HIFU Therapies – A Primer

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AAPM2015

FOCUSED ULTRASOUND FOUNDATION

Overview

- Historical perspective of HIFU
- HIFU physics
  - Ultrasound generation
  - Wave propagation
  - Absorption, refraction, and focusing
- Tissue interaction and bioeffects
  - Mechanical effects
  - Thermal effects
- Clinical HIFU
  - Vendors
  - Indications
  - Clinical trials

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Origins of HIFU

- 1881 – Pierre Curie – piezoelectricity
- 1915 – Paul Langevin – submarine sonar
- 1927 – 1st report of mechanical effects of US
- 1942 – W. Fry creates lesions in cat brains, Lynn produces lesions in bovine liver
- 1954 – Lars Leksell treats neuropathic pain
- 1980s – Sonocare CST, first FDA approved HIFU
- 1990s – Focus Surgery and EDAP-TMS: prostate
- 2000s – Hynynen and Fink, trans-skull HIFU
- Over 30 indications approved or in trials

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Origins of HIFU

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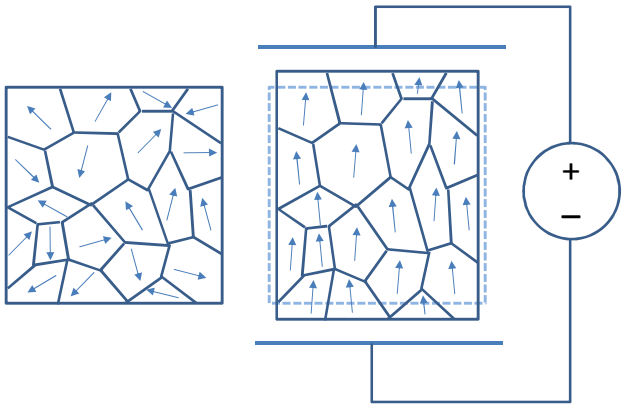
Physics: Piezoelectricity



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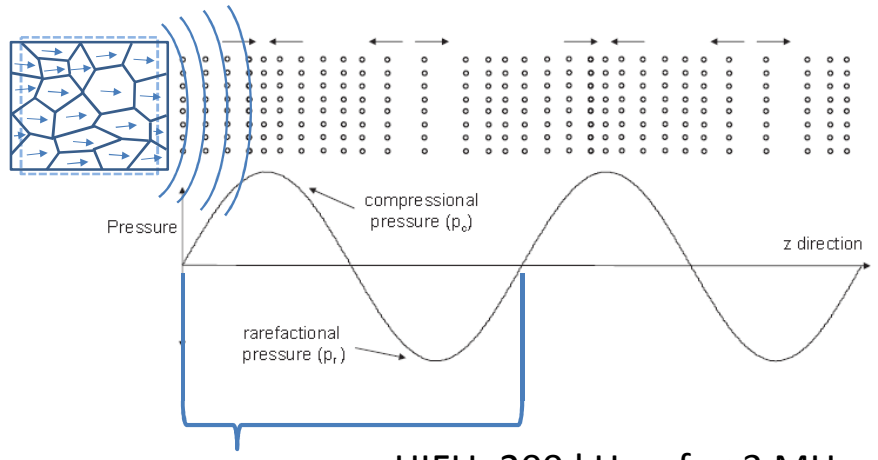
Physics: Compressional Wave



λ = Wavelength
f_c = Frequency = 1/ λ

HIFU: 200 kHz < f_c < 3 MHz
Diag: 1 MHz < f_c < 10 MHz

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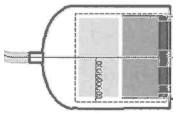
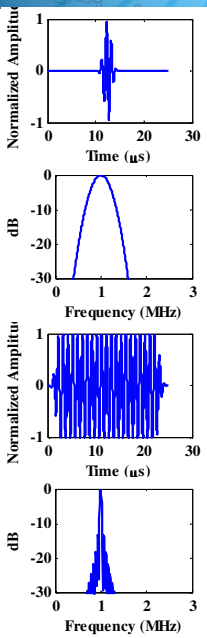
Physics: HIFU Transmission



- Diagnostic transmit
  - Emphasis on short pulse
  - Broad bandwidth
  - Lossy / matched backing material
- HIFU Transmit
  - Emphasis on high energy output
  - Narrow bandwidth
  - Air-backed / mis-matched



