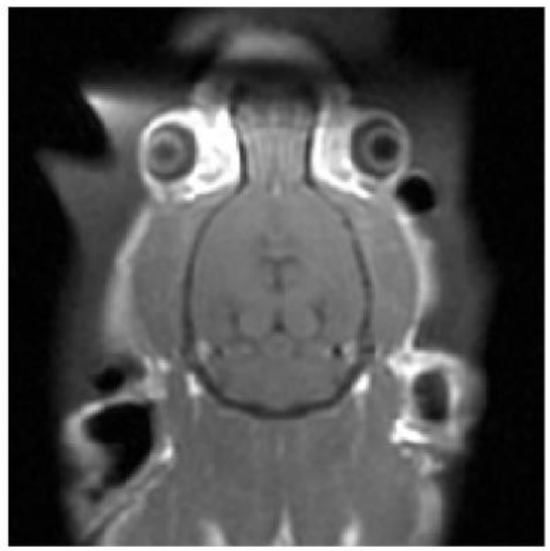
Transcranial Super Resolution Imaging

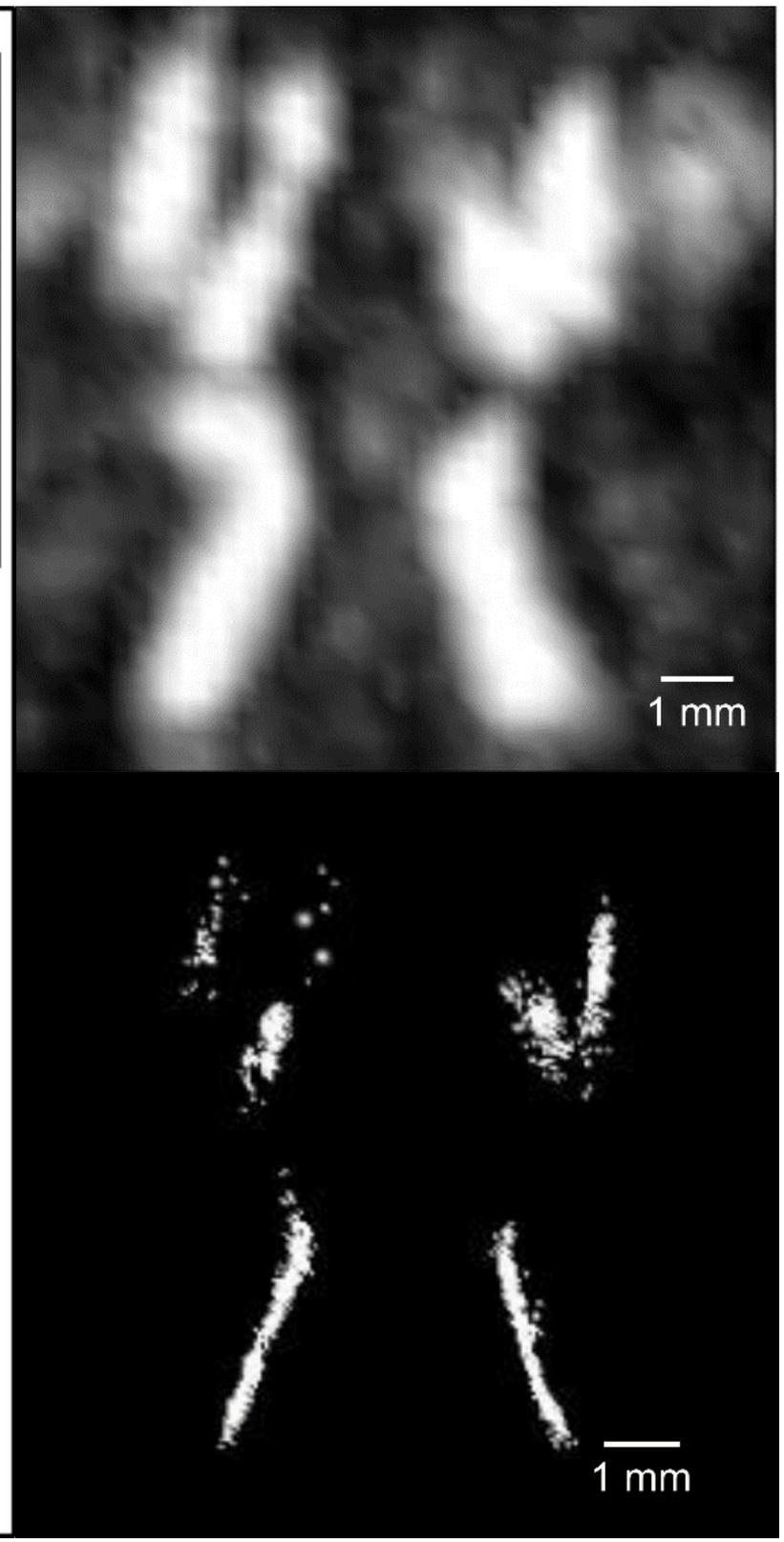


O'Reilly *et al*, *Med Phys* (2013)

