**Specialty area: MR Guided HIFU**

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**Highlights**

- The mechanical and/or thermal effects of ultrasound on tissue form the basis for a range of therapeutic ultrasound applications
- Therapeutic ultrasound can be delivered using endocavitary or extracorporeal transducers, and procedures can be guided by ultrasound imaging and/or MRI
- In MRI-guided high intensity focused ultrasound systems, MRI plays a crucial role for treatment planning and monitoring, and for the evaluation of treatment results
- Examples of current clinical applications of MRI-guided high intensity focused ultrasound are the thermal ablation of uterine fibroids and pain palliation for bone metastases. Translational research topics include applications in breast, prostate and brain and the transition towards applications in moving abdominal organs under continuous real-time image guidance

# Talk Title: Therapeutic Ultrasound Devices

**Target audience:** physicists, clinicians and technologists interested in MRI-guided therapy in general and MRI-guided HIFU in particular

**Purpose:** to provide an introduction to therapeutic ultrasound in general and MRI-guided HIFU in particular

## Introduction

Ultrasound (US), defined as sound waves with a frequency above the limits of human hearing (i.e. above 20 kHz), is best known for its use in diagnostic imaging. In US imaging, ultrasonic waves created using piezoelectric material are transmitted into the patient’s body from an acoustically coupled transducer. Reflections of the sound beam (echoes) travelling back to the transducer are picked up and used to create images mainly showing interfaces between tissue with different acoustic impedances and other structures in tissue that cause reflection of the beam [1]. In therapeutic ultrasound, the concept is not to produce such echoes for imaging, but to use the ultrasound beam to cause local therapeutic effects by some kind of physical interaction between the sound wave and the tissue. As US can interact with tissue in many ways, various bio-effects can be provoked that have a broad range of potential therapeutic applications. The combination of therapeutic US with an imaging modality like US imaging or MRI allows for precise local therapy delivery and monitoring of the therapeutic procedure. In this presentation, the general concept of image-guided therapeutic ultrasound devices is discussed and illustrated by examples of specific clinical and preclinical applications. Considering the focus of the course this presentation is in, the emphasis will be on the role of MRI for guidance of high intensity focused ultrasound (HIFU) procedures.

## Mechanical and thermal effects

Therapeutic ultrasound can interact with human tissue in several ways, depending on a range of ultrasonic parameters like the power used, the pulse duration, the frequency and the acoustic properties of the tissue. Mechanical effects include cavitation, which can be used in the field of local drug delivery for permeabilization of vessel walls [2], cell membranes [3], or even to cause mechanical tissue destruction [4] or a temporal opening of the blood-brain-barrier [5], which holds great potential for enhanced drug delivery in patients with brain disorders. The thermal effects of high intensity ultrasound, caused by the absorption of ultrasound energy in the tissue, are used in many therapeutic ultrasound applications. The bio-effect of increasing the tissue temperature depends on the temperatures reached, the duration of the temperature increase and the properties of the target tissue.

The concept of thermal dose, calculated from a measured time-temperature curve, can be used to quantify exposure of tissue to hyperthermic conditions [6]. Above a certain dose threshold, which depends on the tissue type [7], lethal damage is done to the tissue, which forms the basis for thermal ablation therapy. Interstitial and endocavitary HIFU transducers can produce ultrasonic beams that heat tissue in the area close to the transducer. Transrectal or transurethral probes are for instance used for treatment of prostate cancer [8, 9]. Also extracorporeal focused ultrasound transducers can be used to create thermal effects. By focusing the beam from a wide aperture transducer located outside the body of the patient in combination with adequate acoustic coupling to the patient, a focal area of high intensity ultrasound inside the patient can be created. When phased-array transducers with typically several hundreds to a thousand piezoelectric elements are used, the focus position can be rapidly steered electronically. With HIFU the intensity in the focal area can become high enough to cause a rapid local increase of the tissue temperature, while the heat deposition outside the focus is kept below the thresholds for thermal damage. This provides a means for non-invasive thermal therapy, by which tissue can either be rapidly thermally ablated or locally exposed to mild hyperthermia for a prolonged period of time.

