Advances in MR-guided focused ultrasound induced ablations, hyperthermia and drug delivery

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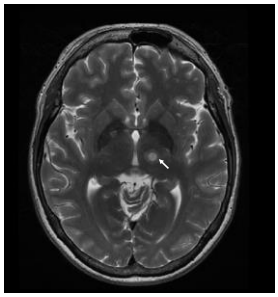
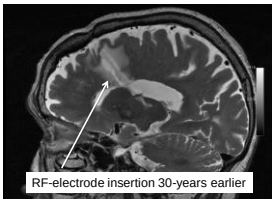
Thalamotomy by Focused Ultrasound

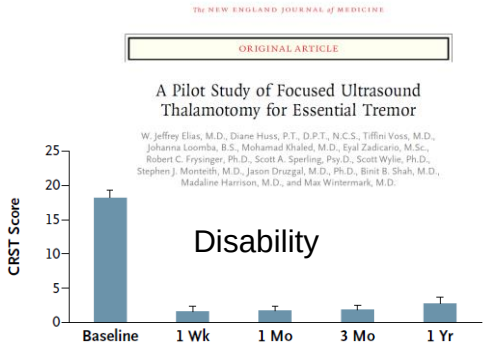


MR Thermometry Guidance

- VIM Location
  centre of the heating volume
- Size of the lesion (5-6mm)
  thermal dose



> 1000 brain patients treated in 35 centers

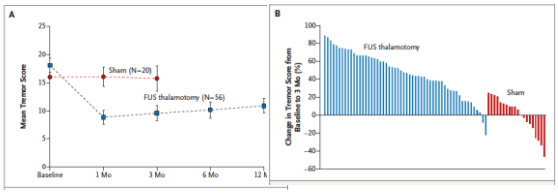


The NEW ENGLAND JOURNAL of MEDICINE

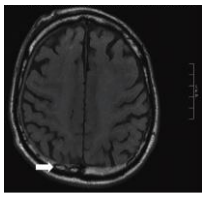
ORIGINAL ARTICLE

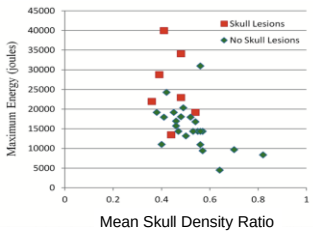
A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor

W. Jeffrey Elias, M.D., Nir Lipsman, M.D., Ph.D., William G. Ondo, M.D., et al.



Acoustic Energy Required for Tremor Ablation Is Variable

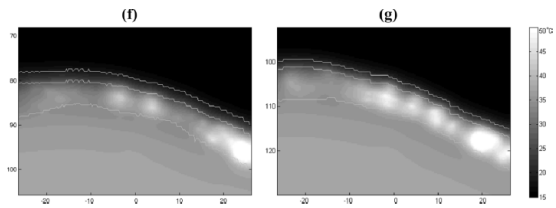




Schwartz et al., Submitted, (ISTU 2016)

5

Simulations of Skull Heating



Connor et al., IEEE TRANS. ON BIOMEDICAL ENGINEERING, VOL. 51,1693-1706 2004

Skull Heating

1. **Ablation in the middle of the feasible but not in all patients**

1. **Off-center Targets or close to skull difficult to treat**

=>Reduction in the needed energy

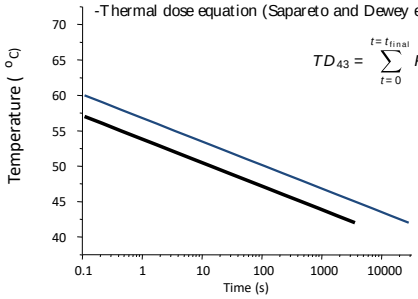
⇒ multiple sonications=> accumulation of thermal dose (70%)
⇒ Reduction in the ablation threshold => chemotherapy (30%)
⇒ Increase in the focal energy absorption => micro-bubbles (<10%)
⇒ Inertial cavitation effects (<0.1%)
⇒ BBB opening for drug delivery (<0.1%)

