Ultrasound waves are mechanical longitudinal pressure waves at a frequency above 20 kHz.

Diagnostic ultrasound usually employs frequencies in the range of 5–20 MHz.

Lower frequency for industrial applications such as cleaning, plastic welding and bactericidal water purification.

Therapeutic ultrasound usually employs frequencies in the range of 1–4 MHz.
High Intensity Focused Ultrasound (HIFU)

High-Intensity Focused Ultrasound (HIFU or FUS) is a medical procedure that applies high-intensity focused sonic energy to locally heat and destroy diseased or damaged tissue through ablation.

HIFU is a hyperthermia therapy that uses temperature to treat diseases.

Other ultrasound treatment methods include ultrasound-assisted drug delivery, ultrasound hemostasis, ultrasound lithotripsy, and ultrasound-assisted thrombolysis.

High Intensity Focused Ultrasound (HIFU)

- HIFU therapy utilizes a localized focus of high intensity ultrasound
  - Local temperature rise is linearly dependent on the local HIFU intensity
  - First publication 1942 (Lynn et al.)

<table>
<thead>
<tr>
<th>Pressure: 1-10 MPa</th>
<th>Intensity: 100-500 W/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>US</td>
</tr>
<tr>
<td>Very short bursts</td>
<td>Continuous wave</td>
</tr>
<tr>
<td>( \epsilon_{son} = 0.094 - 0.790 ) W/cm²</td>
<td>20-80 s</td>
</tr>
</tbody>
</table>

Diagnostic vs. Therapeutic Ultrasound

Diagnostic Ultrasound

- Pressure: 1-3 MPa
- Intensity: 1-100 W/cm²
- Very short bursts
- US

HIFU

- Pressure: 1-10 MPa
- Intensity: 100-5000 W/cm²
- Continuous wave
Therapeutic US Interaction with Tissue

Ultrasound

Vibration of Molecules

Energy Absorption

Temperature Elevation

Tissue Coagulation

2 x 7 mm Focal spot

Tissue

HIFU induced temperature increase

• Pennes' bioheat transfer equation determines the tissue temperature rise induced by HIFU according to

\[
p\rho_c \frac{\partial T(r,t)}{\partial t} = k\nabla^2 T(r,t) - W_b C_v (T(r,t) - T_a) + \alpha_f \frac{p c^2}{\rho c}
\]

• For a localized focus, the temperature rise will also be localized but slightly spread by heat conduction, also called heat diffusion

HIFU thermal ablation

• Thermal necrosis via heat deposition (thermal dose)

Advantages over other techniques

An important difference between HIFU and many other forms of focused energy, such as radiation therapy or radio surgery, is that the passage of ultrasound energy through tissue has no apparent cumulative effect on that tissue.

The absence of cumulative effects of HIFU on the treated tissue means that the treatment can be repeated in case of first HIFU treatment failure or partial treatment of the prostate.

As a non-ionizing treatment HIFU is also an option to treat cancer recurrence after radiation therapy failure.

Imaging guided HIFU

Clinical HIFU procedures are typically performed in conjunction with an imaging procedure to enable treatment planning and targeting before applying a therapeutic or ablative levels of ultrasound energy.

Monitoring required for a controlled therapeutic procedure
- Temperature monitoring can be provided by either MRI (MRigHIFU) or ultrasound (USgHIFU) guidance
- MRI is much more accurate and reliable
- First publications on MRI guided HIFU in 1992

3. US Patent #5247935. filed on March 19, 1992 The technology was later transferred to Insightec in Israel in 1998.

Imaging guided HIFU of Uterine Fibroids

Ultrasound

![Ultrasound Image]

MRI

![MRI Image]

Computed tomography

![Computed Tomography Image]

Courtesy of Lisette Warner, Ph.D.
MRI guided HIFU

• MRI guided focused ultrasound therapy is based on ultrasound-induced local hyperthermia with thermal monitoring using MRI.
MRI guided HIFU

- 5 Degrees of Freedom Positioning System
- Fully MR compatible
- Easy on/off for transition between therapy & imaging
- Accurate to 0.1 mm
- Integrated MR coil

MR Thermometry

- Temperature rise can be measured with several MRI techniques as a number of different MR properties are temperature dependent
  - Spin density
  - $T_1$-constant
  - Diffusion coefficient
  - Water proton resonance frequency
  - Spectroscopy
  - Gd-contrast enhancement
  - etc.