Super Resolution Imaging *In Vivo*





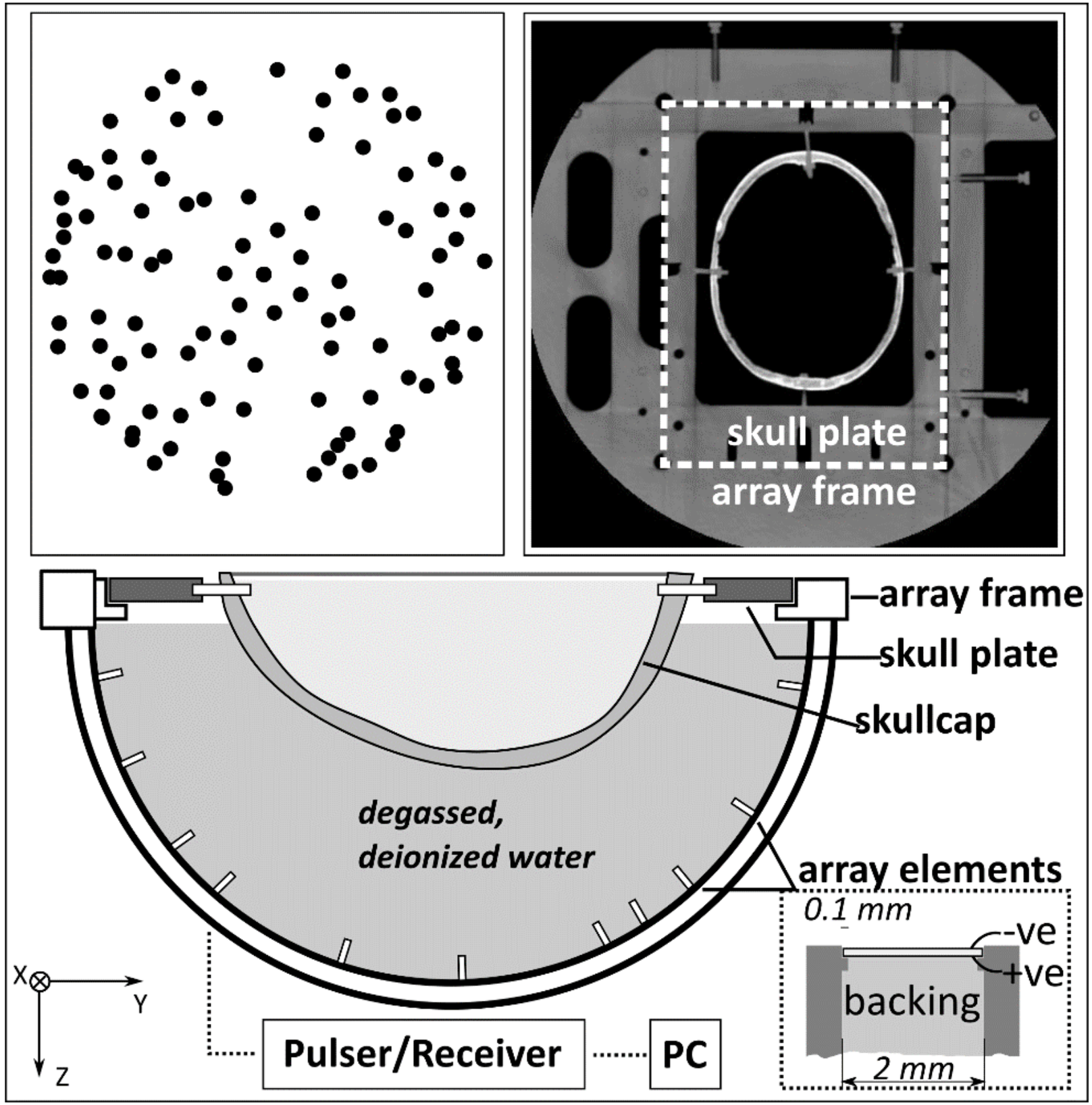


O'Reilly & Hynynen, *IEEE IUS* (2014)