Ultrasound Bioeffects

Temperature Elevation

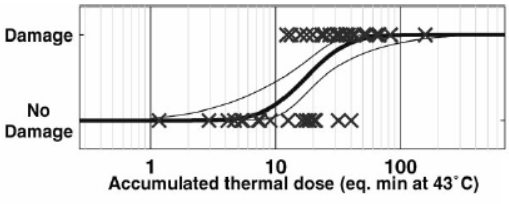
-Thermal dose equation (Sapareto and Dewey equation)

$$TD_{43} = \sum_{t=0}^{t=t_{final}} R^{t_{ref}-t_t}\,\Delta t$$



Dewhirst, et al. Int.J.Hyperthermia 19 (3):267-294, 2003.
Sapareto and Dewey Int.J.Radiation Oncology Biol.Phys. 10:787-800, 1984.

Brain Thermal Threshold (Rabbit)



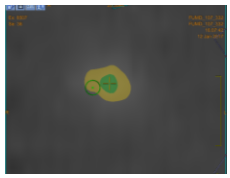
50% probability of brain damage: 17.5 CEM_{43}

McDannold N, et al, MRM 2004

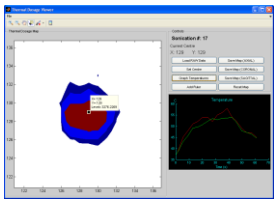
Brain Thermal Threshold (Essential Tremor Trial)

- 36 patients, 232 sonications with peak temperature > 50 ^{o}C
- Accumulated thermal dose over multiple sonications were calculated retrospectively with chemical shift corrections and correlated to lesion size on T2 and T1 MRI at day 1 follow-up

Chemical Shift Artifact



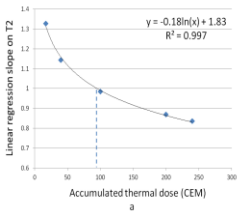
Matlab Manual Correction



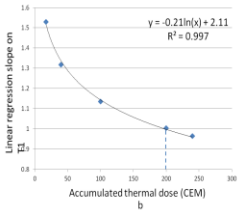
Huang Y, et al, ISMRM 2017

Brain Thermal Threshold (Essential Tremor Trial)

T2 regression



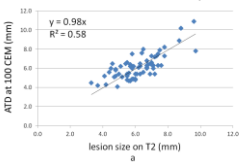
T1 regression



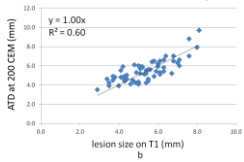
Huang Y, et al, ISMRM 2017

Brain Thermal Threshold (Essential Tremor Trial)

T2 vs. 100 CEM$_{43}$



T1 vs. 200 CEM$_{43}$



Huang Y, et al, ISMRM 2017

17.5 or 100 CEM_{43} ?

MR Thermometry $$\Delta T = \frac{\Delta\phi}{2\pi\gamma \cdot B_0 \cdot \alpha}$$

α= -0.011 ppm/ºC in the rabbit study

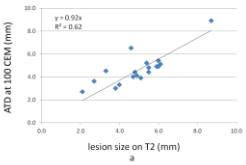
α= -0.00909 ppm/ºC in the ET trial (ExAblate, InSightec)

20% difference in temperature

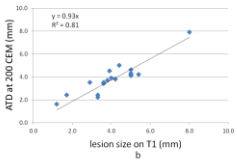
17.5 $CEM_{43\ (\alpha = -0.011)} \cong$ 100 $CEM_{43\ (\alpha = -0.00909)}$

