Guest Editorial to the Special Issue on Therapeutic Ultrasound: Current Status and Future Directions

I. THERAPEUTIC ULTRASOUND: ON THE MOVE

Reports on the basic science and clinical applications of therapeutic ultrasound are rapidly increasing, especially during the last decade. This is best illustrated by Fig. 1, which shows the dramatic increase in the number of publications since 2002 (ISI Web of Knowledge. Keyword: High Intensity Focused Ultrasound. November 15, 2009). These publications cover a full range of research activities from the basic science of wave propagation and bioeffects, to device and technology development, to clinical studies, to post-treatment survival studies. Furthermore, the results are published in top engineering and medical journals (e.g., IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING, IEEE TRANSACTIONS ON ULTRASONICS, FERROELECTRICS, AND FREQUENCY CONTROL; Cancer Research, Radiology, Urology, Circulation, Stroke, etc.) in addition to journals dedicated to acoustics and ultrasonics (e.g., JASA, Ultrasound Medical Biology, Ultrasonics, Ultrasonic Imaging, etc.) Another demonstration of the increased momentum of the field is the heightened importance of the basic science and clinical applications of therapeutic ultrasound at major international meetings (e.g., IEEE Ultrasonics Symposium, IEEE EMBC, ASA, AIUM, ICA, ICU, and WFUM) in addition to a dedicated symposium starting in 2001 (Int. Symp. on Therapeutic Ultrasound, ISTU). The ISTU meetings are organized annually by the International Society for Therapeutic Ultrasound, which was founded in 2002. The 10th ISTU will be held in Tokyo in June 2010. In 2008, a meeting on MR-guided focused ultrasound surgery (MRgFUS) was held in Washington, DC and plans for holding a second meeting in the fall of 2010 are underway.

Therapeutic ultrasound research is moving rapidly in several clinical application areas. The field is led by a number of senior investigators who have sustained continuous activity for more than two decades, but is propelled by a relatively large number of young investigators including students and postdoctoral associates with bright career prospects. At this stage of rapid development phase, a special issue publishing some of the worldwide research activities with high potential impact in the field of therapeutic ultrasound should be valuable. We are pleased to bring this special issue to highlight the significant progress being made in the field of Therapeutic Ultrasound.

A. Current Status of Therapeutic Ultrasound Research

This special issue comes at an exciting juncture in the over 60-year history of therapeutic ultrasound, one in which progress is being made at a truly remarkable pace in clinical and preclinical research on a wide array of applications. To be specific, the overwhelming majority of research efforts in (and clinical applications of) therapeutic ultrasound are concerned with high intensity focused ultrasound (HIFU), which was first proposed in the 1940s with an impressive demonstration in vivo by the Fry brothers at the University of Illinois in the 1950s [1]. Another highly refined system for trackless lesion formation was developed at MIT by Lele [2] whose work spanned the whole range from technology development (e.g., coordinated multiple HIFU transducers), mechanisms and bioeffects (e.g., thermal enhancement by stable cavitation), monitoring using ultrasound and cavitation detection, and treatment planning. Lizzi et al. [3], [4] developed another refined system for ophthalmological applications, which included pulse-echo diagnostic transducer for guidance and extensive use of treatment planning. The vision of these pioneering efforts was the development of a truly noninvasive surgery by ablation of fine tissue structures (within the focal spot of a HIFU transducer) while sparing the intervening and surrounding tissue. In today’s health care environment, where the trend is definitely toward less invasive and less morbid surgical procedures, focused ultrasound provides a unique form of nonionizing radiation capable of producing highly localized therapeutic effects with or without the use of drugs or other adjuvants. For example, HIFU has been shown to produce “trackless lesions” in a variety of tissue targets without causing any damage to the intervening tissues in the path of the beam. These lesions can result from thermal effects (thermo-viscous absorption) or mechanical effects (cavitation) or a mixture of the two.

