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THERAPEUTIC ULTRASOUND – EXCITING APPLICATIONS AND FUTURE CHALLENGES

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ABSTRACT. This paper presents an overview of the applications of ultrasound for the treatment of an ever-growing range of medical conditions. After presenting a brief history of the development of therapeutic ultrasound, the different mechanisms by which beneficial bio-effects are triggered will be discussed. This will be followed by a discussion of some of the more promising applications, some of which have already been licensed and introduced into the clinic. The case of liver tumour ablation will be discussed to demonstrate some of the engineering challenges that still need to be overcome before this technology finds wider uptake in the medical world.

INTRODUCTION

For the past three decades now ultrasound imaging has been one of the main pillars of medical diagnosis. Over the past decade however, the use of ultrasound for therapeutic purposes has been steadily growing. The thermal or mechanical effects of ultrasound have been used for mediating an impressive array of beneficial bio-effects, such as the ablation of tumours, the reversible opening up of cellular junctions and targeted drug release.

Currently, therapeutic ultrasound is being studied for the treatment of 50 different medical conditions at 316 research sites across the world. To date, more than 170,000 patients have been treated at clinical and commercial centres for a range of conditions including prostate cancer, uterine fibroids, brain disorders, breast cancer and palliation for bone metastases [1]. Regulatory approvals are now in place around the world for the treatment of 19 different conditions, and this list is fast growing. Despite this impressive volume of activity, there are still many scientific challenges that need to be overcome in order to fully utilise the potentials of this non-invasive, non-ionising form of therapy for an even wider range of conditions in the clinic.

BRIEF HISTORY

Therapeutic ultrasound has a long history going back to 1920s with the first observations of the bio-effects of ultrasound on living tissue [2]. In fact the earliest successful medical application of ultrasound was for deliberate tissue damage. The Fry brothers (William and Frank) working at the University of Illinois in the 1950s, concentrated high energy ultrasound into a small volume for destruction of specific regions of the brain, performing the first successful operation using ultrasound on a patient with Parkinson's disease [3]. At about the same time and working independently, Burov and Andreevskaya suggested the use of ultrasound for the destruction of cancerous tumors [4].

The early work was performed without effective guidance and monitoring of the procedures. The lack of good quality image guidance was the reason why despite the early promise of ultrasound as a therapy tool its progress into the clinic was extremely slow from the 1950s to the late 1980s. However, major advances in diagnostic imaging (MRI, CT and ultrasound) and monitoring techniques (MR thermometry) since the 1990s have given the field a major impetus [5, 6].

Today, there is Food and Drug Administration (USA) approval and Conformité Européenne (CE) marking for five treatments: destruction of uterine fibroids, destruction of stones in the urinary system by lithotripsy, ablation of prostate tumours, pain palliation for bone metastases and reduction of essential tremor. There are also over 40 on-going international clinical trials for a range of other medical conditions from oncological to cardiovascular and neurological.

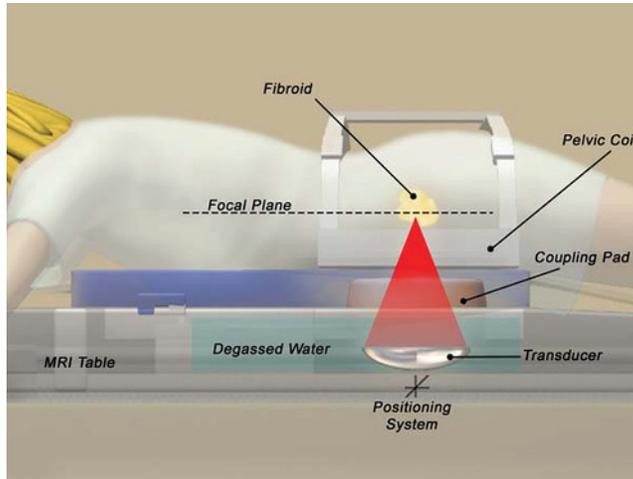


FIGURE 1. A method for focusing the ultrasound energy into the lower abdomen. The example here is using MR-guidance. (Courtesy of INSIGHTTEC Ltd.)

BASIC MECHANISMS

Ultrasound interactions with tissue and the resulting bio-effects can be clearly separated into two forms: thermal and mechanical.