Peak Temperature < 54 ºC

T2 vs. 100 CEM



T1 vs. 200 CEM

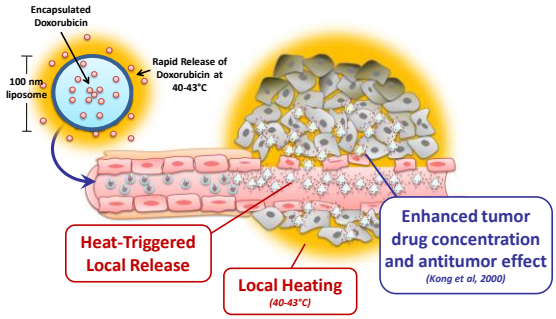


Summary of Thermal Dose

- Thermal dose 100 CEM_{43} correlates to the VIM lesion size in T2 MRI on the first day follow-up
- 100 CEM_{43} with α= -0.00909 is in close agreement to 17.5 CEM_{43} with α= -0.011 ppm/ºC
- Repeated sonications at low peak temperatures (49-54 ºC) may accumulate enough dose volume for creating lesions (70% of the energy)
  => more patients can be treated

MRI-Controlled Hyperthermia+ ThermoDox*

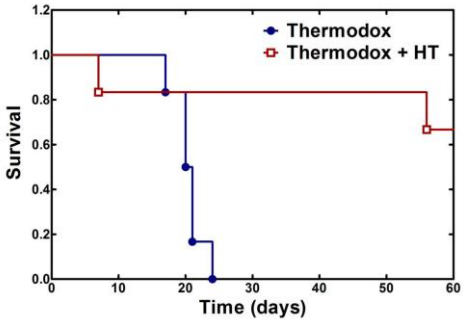
=>Localized Drug Delivery



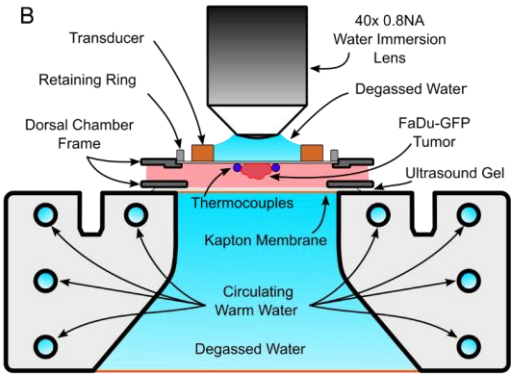
Yatvin MB, Weinstein JN, et al. Science. 1978

*Celsion

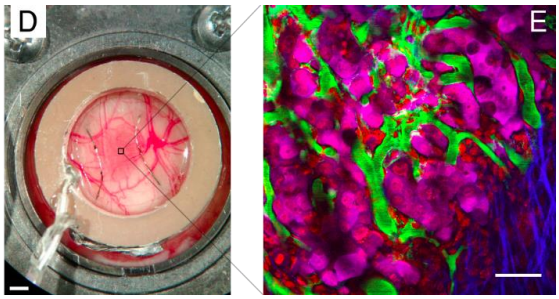
Rabbit VX2 Tumours: Survival



Staruch et al. Int J Hyperthermia. 2015

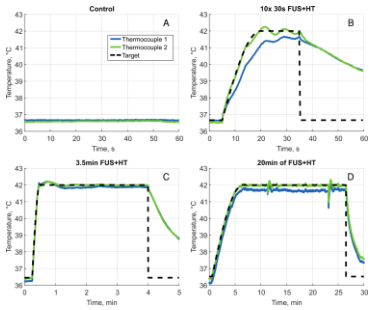


Santos et al. Theranostics 2017



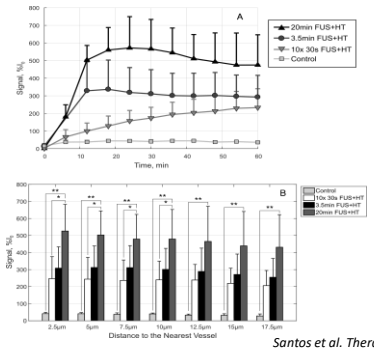
Santos et al. Theranostics 2017

Treatment Tests



Santos et al. Theranostics 2017

Doxorubicin delivery into the tumor



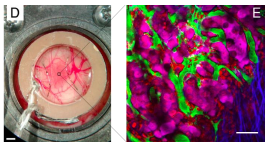
Santos et al. Theranostics 2017

Thermally sensitive liposomes

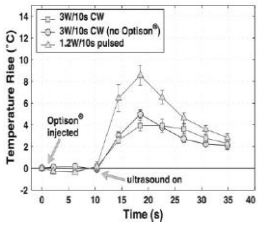
Short exposures able to enhance drug delivery