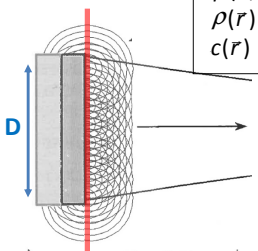
Physics: Wave Propagation

- Wave equation

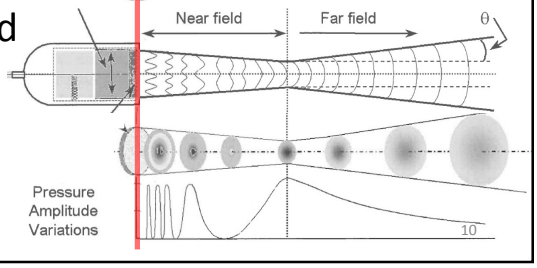
$$\rho(r)\,div\left(\frac{\overrightarrow{grad}p(r,t)}{\rho(r)}\right)-\frac{1}{c^2(r)}\frac{\partial^2 p(r,t)}{\partial t^2}=0$$

$p(\bar{r},t)$ pressure field
$\rho(\bar{r})$ density
$c(\bar{r})$ acoustic velocity

- Huygen's principle – infinite number of point sources



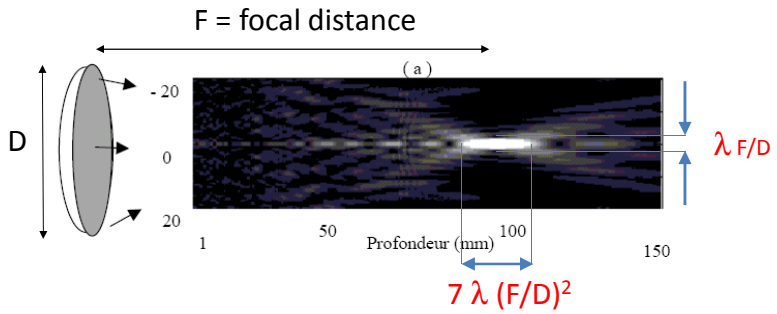
- Nearfield vs. farfield
  - Natural focus of a single element = $D^2/4\lambda$



Bushbeg et. al, *The Essential Physics of Medical Imaging*, 2002.

Physics: Focusing

- Focal size: ideal focused concave transducer
  - Lateral: $\lambda F/D$
  - Azimuthal: $7\lambda(F/D)^2$



Courtesy of Jean-François Aubry, Institut Langevin, Paris, France

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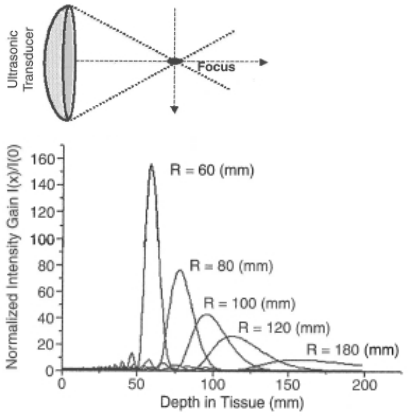
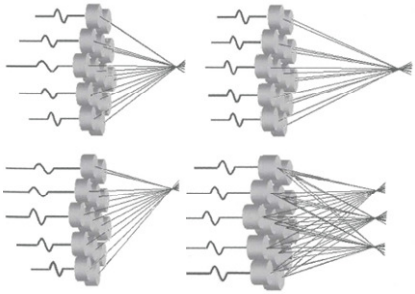
Physics: Focusing

- Spherically-curved transducers have geometric focal gain
- Multi-element transducers permit dynamic focus





Jolesz and Hynynen, *MRI-Guided Focused Ultrasound Surgery*, 2008.

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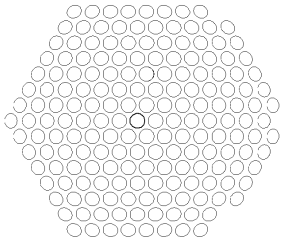
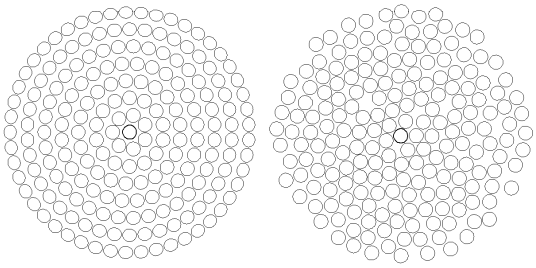
Physics: Array Focusing Patterns



Hexagonal



Annular

Quasi-random

M. Pernot, J.-F. Aubry, M. Tanter, J.-L. Thomas, M. Fink, "High power transcranial beamsteering for non invasive brain therapy", Physics in medicine and biology, 2003.