Ultrasound Registration of CT Data

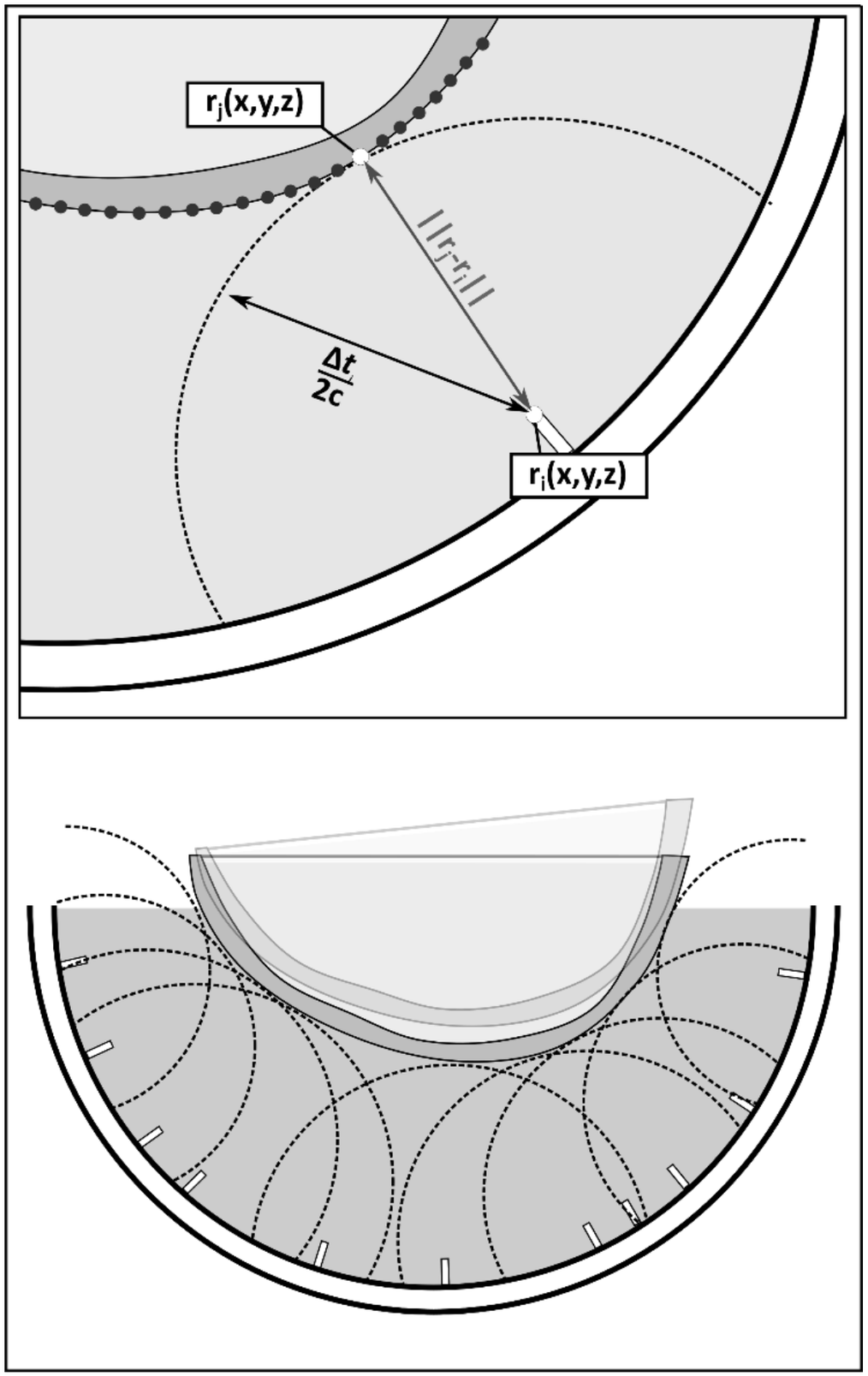
- Clinical FUS treatments register pre-op CT data to intra-op MRI
  - aberration correction
  - “no-pass regions” (sinuses, intra-cranial calcifications…)