- MRI temperature measurement for HIFU is commonly based on the water proton resonance frequency shift which induces phase differences between dynamic frames.

- Proton resonance frequency shift of lipid hydrogens are independent of temperature. Temperature in lipids can not be measured with the PRF method → fat is suppressed

- From MR dynamic phase images a relative temperature change can be calculated.
MR Thermometry

PRF shift measurement

\[ \Delta T = \frac{\Delta \phi}{\alpha \gamma B_0 \cdot TE} \]

\( \gamma = 2\pi \cdot 42.56 \text{ MHz/T} \): Gyromagnetic Ratio
\( \alpha = 0.0101 \text{ ppm/°C} \): Water Frequency Shift
\( T_E \approx 20\text{ms} \): Echo Time
\( B_0 = 1.5\text{ T} \): Magnetic Field

Temperature maps are calculated on-line during sonication and displayed as overlays on the magnitude image.
Multi Slice Monitoring

Six monitoring slices:
- A: 3 x at focal plane
- B: 1 x along beam axis
- C: Near field
- D: Far field

Slice positioning:
- A, B: automatically
- C: abdominal muscle layer
- D: close to bowel or spine

Multi-shot EPI with $TE=20\text{ ms}$, $TR=37\text{ ms}$, resolution $= 2.5\times2.5\times7\text{ mm}^3$, EPI factor $= 11$ and $121$ binomial water-selective excitation, $2.9\text{ s}$ acquisition time for all 6 slices.

Temperature Map Corrections

- Baseline drift
  - Magnetic field drift is corrected for with a zero order correction
  - Uses unheated parts of the image as the baseline

- Motion detection
  - Detection, no correction
  - Checks for intra-scan motion (changes in temperature std dev)
  - Gives a warning if motion is detected
  - Interscan motion has to be manually checked with MR scans
Accumulated temperature over time
Tissue effects depend on temperature and time
Tissue necrosis at 43°C over 240 min.
  - Definition of One Thermal Dose
  - Measure Thermal Dose in 240 equivalent minutes (EM)
  - Time for lethal dose halves with every degree temperature increase

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Thermal Dose</th>
<th>Lethal Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>+2°C</td>
<td>+8°C</td>
<td>+14°C</td>
</tr>
<tr>
<td>120 sec</td>
<td>240 min @ 43°C</td>
<td>120 min @ 44°C</td>
</tr>
<tr>
<td>15 min @ 47°C</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>4 sec @ 55°C</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>1 sec @ 57°C</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Thermal dose (TD) is calculated as a time integral of temperature increase (Arrhenius Equation), based on temperature maps

\[ TD(t) = \int_{0}^{t} r(43 - T(t)) \, dt \]

- 240 EM (equivalent minutes) is commonly defined to indicate full and irreversible coagulative necrosis in muscle tissue
- 30 EM is often taken as the threshold for onset of thermal damage

Thermal Dose Limits

- 0 – 30 EM → no thermal damage
- 30 – 240 EM → possible thermal damage (mostly reversible)
  - edematous, fragmented cell membranes, varying damage to vasculature
- 240 EM < → irreversible coagulative necrosis
  - Generalized thermal coagulation, fragmented cell membranes, necrotic vascularization → no perfusion in CE images

- Limits depend on tissue type
  - e.g. Brain tissue is more sensitive to temperature than muscle tissue
- HIFU may occlude blood vessels within the target region
  - Parts of uterine fibroids downstream of such an occlusion may appear non-perfused even though no thermal damage was inflicted to these areas
Thermal Map and Thermal Dose Map

Thermal Map
(\(\Delta T^\circ C + 37^\circ C\))

Thermal Dose Map
(equivalent minutes at 43^\circ C)

Macroscopic Tissue Effects

Real Time Feedback

- Thermal Map & Dose map
- Real time visualization + Feedback
- \(T > 57^\circ C\) or Dose >240 EM
- Stop heating
- Predictable necrosis volume
- No a-priori knowledge needed
- Simple and robust feedback