Absorption of ultrasound energy by tissue can lead to very rapid and significant temperature rises as the average attenuation coefficient for normal soft tissue is approximately 0.54 dB/MHz.cm. Experimentally observed absorption in tissue, however, has the form $\alpha = \alpha_0 f^b$ where b is typically 1-1.5. Classical thermos-viscous absorption would yield a value of 2 for b . This departure from Stokes' law is because in biological media, there are a large number of internal relaxation processes, e.g., cell membrane rupture, protein denaturation, etc., contributing to the overall absorption of ultrasound energy. To achieve cell destruction through the denaturation of protein chains requires a temperature rise to $>56^\circ\text{C}$ and held for >1 s. Therapeutic ultrasound systems are designed to produce this temperature rise in a matter of milliseconds. This is achieved using high ultrasound power outputs and beam focusing using either low f -number lenses or large phased arrays that produce in-situ intensity values of more than 10 kW/cm^2 . For this reason ablation of tissue using ultrasound is often referred to as High Intensity Focused Ultrasound or HIFU. Table 1 shows a comparison of intensity and frequency values used for therapeutic ultrasound, as compared to those for diagnostic applications.

TABLE 1. Comparison of therapeutic and diagnostic ultrasound parameters. Diagnostic imaging intensities shown are based on FDA's safe levels for diagnostic ultrasound devices (FDA, 1987).

	Frequency	Intensity (I_{SPTA})	
Diagnostic ultrasound	1 – 18 MHz	Cardiac	420 mW/cm^2
		Peripheral vessel	720 mW/cm^2
		Ophthalmic	17 mW/cm^2
		Foetal imaging	94 mW/cm^2
Therapeutic ultrasound	0.3 – 5 MHz	400 to 12,000 W/cm^2	

The mechanical effects of ultrasound on tissue can be due to two different phenomena. The first phenomenon is the presence of an acoustic radiation force, which is a time-averaged forward force resulting from the change in the energy density of the propagating wave due to absorption. In viscous fluids (of which there are plenty in the body) this could set up a bulk flow, called acoustic streaming.

The other phenomenon is acoustic cavitation of gas/vapour bubbles, which can be either stable or inertial. Vapour or gas bubbles can be formed through the action of ultrasound either due to the boiling of blood/fluids or by drawing gas out of solution due to the high negative pressures of the ultrasound wave. Once bubble nuclei are formed, those of the right size are driven to oscillate in the ultrasound field. Again depending on the size of the bubble and the ultrasound protocol, these oscillations could be made to follow the acoustic pressure fluctuations (stable cavitation), or the bubble could be made to expand to an unstable size during a few negative pressure half cycles and then made to collapse violently when the pressure goes positive (inertial cavitation). Inertial cavitation is a very energetic process and has been seen to cause shock wave generation, rapid local temperature rises, tissue destruction and sonoporation. Stable cavitation has been seen to cause micro-streaming, in particular if the bubble is close to the surface of a membrane or vessel, thereby causing shear stresses to act on that surface.

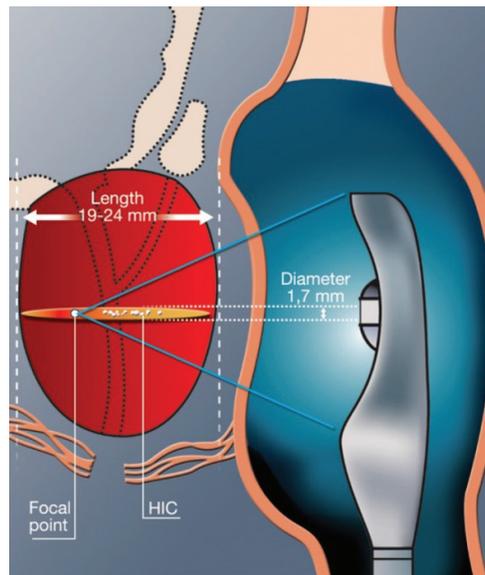


FIGURE 2. A trans-rectal HIFU probe for the treatment of prostate cancer. This device has a small phased array imaging probe at the centre of the HIFU transducer for providing ultrasound guidance. (Courtesy of EDAP TMS, France).

IMAGE GUIDANCE

Ultrasound therapy is a non-invasive medical procedure. Accurate targeting of the treatment site and monitoring of the intraoperative effects are essential for ensuring successful outcomes and avoiding damage to healthy, non-target sites, especially in high intensity applications. There are two imaging modalities currently available for clinical use: ultrasound and Magnetic Resonance Imaging (MRI).