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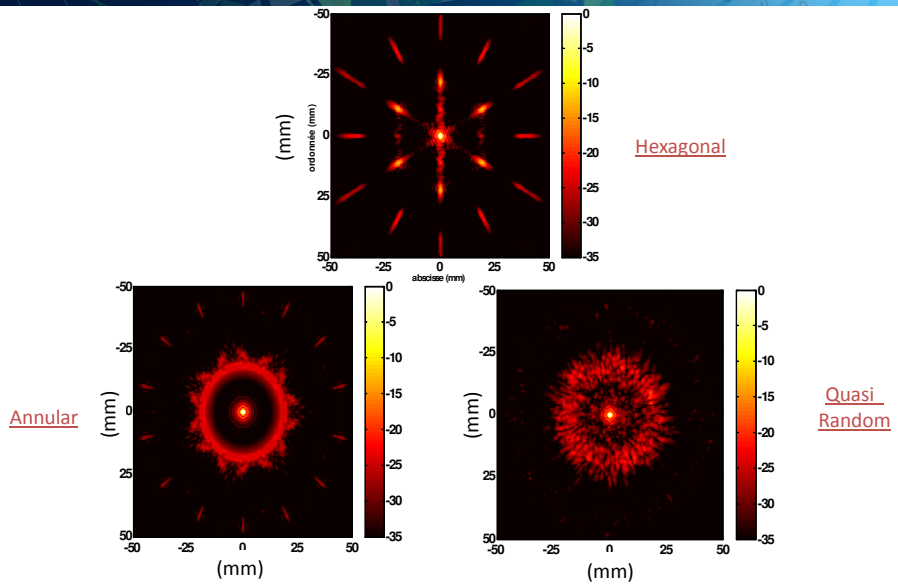
Physics: Array Focusing Patterns



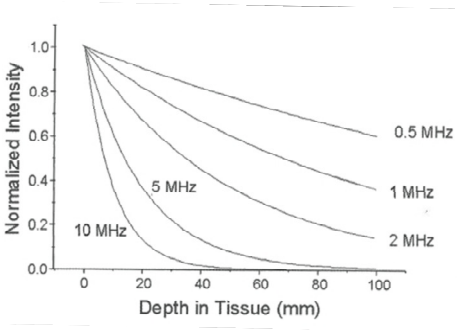
M. Pernot, J.-F. Aubry, M. Tanter, J.-L. Thomas, M. Fink, "High power transcranial beamsteering for non invasive brain therapy", Physics in medicine and biology, 2003.

Physics: Absorption

- Acoustic intensity (I) at a given depth (z).

$$I(z) = I_0 e^{-\mu_A z}$$

Where μ_A is the amplitude attenuation factor and has units of cm^{-1}.



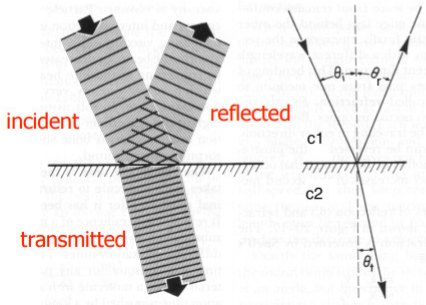
Tissue Composition	Attenuation coefficient (1 MHz beam, dB/cm)
Water	0.0002
Blood	0.18
Soft tissues	0.3–0.8
Brain	0.3–0.5
Liver	0.4–0.7
Fat	0.5–1.8
Smooth muscle	0.2–0.6
Tendon	0.9–1.1
Bone, cortical	13–26
Lung	40

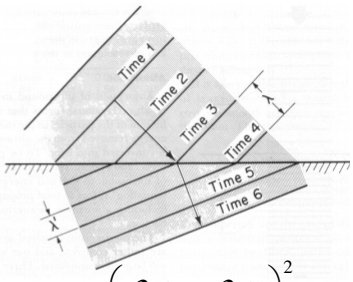
Bushbeg et. al, *The Essential Physics of Medical Imaging*, 2002.

Physics: Reflection and Refraction

- Constant frequency, materials with differing speed of sound
- Snell's law

$$\frac{\sin\theta_i}{c_1} = \frac{\sin\theta_r}{c_1} = \frac{\sin\theta_t}{c_2}$$





$$I_r = I_i \left(\frac{\rho_2 c_2 - \rho_1 c_1}{\rho_2 c_2 + \rho_1 c_1} \right)^2$$

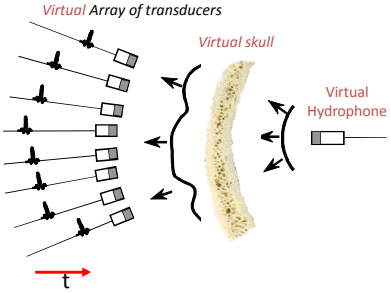
$$I_t = I_i - I_r$$

Bushbeg et. al, *The Essential Physics of Medical Imaging*, 2002.