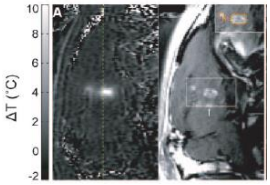
Feasible in the brain - at least in small volumes

Require 30 % of the ablation energy
=>Can increase the treatable volume significantly



Microbubbles IV
Potentiated Ultrasound Thermal Effects



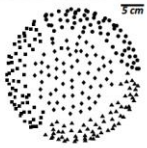


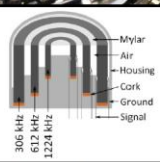
Microbubbles
=> increased temperature rise/W x 4
=> Temperature Threshold for tissue damage is reduced to half

McDannold, et. al., *Radiology. 241 (1):95-106, 2006.*

Clinical-Scale Prototype System

- **256 Transducer Modules[1]**
  - 3 x PZT4 tubes; lateral mode
  - $f_{Tx/Rx}$ = 306/612/1224 kHz
  - OD = 2.0 λ; ID = 1.4 λ
  - Sparse, optimized layout[2]
  - Acoustically characterized[3]

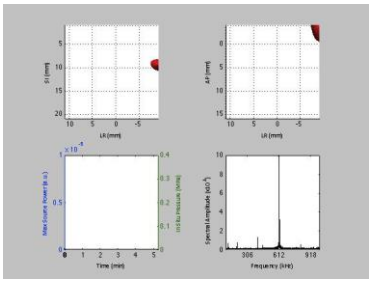


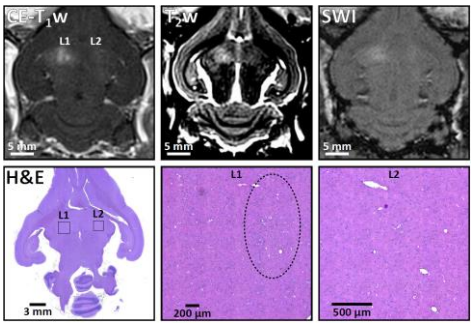


[1] Deng *et al*, *PMB*. (2016)
[2] Jones *et al*, *PMB*. (2013)
[3] Deng *et al*, *IEEE IUS*. (2016)

Acoustic Mapping During MB Enhanced Ablation:

Rabbit Brain in vivo





Bubble enhanced ablation

-Tissue ablation feasible but variable

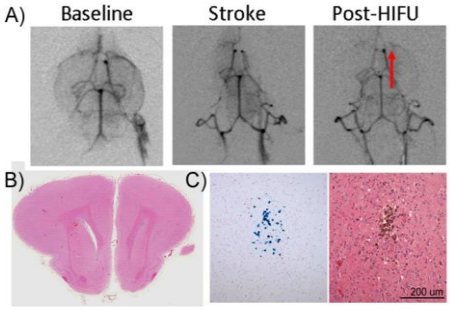
-Requires online monitoring and control

-Requires less energy (<10%)

=>May allow whole brain ablation

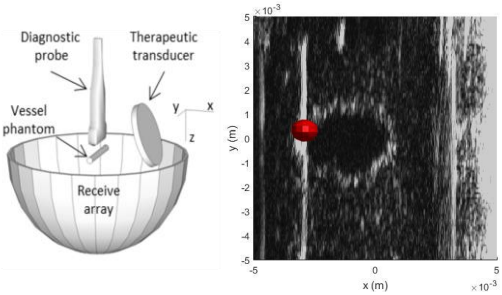
-Requires more research

High-Intensity Focused Ultrasound (HIFU) for Dissolution of Clots of Embolic Stroke.