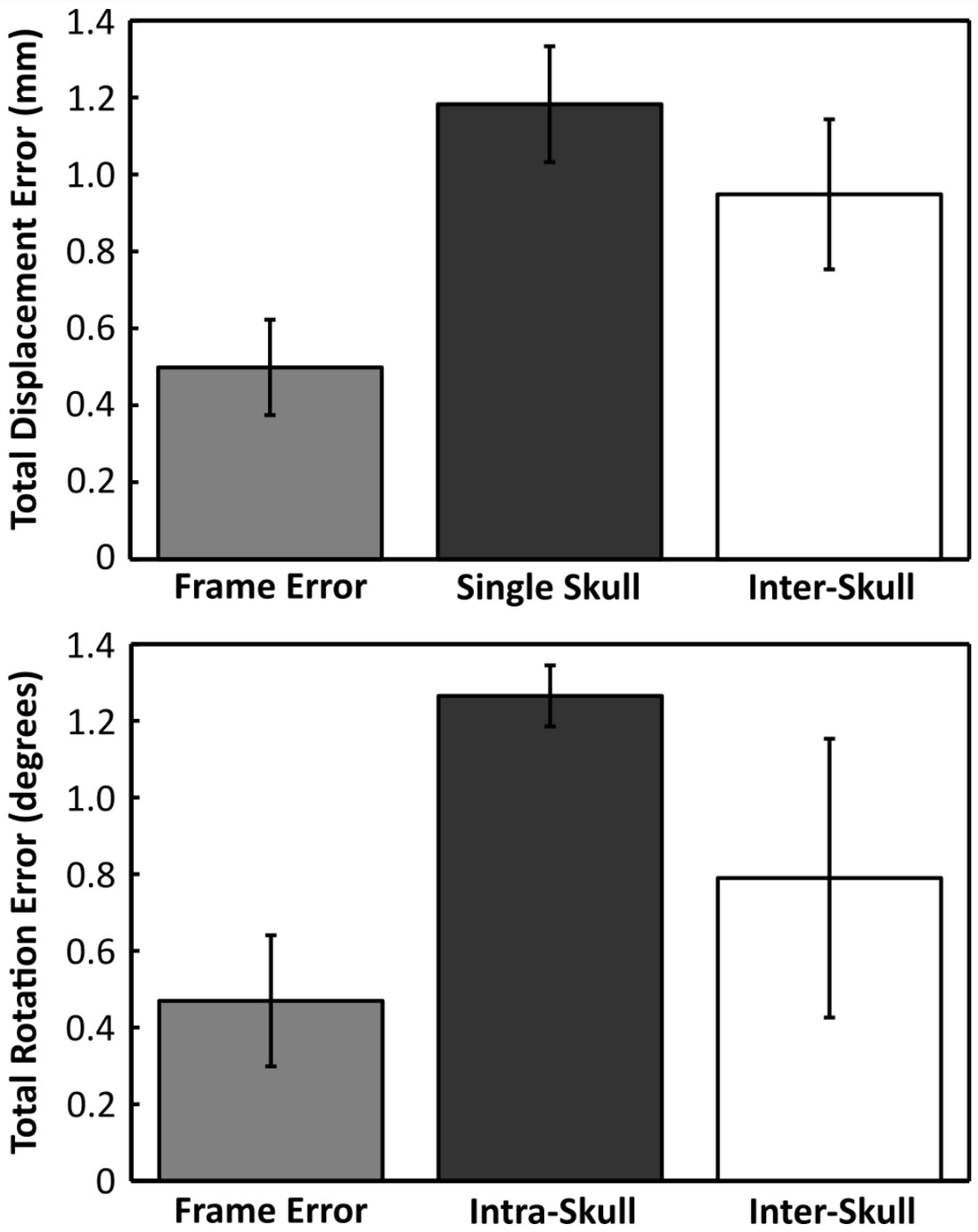
- US-based registration; for interventions not requiring MRI
  - 128 elements (PZT, 11 MHz)
  - $\text{sparsity}_{\text{area}}$ = 0.4%
  - 5 *ex-vivo* human skullcaps



O’Reilly *et al*, *Med Phys* (2016)

Ultrasound Registration of CT Data





- Simulations[1]: 1.0±0.2 mm targeting error, 1.0±0.6% focal pressure drop

[1] Ray-Acoustic Model (230 kHz InSightec System)

O'Reilly *et al*, *Med Phys* (2016)

Summary

Sparse Hemispherical Transmit/Receive Ultrasound Arrays

- Numerical simulations to optimize array layouts
- 3D microbubble mapping *in vivo*, *ex-vivo* human skullcaps
- Subharmonic imaging calibration of BBB opening
- Trans-human skull acoustic imaging beyond diffraction limit
- Skull CT – array registration

Future Work – Clinical Translation

- Develop next generation ultrasound brain therapy systems
- Combined system: large animal testing w/ *ex-vivo* human skullcaps

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