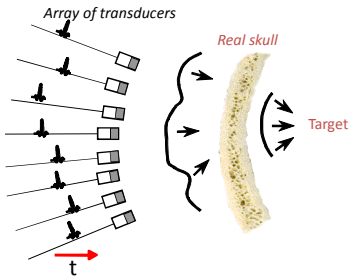
Physics: Trans-skull Refocusing

- Hynynen and multi-element transducer, CT.
- Fink and time reversal

Step one: Simulating p(r,t)



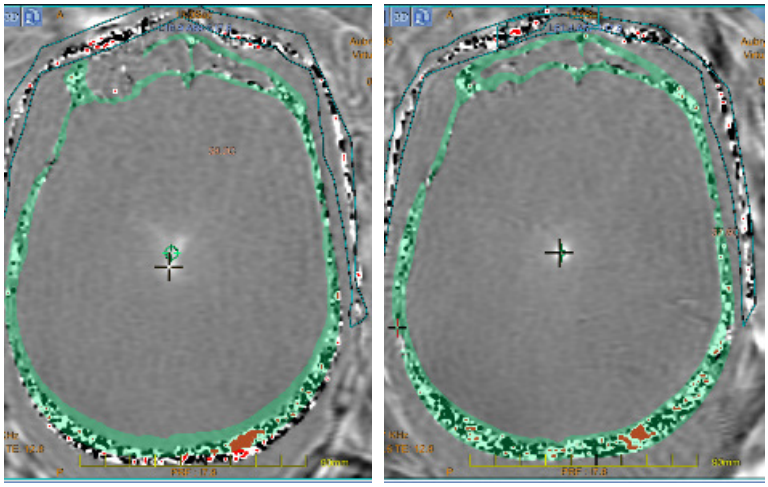
Step two: emitting reversed signal



Courtesy of Jean-François Aubry, Institut Langevin, Paris, France

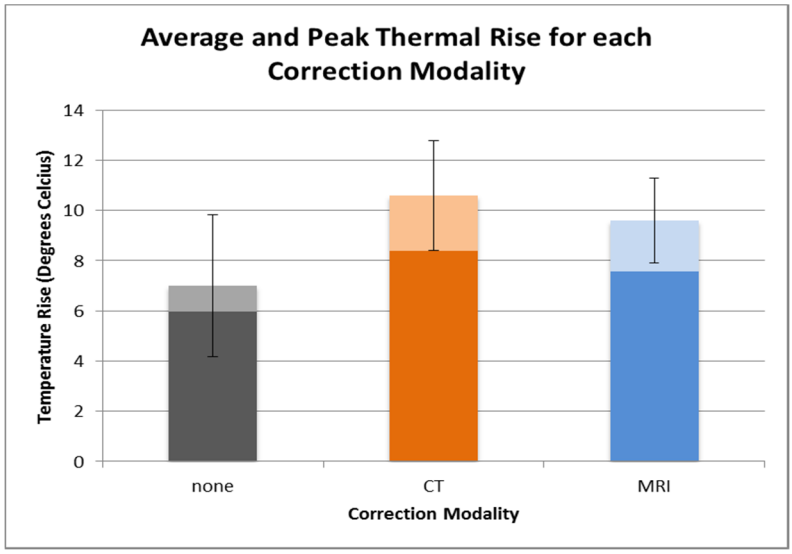
Physics: Trans-skull Refocusing

No Correction	Standard Correction



Wintermark et. al, "T1w MRI as a substitute to CT for refocusing in MRg-FUS", PMB 2014 19

Physics: Trans-skull Refocusing

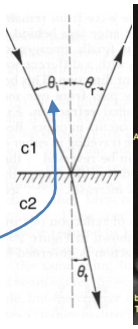


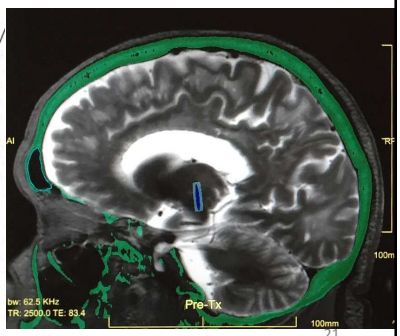
Wintermark et. al, "T1w MRI as a substitute to CT for refocusing in MRg-FUS", PMB 2014 20