Burgess et al. Plos One 2012

Acoustic Mapping of bubbles during Thrombolysis



Christopher N. Acconcia et al. In preparation

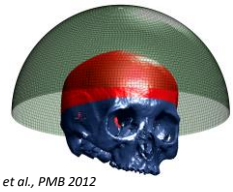
Through Skull Stroke Treatments
Inertial cavitation

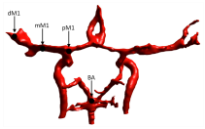
In vivo experiments show promise in restoring blood flow

Fast acoustic imaging can provide means to control

Requires less than 0.1% of the ablation energy=> whole brain feasible

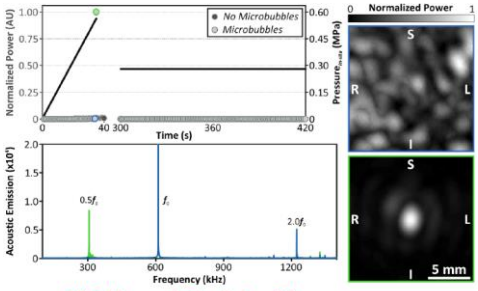
New array technology is needed for the high peak power





Pajek et al., PMB 2012

BBB Opening
Calibration of the Bubble Effect

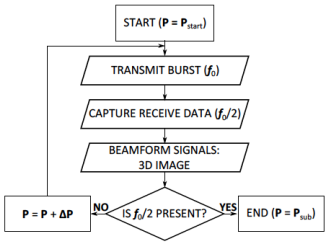


All Subharmonic Events (n = 49)

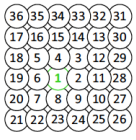
P_{sub} (*in situ*)	$\Delta R_{tgt->src}$	$FWHM_{-3dB,lat}$	$FWHM_{-3dB,ax}$
0.67±0.16 MPa	0.7±0.5 mm	3.0±0.5 mm	5.4±0.5 mm

Calibration Procedure & Parameters

- Based on previous work: single-element detector[1]



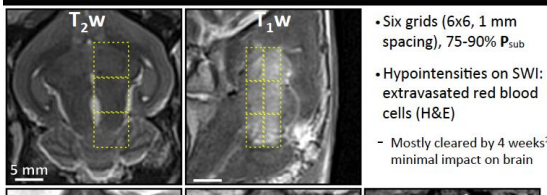
Multi-Point Steering



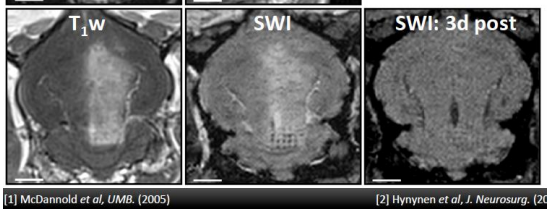
- Microbubbles: Definity™ (20 µL/kg, 1 min infusion)
- f_{Tx} = 612 kHz, 10 ms bursts, 1 Hz repetition rate, **ΔP** ≈ 15 kPa, t_{multi} = 2 min
- f_{Rx} = 306 kHz, capture$_{calib}$ = 3.2 ms, capture$_{multi}$ = 0.7-1.5 ms, 10 MS/s
- GPU delay & sum beamforming[2] [FOV: 10x10x10 mm^3, voxel size: 1x1x1 mm^3]

[1] O'Reilly & Hynynen, *Radiology*. (2012) [2] Jones *et al*, *Med. Phys.* (2015)

Large Volume BBB Opening



- Six grids (6x6, 1 mm spacing), 75-90% P_{sub}
- Hypointensities on SWI: extravasated red blood cells (H&E)
  - Mostly cleared by 4 weeks[1,2]; minimal impact on brain



[1] McDannold *et al, UMB.* (2005) [2] Hynynen *et al, J. Neurosurg.* (2006)

Rabbit Brain BBB Opening

All Focal Spots (n = 720)

Time Point	CE-T_1w Hyper	T_2w Hyper	SWI Hypo	H&E Extravasations
Immediate	336	12	0	N/A
1 Week	0	0	0	1

Control Points (n = 20)

Time Point	CE-T_1w Hyper	T_2w Hyper	SWI Hypo	H&E Extravasations
Immediate	20	0	0	N/A
1 Week	0	0	0	0