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1HIFU is widely, but not universally used, e.g., some authors use FUS to allow for both low and high intensity applications.
HIFU systems in clinical use today employ image-guided lesion formation for the routine treatment of prostate cancer [5], [6], uterine fibroids [7], and other tumors [8]–[10]. Based on clinical results from prostate cancer treatments from two commercially available systems, it is safe to say that HIFU surgery is here to stay. Indeed, judging by the ongoing research activities at leading institutions worldwide, the list of applications will expand beyond the treatment of cancer to cardiovascular applications, including sonothrombolysis [11], [12] and the treatment of atrial fibrillation [13]. Some of these applications utilize microbubble ultrasound contrast agents (UCAs), together with pulsed HIFU (pHIFU), in nonthermal applications for enhanced drug and gene delivery. In addition, research efforts in this important area increasingly use image-guided drug delivery (IGDD) techniques using ultrasound and other imaging modalities.

In summary, device and image-guidance technology developments for HIFU applications have advanced to the point of allowing routine clinical use with much development currently underway in research laboratories around the world. Thermal therapy applications of HIFU have been demonstrated clinically and efforts in this area have led to clinical devices with large number of applications on the horizon. Laboratory experience with drug and gene delivery is on the move with in vivo preclinical testing of a number of agents, delivery vehicles, and pHIFU release/activation protocols.

B. Scope of the Special Issue

Therapeutic ultrasound research activities have picked up the pace significantly during the last decade, especially with the apparent success of HIFU in the clinic. As recently as the mid 1990s, a handful of laboratories appeared to be working on complementary, but largely non overlapping, research problems related to therapeutic applications of HIFU and routine clinical use was still uncertain. The field has now moved to the point where numerous research laboratories are investigating various approaches to fairly well defined research problems, e.g., adaptive refocusing of HIFU beams, monitoring, image guidance, thermal and nonthermal use of HIFU or pHIFU, etc. Furthermore, we now have several research groups with global perspective on therapeutic ultrasound research; efforts spanning the whole range from device technology development, to treatment protocol, to monitoring, guidance and damage assessment. For this reason, it was felt that we only needed to issue a Call for Papers for the Special Issue without inviting specific authors to submit survey papers reflecting their perspective on one or more aspects of therapeutic ultrasound. It is indeed a pleasure to report that the response to the call for papers was gratifying in terms of the number of submissions and, more importantly, the range of activities described by the contributions. We have received 19 regular paper contributions that received at least one round of review by experts in the field. The quality and originality of each manuscript were the determining factors in accepting the 14 papers appearing in the special issue. It is hoped that the TBME readership will appreciate the breadth and depth of activities in this fast developing area of biomedical engineering research. The following paragraphs attempt to provide perspective and shed some light on one or more contributions of the papers accepted for publication in this special issue.

Progress toward routine clinical application of HIFU technology was hampered by, among other things, the lack of reliable noninvasive methods to monitor and control the therapeutic HIFU beam. This situation began to change in the 1990s with the advent of ultrasound [14] and MR [15] systems for monitoring and control of thermal therapy. By now, all clinically available HIFU systems rely on either diagnostic US or MRI for guidance and monitoring. In addition, almost all active research groups worldwide employ one or both of these modalities for guidance and monitoring. This special issue contains several papers that describe the use of imaging technology in guidance, monitoring, and control of HIFU treatments. The paper by Seip et al. describes a therapy imaging probe system (TIPS) for targeted ultrasound-mediated delivery of nanoparticles. The paper by Zheng and Vaezy describes a targeting method that utilizes backscatter (obtained using diagnostic US) for treatment planning in tissue ablation using HIFU. The paper by Owen et al. describes an interstitial dual mode array for imaging and therapy of liver tumors. The paper by Ballard et al. describes a dual-mode array system where images obtained using the DMUA are used for adaptive refocusing the HIFU beam to maximize the power deposition at the target while minimizing the power deposition at the ribs in transthoracic focusing applications, e.g., targeting liver and kidney tumors. The paper by Enholm et al. presents in vivo results on the application of a binary feedback control system for improved lesion formation in a MRgFUS system.