Physics: Total Internal Reflection

- Incident wave reflected: does not penetrate the material interface
- Occurs at θ_i > Critical
  - Compute by setting $\theta_t = 90°$
  - $\sin(\theta_i) = c_1/c_2$
- Important in trans-skull treatments.
  - $\theta_i = \sin^{-1}(c_1/c_2) = \sin^{-1}(1480/4080) =$ **21.3°**

$$\frac{\sin\theta_i}{c_1} = \frac{\sin\theta_t}{c_2}$$





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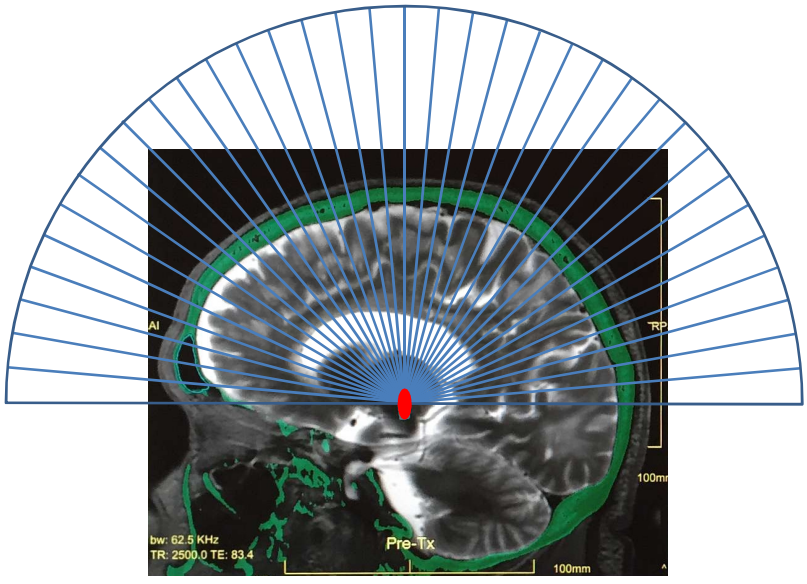
Physics: Total Internal Reflection



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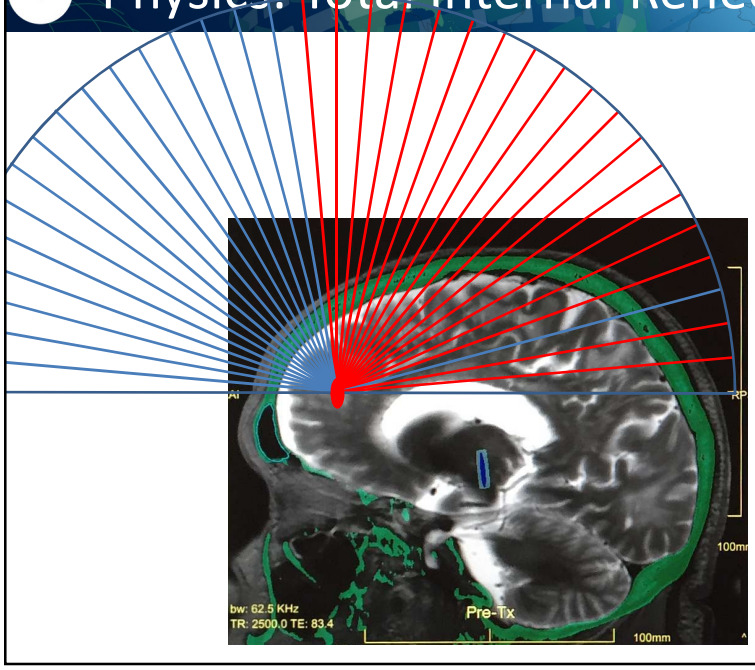

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Physics: Conversion to Heat

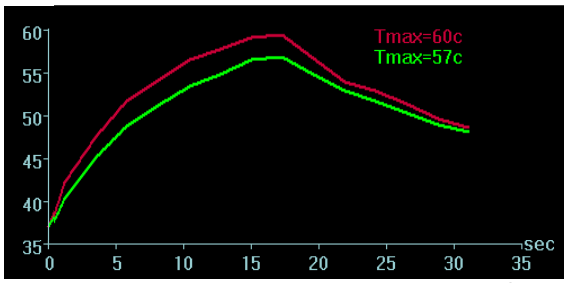
- HIFU-induced heat deposition

$$Q = \frac{\alpha |p|^2}{\rho c}$$

Heat source term for time harmonic acoustic pressure

p acoustic pressure
ρ density
c sound velocity
α absorption = 0.65 dB.mm^{-1}.MHz^{-1}

- Thermal tissue effects



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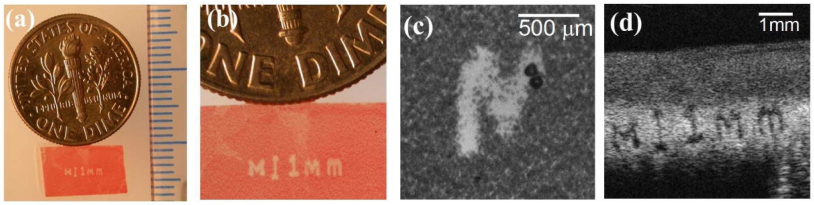
Physics: Cavitation ME5