BBB Tumor Clinical Trial

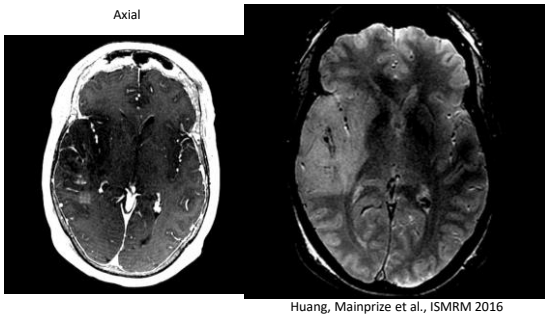
Support
Focused Ultrasound Foundation
InSightec
Canada Researcch Chair Program
NIH

Sunnybrook HEALTH SCIENCES CENTRE when it matters MOST

First Patient Tests

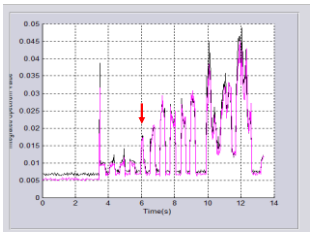
MRI Gad Enhancement (T1)
Delivery of Doxil to a brain tumor

Axial



Huang, Mainprize et al., ISMRM 2016

Acoustic Emissions at sub-harmonic frequency during BBB Opening
4 hydrophones



Clinical Experience:
-13 Treatments
-9 Patients
-Two Phase 1 Trials:
--Tumor
--AD

Plans:
-ALS
-Breast Meths.
-Tumor Phase 2

FUS Brain Treatments

Thermal ablation of central targets clinically feasible
Skull heating prevents targets closer to skull to be ablated

1. Multiple lower temperature exposures can be used to accumulate damage
   Required Energy 70%
2. Drugs can be released from temperature sensitive carriers with 30s exposure
   Required Energy 30%
3. Pre-formed microbubbles enhance ablation
   Required Energy <10%
4. Inertial cavitation controllable and potential for stroke treatments
   Required Energy <0.1%
5. BBB opening feasible in humans
   Required Energy <0.1%

Transmit/receive arrays allow large volume controllable BBB opening

=> FUS has the potential to have a large impact

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National Institutes of Health
Weston Brain Institute

Industry:
General Electric
InSightec
Philips
Celsion
Artenga
Fus Instruments

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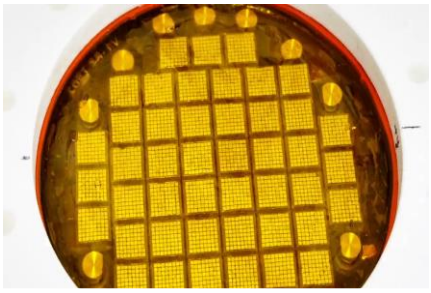
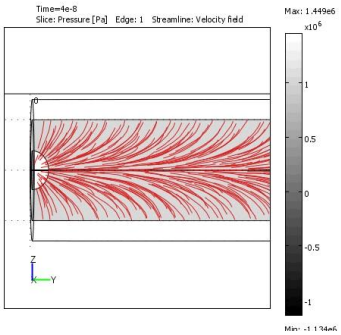
J. McLaurin, PhD
B. Stefanovic, PhD
M.Schwartz, MD
G.Wright, Ph.D.

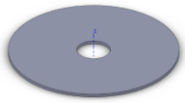
Future:
4096 element MRI-compatible array

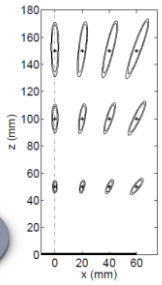


Non-thermal Bubble Induced Ablation

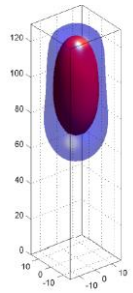


Planar Array: 4912-elements
Thermal Lesion Simulations





Single focus



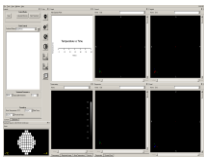
Scanned beam

Ellens et al, PMB 2011

Platform Technology

Transducers
500kHz, 8x8

Custom Electronics
64 channels



Software
Focusing speed scalable

Extensible – Stackable - Modular

- Compatible with Standard Imaging: MRI or Ultrasound
- Focused Ultrasound Systems tailored to any indication