Predictable necrosis volume
No a-priori knowledge needed
Simple and robust feedback

Focusing the Ultrasound Beam

Ultrasound can be focused into a small focal zone, either via
1. a lens (for example, a polystyrene lens), or
2. a curved transducer, or
3. a phased array
4. or any combination of the three

HIFU Transducer

- Phased Array Transducer
  - 256 Independent channels
  - Ultrasound Frequency: 1-1.5 MHz
  - Power Max 300 Watts Acoustic

- Advantages
  - Allow electronic displacement along all directions (about ±2cm)
  - Very fast electronic displacement: position update < 10ms
  - Allow to heat a large area without transducer displacement
  - Allow temperature control over large volume
HIFU Transducer

Electronic displacement of the focal point
Phase change of the electronic signal moves the focal point

\[ \phi_2 - \phi_1 = 2\pi \frac{L_2 - L_1}{\lambda} \]

HIFU Transducer

High power output (up to 150 W)
Adjustable frequency (1~10 MHz)
Tailor-made transducers with various focal lengths, aperture sizes

HIFU Transducer

Tissue mimicking gel insonated with a HIFU transducer. The gel shows a lesion in the region of the ultrasonic focus due to the temperature rise.
HIFU Transducer

Pressure calculation in the tissue mimicking gel insonated with a HIFU transducer.

HIFU Transducer

HIFU tabletop transducer

For details see: M. Köhler et al., Med.Phys. 36 (8), 2009.


Volumetric Heating

For details see: M. Köhler et al., Med.Phys. 36 (8), 2009.
Volumetric Heating

• Larger cells require a longer sonication duration at the same power level, meaning more energy
• Resulting necrosis volume scales with cell size
• Treatment energy efficiency improved with cell size

![Thermal map & Dose map](image)
[Real time visualization](image)
[Automatic control](image)

**4mm cell**
- 1.6kJ
- 0.04ml/kJ

**12mm cell**
- 5.3kJ
- 0.34ml/kJ

**16mm cell**
- 7.7kJ
- 0.56ml/kJ

* Applies to the border of the cell. Temperatures at the center are higher, especially for larger cells.

Volumetric Treatment with Feedback

- Thermal map & Dose map
- Real time visualization
- Automatic control
- T > 57°C or Dose >240 EM
- Stop heating
- Reliable necrosis volume

[Courtesy of Ari Partanen, Ph.D.]
Clinical Applications

**Clinical Applications**

**Uterine fibroids**

HIFU treatment for uterine fibroids was approved by the US Food and Drug Administration (FDA) in October 2004.

Most patients benefit from HIFU and symptomatic relief is sustained for two or more years. Up to 16-20% of patient will require an additional treatment.

https://www.fusfoundation.org/diseases-and-conditions/overview
**Clinical Applications**

Pre and post HIFU contrast Enhanced MRI of Uterine Fibroids

Left: Pre-procedure C+
Right: Post-procedure C+ following MR-HIFU therapy

Dark areas indicate necrotic, non-perfused volume

Courtesy of S. Bordeaux Hospital, Bordeaux, France

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**Clinical Applications**

Uterine fibroid

**Very large uterine fibroid**
- 40/F, urinary frequency, pain
- 123 x 93 x 92 mm, 599.5 ml

**Treatment**
- Treatment time: 163 minutes
- Ablation speed: 179 ml/h

**Post treatment**
- Large Non-perfused Volume:
  - 568 ml
  - 89% reduction

Temperature map, real-time, ø16 x 40 mm cell

Non-perfused volume, T1 TSE THRIVE 3D SPAIR C+

Courtesy: Samsung Medical Center, Seoul, Korea & AJOG 2011;205:292.e1

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**Clinical Applications**

Functional Neuro Surgery

Transcranial Magnetic Resonance-guided Focused Ultrasound Surgery (tcMRgFUS) is a technology for the non-invasive treatment of various brain disorders such as Essential Tremor, Neuropathic Pain and Parkinson's Disease.