- At high power, peak-negative-pressure can be sufficiently low to nucleate gas bubbles in-situ
  - Cavitation activity is increased with reduced ultrasound frequency
- Mechanical tissue effects



Cain CA et. al, "Histotripsy beyond the intrinsic cavitation threshold using very short ultrasound pulses: microtripsy" IEEE TUFFC, Feb. 2014

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  - Clinical trials

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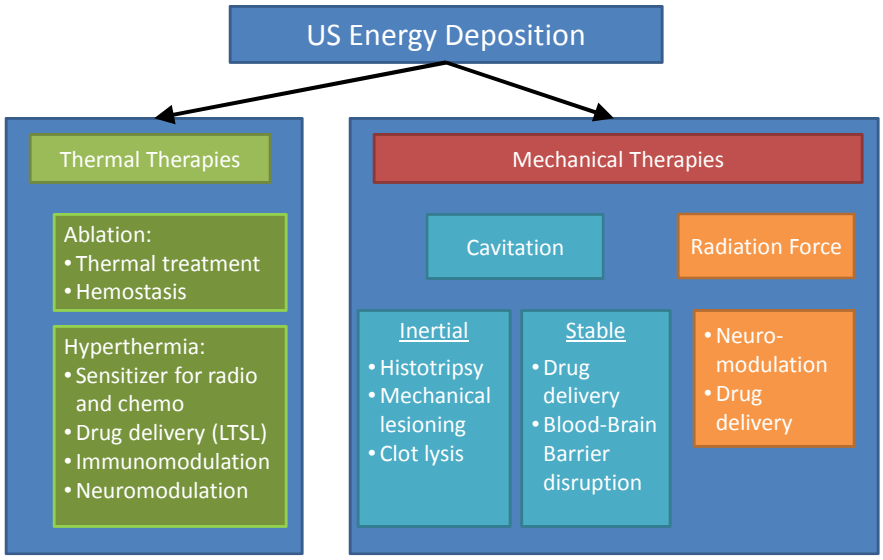
HIFU: Clinical Utility



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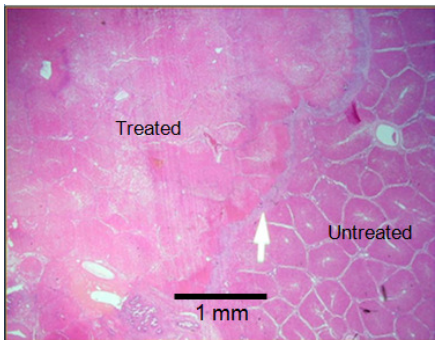
Thermal Ablation

- Induce protein denaturation
  - Single-cell boundary treated/untreated
  - Clinicians aim to reach 58-60°C for >1 second



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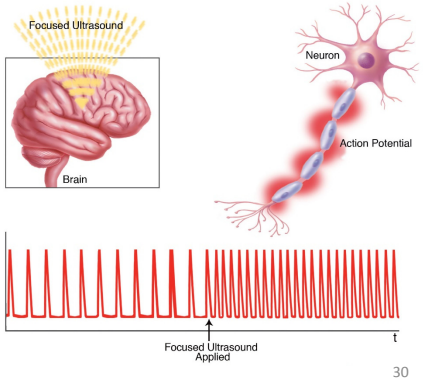
Neuromodulation

- Thermal
  - Sub-ablative temperature elevation can temporarily affect neuron function
- Mechanical
  - Gated, low duty-cycle
  - Time-averaged power less than diagnostic ultrasound



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Drug Delivery

- Mechanical: Microbubble-mediated
  - …with drug payload
  - …co-injection with vascular permeability
- Low-temperature liposomes
  - Attached drugs released with temperatures above ~43°C

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Immunomodulation

- Thermal and mechanical therapies are both capable of inducing a systemic immune response against cancer cells. Tumor associated antigens from the treated region are recognized by dendritic cells, which create a T cell mediated response against the cancer.