Ultrasound imaging, using conventional scanners, is used extensively particularly in applications where costs are to be kept low. But although ultrasound can show the main anatomical features in the region of interest, it only shows successful ablation when hyperechoic changes appear in the image due to the formation of boiling bubbles. Tissue boiling of course happens at temperatures exceeding what is normally required to just destroy cells, which suggests that the region of interest is being over-treated.

MRI in comparison provides not only high quality images of anatomical features, but coupled with MR-thermometry, the operator can see a thermal map of the region of interest, pin-pointing the ultrasound beam focus which is superimposed onto the background anatomical features. On-line monitoring of the thermal field using MR thermometry thus provides feedback control of the therapy parameters [7]. MR guidance however is the more expensive option and could be subject to inaccuracies in the presence of organ motion and high fat content, or when near low signal tissues, such as bone.

EXAMPLES OF APPLICATIONS

Thermal Ablation

One of the most exciting applications of HIFU is for ablation of solid tumours. HIFU tumour ablations are either being performed routinely in the clinic (for prostate cancer and for uterine fibroids, which are benign tumours) or are the subject of on-going research and clinical trials for many other tumours in the abdomen, breasts, brain and bone. The least suitable targets are those in locations that contain a high air or gas content, such as in the lungs and bowels, due to strong reflections from any gas/tissue boundaries.

Raising the temperature of cells to about 56°C for 1s causes cell death through a process called coagulative necrosis. HIFU transducers can be designed to deliver sufficient energy into a small volume of about 1x10 mm to achieve the required thermal dose. Complete destruction of pathologic tissue can be achieved while leaving healthy tissue unaffected with sharply defined boundaries 2-3 cells wide. The non-invasive nature of HIFU means that this “bloodless” operation can potentially lead to fewer complications and shorter hospital stays and even be offered as an out-patient procedure.

One of the most effective applications of HIFU ablation to date is for the treatment of a debilitating neurological disorder called essential tremor. This disorder leads to uncontrollable shaking of different parts of the body, mainly the hands, arms and head. The conventional treatment involves inserting a probe into the brain through a hole in the skull and passing pulses of current via an electrode at the tip of the probe to disrupt the abnormal signal pathways in the brain responsible for causing the tremors. HIFU achieves the same result by creating a small lesion in the ventral intermediate nucleus of the thalamus to interrupt abnormal signaling, but without incisions in the skull or a craniotomy. The improvements to patients’ tremor scores can be seen in almost real-time [8]. Clinical trials are under way using the same method for Parkinson’s related tremors and other forms of dyskinesia [9].

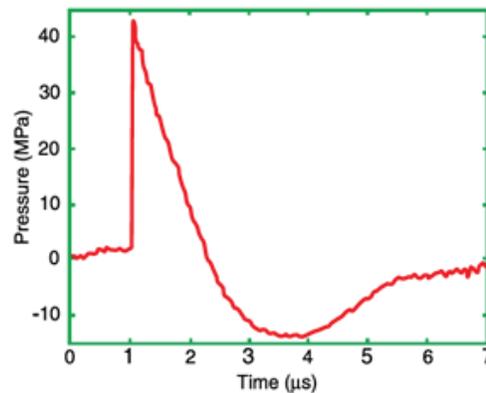


FIGURE 3. A typical shock wave pressure profile used for lithotripsy.

Mechanical Techniques

The longest clinically established method that uses the mechanical effects of ultrasound for therapy is lithotripsy that is used for the fragmentation of calcium-based stones in the urinary system. Shock-wave lithotripters use from 60 to 120 shocked wave pulses per minute with peak positive pressure amplitudes of up to 160 MPa to fragment the stones, mainly due to inertial cavitation at the proximal surface of the stone [10]. Most lithotripters these days use electromagnetic coil shock sources. An example of a shock wave pulse is shown in Fig. 3.

A very exciting development in recent years has been the discovery that exposure to focused ultrasound can temporarily open the Blood-Brain Barrier (BBB). The junctions between endothelial cells lining the walls of the blood vessels in the brain are more tightly arranged than in other parts of the body. The BBB is a natural defence against infections in the brain. The tight junctions of the blood vessels in the brain, however, also make the delivery of therapeutic drugs extremely difficult. There are a host of pathologies in the brain, ranging from malignant tumours such as glioblastomas to Alzheimer’s and Parkinson’s that can be potentially treated with

drugs, only if the drug particles could cross the BBB. The basic mechanism behind the temporary disruption of the BBB using ultrasound is thought to be cavitation [11]. But since bubble nuclei are not to be readily found in the brain, stabilised micro-bubbles (<10 µm in diameter) are introduced into the bloodstream prior to ultrasound exposure. The combination of HIFU and micro-bubbles is seen to reversibly and non-destructively open up the BBB to allow therapeutic agents to be delivered locally to the brain.

