HIFU Therapies – A Primer

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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
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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Physics: Piezoelectricity
Physics: Compressional Wave

\[ \lambda = \text{Wavelength} \]
\[ f_c = \text{Frequency} = \frac{1}{\lambda} \]

HIFU: \[200 \text{ kHz} < f_c < 3 \text{ MHz}\]

Diag: \[1 \text{ MHz} < f_c < 10 \text{ MHz}\]

- 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
  \[ \rho(r) \frac{\partial}{\partial t} \left( \frac{\text{grad} p(r,t)}{\rho(r)} \right) - \frac{1}{c^2(r)} \frac{\partial^2 p(r,t)}{\partial t^2} = 0 \]
  
  \( \rho(r) \) pressure field
  \( \rho(r) \) density
  \( c(r) \) acoustic velocity

- Huygen’s principle – infinite number of point sources

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


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
Physics: Focusing

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


Physics: Array Focusing Patterns

- Hexagonal
- Annular
- Quasi-random

Physics: Array Focusing Patterns

- Hexagonal
- Annular
- Quasi
- Random


Physics: Absorption

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

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

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

Physics: Reflection and Refraction

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

\[
\frac{\sin \theta_1}{c_1} = \frac{\sin \theta_2}{c_2} = \frac{\sin \theta'_1}{c'_1}
\]

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

\[
I_i = I_i - I_r
\]


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

Average and Peak Thermal Rise for each Correction Modality

Wintermark et. al, “T1w MRI as a substitute to CT for refocusing in MRg-FUS”, PMB 2014
Physics: Total Internal Reflection

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

Physics: Conversion to Heat

- HIFU-induced heat deposition
  \[ Q = \frac{d|p|^2}{\rho c} \]
  Heat source term for time harmonic acoustic pressure
  \( p \) acoustic pressure
  \( \rho \) density
  \( c \) sound velocity
  \( \alpha \) absorption = 0.65 dB.mm\(^{-1}\).MHz\(^{-1}\)

- Thermal tissue effects
• 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


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HIFU: Clinical Utility

US Energy Deposition

Thermal Therapies
Ablation:
• Thermal treatment
• Hemostasis

Hyperthermia:
• Sensitizer for radio and chemo
• Drug delivery (LTSL)
• Immunomodulation
• Neuromodulation

Mechanical Therapies

Cavitation

Inertial
• Histotripsy
• Mechanical lesioning
• Clot lysis

Stable
• Drug delivery
• Blood-Brain Barrier disruption

Radiation Force
• Neuromodulation
• Drug delivery

Thermal Ablation

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

Treated

1 mm

Untreated
Neuromodulation

- Thermal
  - Sub-ablative temperature elevation can temporarily affect neuron function

- Mechanical
  - Gated, low duty-cycle
  - Time-averaged power less than diagnostic ultrasound

Drug Delivery

- Mechanical: Microbubble-mediated
  - ...with drug payload
  - ...co-injection with vascular permeability

- Low-temperature liposomes
  - Attached drugs released with temperatures above ~43°C
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.
Mechanical focused ultrasound is capable of disrupting the fibrin matrix of blood clots and restoring normal blood flow to the obstructed vessel.

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

Indications
- Clinical HIFU
  - Vendors
  - Indications
  - Clinical trials
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
- Theracion

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...
**UVa Trial: Essential Tremor Treatment**

- Awake, no anesthesia
- No incisions
- No burr holes
- No electrodes
- No infection
- No blood clots
- No brain damage

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**Clinical Indication: State of Field**

<table>
<thead>
<tr>
<th>Conceptual</th>
<th>Preclinical</th>
<th>Anecdotal</th>
<th>Pilot Trials</th>
<th>Pivotal Trials</th>
<th>Outside US Approval</th>
<th>FDA Approval</th>
<th>Reimbursement</th>
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<td>Cardiovascular</td>
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<td>Essential Tremor</td>
<td>Bone Metastases</td>
<td>Hypertension</td>
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<td>Septal Perforation</td>
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**Musculoskeletal**

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<th>Back Pain</th>
<th>Uterine Fibroids</th>
<th>Endocrine Disorders</th>
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<td>Osteoarthritis</td>
<td>Uterine Adenomyosis</td>
<td>Thyroid Nodules</td>
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<td>Scoliosis</td>
<td>Breast Fibroadenomas</td>
<td>Obesity</td>
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<td>Tubal Pregnancy</td>
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<td>Fetal Surgery</td>
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**Women’s Health**

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<th>Endocrine Disorders</th>
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<tbody>
<tr>
<td>Uterine Adenomyosis</td>
<td>Hypo/hyperthyroidism</td>
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</tbody>
</table>

**Miscellaneous**

- Hyperparathyroidism