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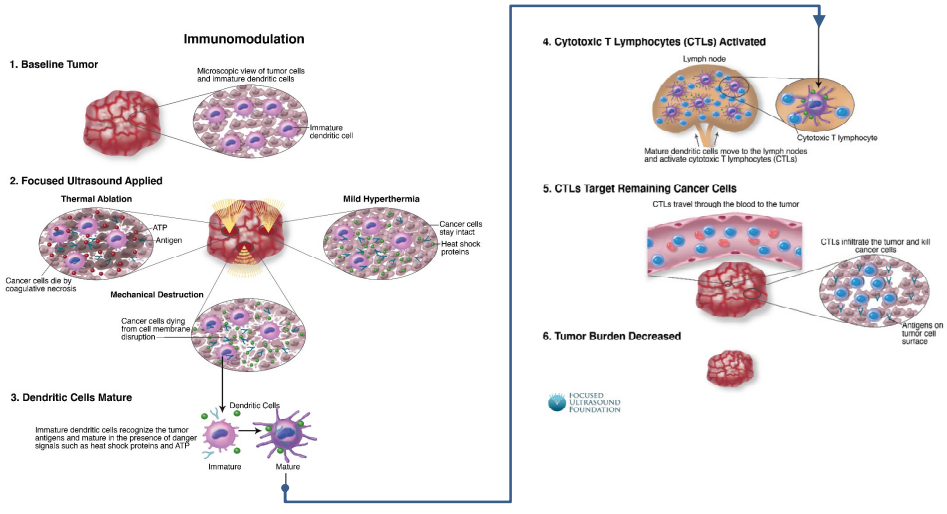
Immunomodulation



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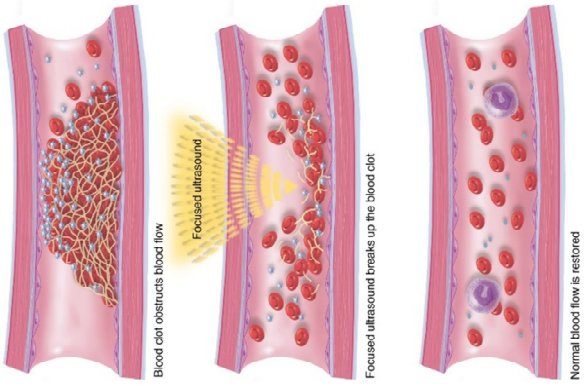
Clot Lysis

- Mechanical focused ultrasound is capable of disrupting the fibrin matrix of blood clots and restoring normal blood flow to the obstructed vessel



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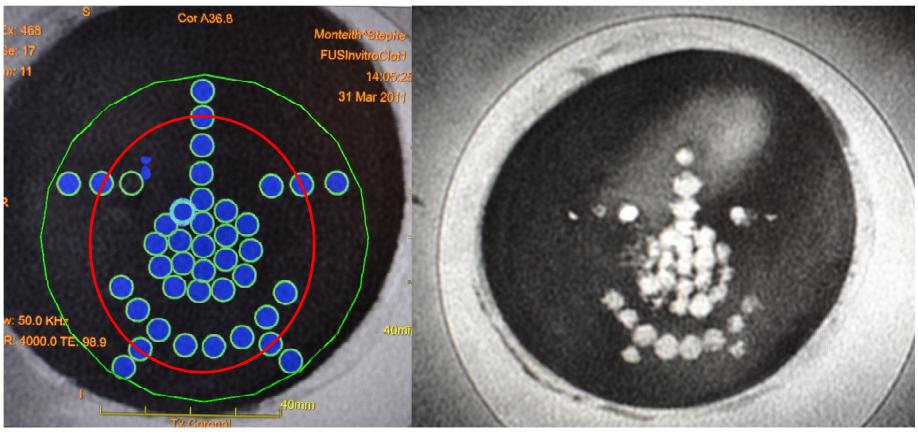
Clot Lysis: First sonications….



S. Monteith et. al, "Minimally invasive treatment of intracerebral hemorrhage with magnetic resonance-guided focused ultrasound". J Neurosurg, 01/2013

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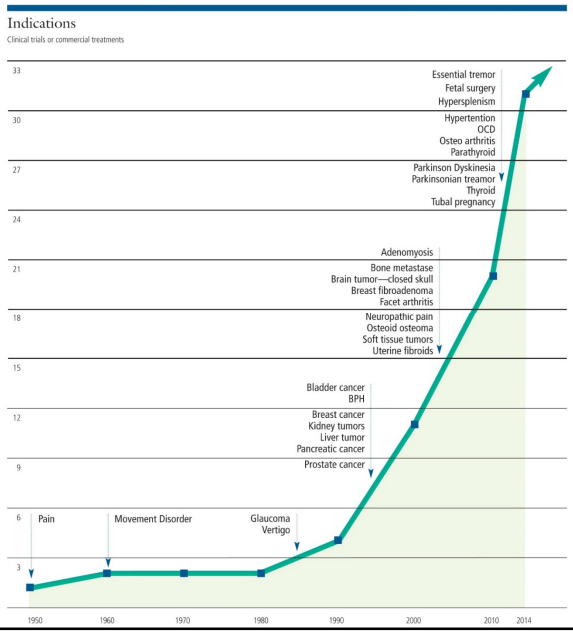
Clinical Indication Development