Preliminary results demonstrate the ability to effectively ablate targets deep in the brain with high precision.
Delivering drugs to brain
In current research, HIFU is being used to temporarily open the blood–brain barrier, allowing absorption of drugs into the brain. It is most effective when used in combination with a calcium channel blocker like verapamil.

Treatment of atrial fibrillation
HIFU has been used to treat the most common heart arrhythmia, atrial fibrillation (AF). A minimally invasive catheter based system designed to ablate heart tissue responsible for propagating AF has been approved for use in Europe and is undergoing an FDA approved phase III pivotal efficacy trial in the United States.

Cancers
HIFU has been successfully applied in treatment of cancer to destroy solid tumors of the bone, brain, breast, liver, pancreas, rectum, kidney, testes, prostate. At this stage, cancer treatments are still in the investigatory phases as there is a need to find more about their effectiveness.

HIFU has been found to offer palliative care. CE approval had been given in the past for palliative treatment of bone metastasis and recently Insightec’s ExAblate received also FDA approval. Experimentally, a palliative effect was found in cases of advanced pancreatic cancer.

Several thousand patients with different types of tumors have been treated in China with HIFU using ultrasound image-guided devices built by several different companies.

Prostate cancer
HIFU prostate treatment is administered through a trans-rectal probe and relies on heat developed by focusing ultrasound waves.

Promising results approaching those of surgery have been reported in large series of prostate cancer patients. These treatments are performed under ultrasound imaging guidance, which allows for treatment planning and some minimal indication of the energy deposition.
Transrectal MR-HIFU of the Prostate

Clinical Applications

Prostate cancer
HIFU may also be used to ablate the entire prostate gland using a transrectal probe. This is an outpatient procedure that usually lasts 1–3 hours. First results show that it greatly reduces some of the side effects common with other treatments for prostate cancer.

During HIFU, the entire prostate is ablated, including the prostatic urethra.

While the urethra is an important anatomical structure, the sphincter and bladder neck are more important to maintaining the urinary function. During HIFU the sphincter and bladder neck have to be identified and avoided.

Transrectal MR-HIFU of the Prostate

Transrectal HIFU uses sound waves produced by a rectal probe to ablate cancer. Since the urethra runs through the treatment area, urinary infections, bladder obstruction, and incontinence are relatively common side effects.
Transurethral MR-HIFU of the Prostate

1. Transurethral ultrasound therapy
   - Urethra
   - Heating Pattern
   - Thermal Damage Boundary
   - Rectal Wall
   - Bladder

2. MRI-temperature control
   - MR images
   - Quantitative Temperature Feedback

Transurethral Applicator

- Rectal Wall Heating Pattern
- Thermal Damage Boundary
- Bladder

Table top assembly (on standard Achieva table top):
- Transducer catheter in holder and rotation device (white)
- Positioning system (grey), Interface box (pink)

Courtesy of Ari Partanen, Ph.D.

Transurethral Applicator

- Axially rotating applicator under robotic control
- Eight colinear 0.5 cm elements (f= 3 MHz, max P_{ac} = 4 W)
- Cooling via circulating degassed water

Courtesy of Ari Partanen, Ph.D.
**Set-up / Image guidance**

![Set-up / Image guidance Image]

**Results**

**Temperature maps**

![Temperature maps Image]

**Dose images**

![Dose images Image]
HIFU Mediated Drug Delivery

HIFU may be used to create high temperatures not necessarily to treat the cancer alone, but in conjunction with targeted delivery of cancer drugs.

For example, HIFU and other devices may be used to activate temperature-sensitive liposomes, filled with cancer drug “cargo” to release the drug in high concentrations only at the tumor site(s) only where triggered to do so by the hyperthermia device.