### Devices

The general set-up for image-guided therapeutic ultrasound equipment consists of an ultrasound transducer, often consisting of many individual elements, an ultrasound generator and imaging equipment, most often based upon ultrasound imaging, MRI or both. Many types of transducers exist. The requirements of the application at hand determine what kind of transducer and sonication strategy can best be used. In general, imaging is used to target the area that needs to be treated and preferably also to monitor or even steer the treatment and to evaluate the treatment effects after the procedure.

### US and MRI-guided HIFU

Ultrasound imaging seems a natural choice for guidance of HIFU therapy, as it provides very rapid imaging of the target region. Ultrasonic monitoring of thermal treatment procedures by visualization of the ablated region or by measuring temperatures however is challenging. Although it is less rapid and much more expensive than US imaging, MRI is very well suited for image-guidance of thermal therapy with high-intensity therapeutic ultrasound [10]. The physical nature of ultrasound, i.e. a mechanical pressure wave travelling through tissue, does not interfere with the electromagnetic fields used in MRI. Therefore, US and MRI are intrinsically compatible. Using adequate filtering, HIFU equipment can be integrated into an MRI scanner. MRI's excellent soft-tissue contrasts are of particular value during the treatment planning stage, where high-quality tumor visualization in relation to organs or structures in the tumor's vicinity is crucial. During the therapy stage, MRI offers the possibility to measure tissue temperature non-invasively, by making use of the fact that several parameters influencing the MRI signal exhibit temperature dependence. The most commonly used MR thermometry technique uses the temperature dependence of the electron screening constant of water protons, resulting in a temperature dependence of the proton resonance frequency shift (PRFS) of water [11]. Also the relaxation times T1 and T2 show temperature dependence, which may be of particular interest when temperature measurements in fat are required [12-14]. Pulse sequences can be designed to acquire images that highlight variations in such temperature dependent parameters, thereby providing the possibility to measure temperature maps during thermal therapy. Such temperature maps may serve to monitor the heating process, i.e. to ensure adequate heat buildup in the target area, while preventing unwanted thermal damage to surrounding healthy tissue. It is also possible to use the MR temperature maps for automatic feedback controlled heating using the HIFU device, to ensure that a prescribed thermal dose is delivered to the target area, without overheating [15, 16]. After treatment, MRI can be used to visualize the therapeutic effect, for instance by using contrast-enhanced imaging to show the non-perfused volume after thermal ablation [17], or by using diffusion-weighted imaging for this purpose [18].

## Examples of clinical applications

In the clinic, MR-HIFU is currently mainly used for the ablation of benign uterine fibroids and also for palliation in patients with painful bone metastases. In patients with uterine fibroids, MR-HIFU provides a non-invasive alternative to other therapeutic options like surgical treatment or uterine artery embolization [19]. In patients suffering from painful bone metastases, MR-HIFU ablation of the pain-reporting nerves in the periosteal membrane may cause rapid pain relief [20]. Many other applications of MR-HIFU are currently in various stages of (pre)clinical development, many of them in the field of oncology, like the ablation of breast tumors using dedicated breast MR-HIFU systems [21, 22] and prostate cancer [23]. A lot of work is also dedicated to applications in the brain, where technological challenges lie in focusing the ultrasound beam through the intact skull [24]. Applications of MR-HIFU in the abdomen, like the treatment of liver metastases, require methods to deal with the motion and deformation of the target organs [25-27] and the partial obstruction of the target by the ribs [28], which requires new sonication strategies [29, 30].

## Conclusion

The biological effects that ultrasound can provoke in human tissue make it a very interesting therapeutic modality. The thermal effects induced by high intensity focused ultrasound are currently clinically used for ablation therapy, although also non-thermal, mechanical effects have great potential, especially in the field of drug delivery. Therapeutic ultrasound is best delivered under image guidance, for which ultrasound imaging and/or MRI can be used. MRI is well suited for this role, since it combines excellent soft-tissue contrasts with MR thermometry and other functional imaging methods that may be used to guide the procedure and to evaluate the therapeutic effects.

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