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Clinical HIFU System Vendors

- Acublate
- Alpinion
- Haifu
- EDAP-TMS
- EyeTechCare
- HistoSonics
- InSightec
- Kona Medical
- Mirabilis Medica
- Philips
- Profound
- Shanghai A&S
- Slender Medical
- SonaCare Medical
- Theraclion

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Current Clinical Activity

- FDA approved applications
  - Uterine fibroids
  - Bone mets
- Completed and active clinical trials
  - Neuropathic pain (12 patients)
  - Essential tremor (97 patients)
  - Parkinson's (Tremor, Gpi) (34 patients)
  - Brain tumors, OCD, Depression, Dystonia, prostate, pancreas, osteoid osteoma, osteoarthritis, liver, kidney…

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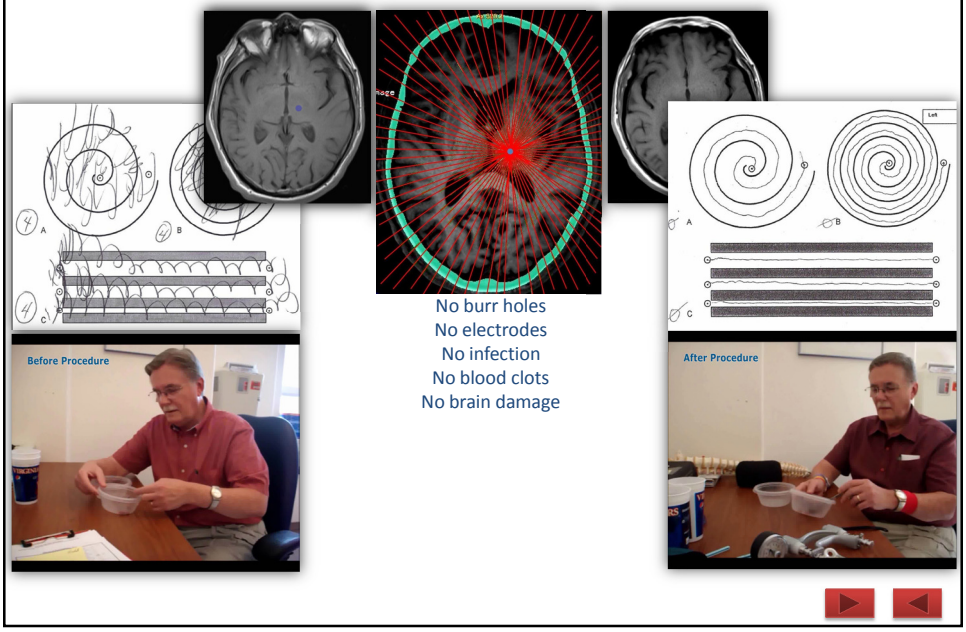
UVa Trial: Essential Tremor Treatment



No burr holes
No electrodes
No infection
No blood clots
No brain damage

Clinical Indication: State of Field

Conceptual | Preclinical | Anecdotal | Pilot Trials | Pivotal Trials | Outside US Approval | FDA Approval | Reimbursement

Neurological
- Essential Tremor
- Parkinson's Disease
- Neuropathic Pain
- Brain Tumors
- OCD
- Epilepsy
- Stroke
- Hydrocephalus
- Trigeminal Neuralgia
- Alzheimer's Disease
- Traumatic Brain Injury
- Multiple Sclerosis
- Cancer Pain
- Depression
- AVM's

Musculoskeletal
- Back Pain
- Osteoid Osteoma
- Osteoarthritis
- Sacroilitis
- Disc Degeneration
- Spinal Tumors

Oncological
- Bone Metastases
- Prostate Cancer
- Breast Cancer
- Pancreatic Cancer
- Soft Tissue Tumors
- Liver Cancer
- Kidney Cancer
- Brain Tumors
- Head & Neck Cancer
- Lung Cancer
- Bladder Cancer
- Colon Cancer
- Esophageal Cancer

Women's Health
- Uterine Fibroids
- Uterine Adenomyosis
- Breast Fibroadenomas
- Tubal Pregnancy
- Fetal Surgery
- Polycystic Ovarian Syndrome

Cardiovascular
- Hypertension
- Atherosclerosis
- Atrial Fibrillation
- Septal Perforation
- Deep Vein Thrombosis
- Cardiac Pacing
- Hypoplastic Left Heart Syn.

Urological
- Prostate Cancer
- Kidney Cancer
- Benign Prostatic Hypertrophy
- Acute Tubular Necrosis
- Ureterocele
- Bladder Cancer

Endocrine Disorders
- Thyroid Nodules
- Obesity
- Diabetes

Miscellaneous
- Hypersplenism

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