Thermo-Mechanical Techniques

Targeted drug delivery is an area of enormous interest in the medical field. The effectiveness of therapeutic agents is increased if the correct dose is delivered where they are needed in the body. This is of course a crucial requirement with chemotherapeutic drugs that are often delivered systemically by injection into the bloodstream. Not only a large fraction of the drug particles are often cleared by the renal and hepatic systems, but also the fact that the drug is taken up by many healthy organs causes severe side-effects due to the toxicity of these drugs even to normal cells.

Therapeutic ultrasound has recently shown great promise for the targeted release of therapeutic agents, often encapsulated in thermally-sensitive polymers or liposomes [12]. The encapsulation ensures that the drug stays within the blood vessels and its toxicity is contained. The thermal effect of ultrasound is used to raise the temperature of tissue over a pre-determined target volume to about 43°C. This is the phase transition temperature for liposomes, thus releasing the encapsulated drug exactly where it is needed, such as at the site of the tumour. However, this is a lower temperature than what would cause thermal damage to cells. Furthermore, stabilised micro-bubbles can also be co-administered with the encapsulated drug so that under the action of the same ultrasound field, after the drug is released from its liposome shell, cavitating bubbles and their mechanical effects are used to increase the amount of the drug extravasating from the blood vessels and even pump the drug further into the body of the tumour.

CASE STUDY

One of the hot topics in the field of HIFU is the ablation of cancerous liver tumors. The Ultrasonics Group at University College London, in collaboration with the Institute of Cancer Research and the University of Oxford, conducted a multi-faceted research project to overcome some of the obstacles that need to be removed, before this method of therapy is made available in the clinic to sufferers of this serious disease.

Liver tumours of interest to our study (whether primary or secondary metastases) could lie at depths of 4 to 20 cm below the skin surface and could be from 1 to 5 cm in diameter. The ultrasound beam is coupled through a circulating de-gassed water layer and has to go through overlying layers of skin, fat, peritoneum and muscle. But the biggest challenge is that a large volume of the liver is shadowed by the ribs. Ribs not only strongly reflect and diffract the ultrasound leading to possible hotspots in undesirable locations, but they also absorb a substantial fraction of ultrasound energy that would heat the ribs and lead to unwanted damage. The targeting of the tumour therefore needs to be mainly through the intercostal spaces. The other big challenge is the breathing motion, which by virtue of the connection between the liver and the diaphragm, not only causes substantial displacement of the target, but also changes the position of the ribs and the size of the intercostal spaces.

To overcome these problems, we developed an image-based treatment plan that not only optimises the phases and amplitudes of the drive signals on each element of a phased-array HIFU transducer for delivering the correct thermal dose at the target, but also allows for motion compensation by predicting the correct firing times based on a pre-operatively measured organ displacement map.

The transducer parameters were obtained using a constrained optimisation approach applied to a Boundary Element model of the ultrasound field propagation in tissue in the presence of the ribs [13]. The motion model for the liver was based on a non-rigid registration method applied to 4D CT scans of the subject described in [14]. We have now successfully demonstrated *in vivo* transcostal ablation of the liver in porcine subjects. The ablations were performed under ultrasound guidance. Rib-sparing and effective ablation of the target in the liver were thus achieved through model-based treatment planning.

TRENDS AND CONCLUSIONS

The many different mechanisms by which ultrasound can cause beneficial bio-effects in the body are being used in more and more medical applications. The number of positive outcomes in both laboratory based studies and in the clinic are growing at such a fast pace that keeping up with the latest developments becomes in itself a challenge. Today there are 75 different medical conditions for which therapeutic ultrasound is either being offered

as a treatment or is being actively investigated. There are now 14 commercial companies with approved ultrasound therapy equipment in clinical use and about 170,000 treatments have been provided worldwide. These numbers have grown from a handful less than a decade ago. The trend is very much upwards for an ever-increasing range of applications from oncology to targeted drug delivery and neurological disorders. But it would be accurate to say that the mechanisms by which some bio-effects are produced are still not completely understood and many scientific and technical challenges remain that can be addressed only through multi-disciplinary collaborations between engineers, physicists, clinicians and biologists.

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