This novel approach is resulting in drug concentrations 10 times or more than traditional chemo with a fraction of the side effects since the drug is not released system-wide.
HIFU Mediated Drug Delivery

Liposomes: Temperature sensitive nanoparticles

- Temperature sensitive liposomes (TSL) rapidly release their therapeutic payload with heat
  - For use with low temperature hyperthermia (40 – 45 °C)
  - Enhanced drug delivery
- For use with ablative hyperthermia (> 60 °C)
  - Deposit drug in thermal margin → Increase treatment volume

37 °C – Stealth liposome
42 °C – Temperature sensitive liposome

Key Benefits: High dose (10x) of Chemotherapy targeted at tumor sites with reduced systemic toxicity

- Load TSL with
  - Doxorubicin (Dox)
  - ProHance® - MRI contrast
- Monitor release
  - Stable at 37°C
  - Fast release at 41°C
  - Dox and ProHance®
    - Release rates
- Stable for > 7 days
HIFU Mediated Drug Delivery

- Relaxivity $\uparrow$ (2x) with heating
- Relaxivity of heated liposome-ProHance®
- Release is visualized with MR-HIFU

![Graph showing relaxivity with and without heating]

Limitations of HIFU

- **Bone** and metallic objects are problematic due to very high absorption, and speed of sound
  - High absorption coefficient may cause rapid and significant temperature rise even when local intensity is relatively low
  - Very different speed of sound than soft tissues may cause significant refraction and diffraction
    - Unpredictable wave propagation in tissues beyond the bone
    - Local intensity maxima or foci may be produced in unexpected locations causing significant local heating in unintended regions
  - Due to the above reasons bone and surgical clips must be avoided in beam path

- **Scar tissue** is also problematic due to high absorption and lack of perfusion
  - Rapid heating and no cooling mechanism through perfusion (only cooling through heat diffusion)
  - Large scars, cesarean sections, etc. must be avoided in beam-path

Limitations of HIFU

- **Air filled cavities**
  - Ultrasound cannot propagate in air
    - Ultrasound waves that encounter a tissue-air interface will be fully reflected
  - Reflected beam is also partially absorbed in tissue
    - Can cause unpredictably large temperature rise in tissues close to air-interfaces
    - Air-pockets, skin-folds, belly-button, bowels, intestines, lungs, etc. must be avoided in beam path since temperature rise may be fast and unexpected
What is cavitation?

- Interaction of ultrasound field and microbubbles within a medium or tissue
- Oscillation of bubbles
  - Stable or non-inertial cavitation ➔ sub-harmonic US emission
    - Stable oscillation
    - Negligible effects in tissue level
  - Instable or inertial cavitation ➔ broadband US emission
    - Typically fast bubble growth and violent collapse
    - Mechanical tissue damage, thermal effects, free radicals
Cavitation in HIFU

- Harmful inertial cavitation is unlikely with diagnostic ultrasound, but may occur at intensities used in HIFU.
- Factors increasing risk of cavitation:
  - High sonication power/intensity
  - Pre-existing bubbles in beam path
  - Long pulse lengths or continuous wave sonication (such as in HIFU)
  - High temperatures
  - Low ultrasound frequency
- Risk of thermal effects of cavitation may be reduced by:
  - Using degassed water/gel and avoiding bubbles within the ultrasound beam path
  - Using high ultrasound frequencies
- Risks may be mitigated using cavitation detection
  - I.e. listening for broadband emission

Tissue Liquefaction with Histotripsy

Most clinically advanced focused ultrasound therapies use heat to destroy unhealthy tissue. Histotripsy is a non-thermal ultrasonic method that mechanically destroys target tissue using high intensity pulses from 2 to 20 microseconds in length. Histotripsy controls cavitation to mechanically fractionate soft tissue through high pressure (>10 MPa), short duration (<20 μs) ultrasound pulses at low duty cycles (<1%).

- Mechanical ablation with shock-induced microbubble clouds
  - Clinical trial to treat benign prostatic hyperplasia
- Need methods to monitor treatment progress
  - Limited heating observed with histotripsy
  - Need mechanical equivalent to thermal dose

Summary

High-Intensity Focused Ultrasound (HIFU) is a hyperthermia therapy procedure that applies high-intensity focused sonic energy to locally heat and destroy diseased or damaged tissue through ablation.

Temperature monitoring for a controlled therapeutic procedure can be provided by MRI (MRigHIFU).

MRigHIFU can be used to effectively deliver chemotherapy to tumors with temperature-sensitive liposomes.
Grant Support

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3. National Institute of Neurological Disorders and Stroke
4. American Institute of Ultrasound in Medicine (AIUM)
5. Philips Healthcare
6. University of Chicago Comprehensive Cancer Center (UCCC)

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