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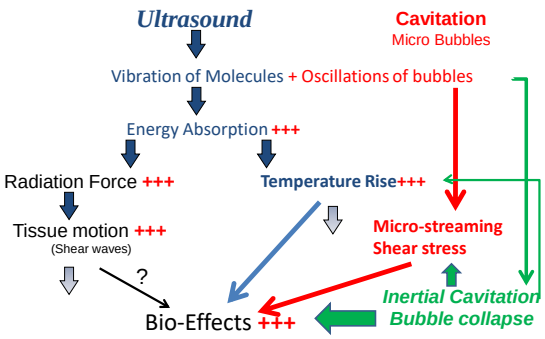
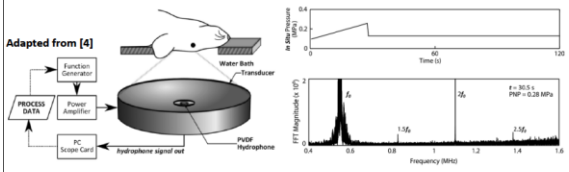
Ultrasound Interactions with Tissue



Acoustic Emissions

- MB emissions correlated w/ bioeffects[1-4]; existing controllers: single detectors[3,4]

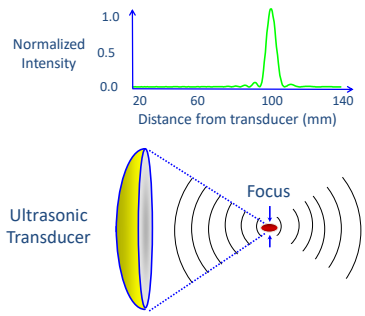


- Single-element trade-off: **volume of sensitivity** vs. **spatial specificity**

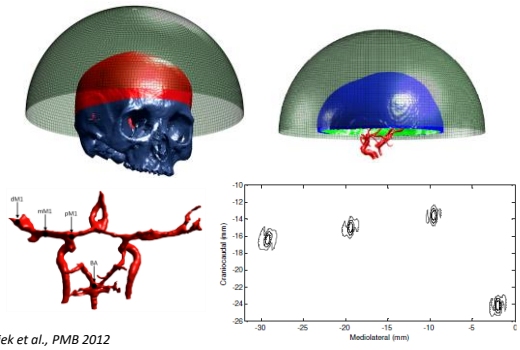
[1] McDannold *et al, PMB.* (2006)
[2] Tung *et al, PMB.* (2010)
[3] Arvanitis *et al, PLoS ONE.* (2012)
[4] O'Reilly & Hynynen, *Radiology.* (2012)

Bubble Enhanced Thermal Ablation

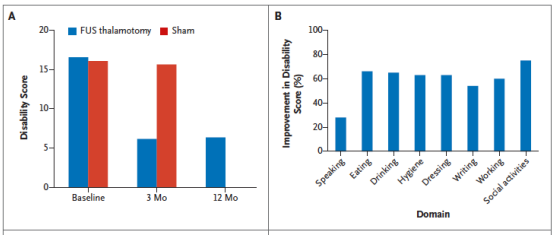
Focused Ultrasound



Through Skull Stroke Treatments Simulations

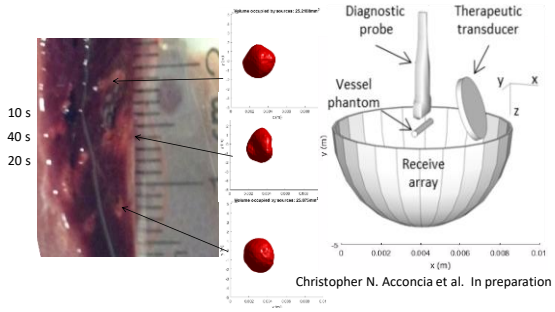


Pajek et al., PMB 2012



Passive Cavitation Imaging for Thermal Ablation Monitoring:

Ex vivo muscle



Christopher N. Acconcia et al. In preparation

Progress Towards Clinical Testing