Advances in transducer technology have also played a key role in the increased acceptance of HIFU in the clinic. Piezocomposite technology for HIFU transducers was introduced in the early 1990s and led to the realization of a new generation of array transducers with reduced cross coupling allowing for improved field control and array efficiency [16]. Just as with diagnostic ultrasound systems, transducer technology will continue to play a key role in the advancement of therapeutic ultrasound technology for the foreseeable future. Two papers in this special issue deal directly with transducer technology for HIFU applications. The paper by Wong et al. describes the use of capacitive micromachined ultrasound transducer (CMUT) technology as HIFU sources. The paper by Song and Hynynen introduces a new approach for the design of large transducer arrays using existing PZT technology. However, the array design utilizes the lateral mode coupling rather than the usual longitudinal mode coupling. Other papers in the special issue describe applications that were enabled by improved transducer technology for high power applications, e.g., Gateau et al., Owen et al., and Ballard et al.

Ultrasound-mediated drug and gene delivery is an area that has received significant attention in recent years [17]–[19], thanks to advances in a number of enabling technologies, including transducers, imaging, and delivery vehicles with specific response to diagnostic and therapeutic ultrasound, e.g., US contrast agents (UCA), acoustically active liposomes, etc. This is an area with huge potential growth due to the unique advantages of ultrasound as a means for localized spatial and temporal...
control of the release mechanism(s) with some vehicles and/or tissue barriers. The special issue contains a number of papers addressing various aspects of ultrasound-mediated drug delivery. The paper by Choi and Konofagou et al. describes an in vivo study on the size dependence of UCA microbubbles in transient opening of the blood brain barrier. The paper by Seip et al. presents experimental results from image-guided ultrasound-mediated delivery of pDNA in murine models in vivo using their TIPS system. The paper by Kruse et al. describes the use of a two-array probe on a commercial diagnostic system for image-guided induction of mild hyperthermia suitable for drug delivery applications (using thermally-sensitive drug delivery vehicles).

Cavitation plays a significant role in therapeutic ultrasound applications, but its mechanisms in vivo have not yet been fully elucidated. Controlled cavitation, with and without the use of UCAs, may be a key to a wide range of therapeutic applications, including enhanced thermal therapy, drug and gene delivery, and targeted occlusion of blood vessels. This is an area where there is a need for both improved modeling to better understand the relevant phenomena and improved spatio-temporal monitoring of cavitation activities during HIFU exposure. This special issue contains a number of papers addressing cavitation-related phenomena in the context of therapeutic ultrasound. The complexities of observing and quantifying cavitation phenomena in vivo are illustrated by the research described in the paper by Miller et al. While the conclusions of this paper are somewhat weak, it presents an interesting experimental setup for generation and monitoring of cavitation activities by two separate diagnostic scanners. The paper by Farney et al. provides an experimental demonstration of the correlation between the temperature rise due to cavitation (i.e., above and beyond thermo-viscous absorption of the HIFU beam) and the measured cavitation power obtained using a passive cavitation detector during exposure. The paper by Gateau et al. describes an elegant approach to adaptive refocusing by inducing cavitation bubbles at the desired focus location. The signature echoes from the induced bubble are utilized in improving the quality of the therapeutic HIFU focus upon refocusing. This paper provides an example of indirect use of controlled cavitation to improve the therapeutic outcome by improving the quality of the HIFU focus in the presence of tissue heterogeneity (in this case for transcranial focusing). While not originally submitted for the special issue, the communication paper by Tang and Clement describes the use of random modulation of the HIFU beam in order to suppress standing waves in transcranial focusing. Standing waves at low frequencies have been associated with increased incidence of cavitation. This paper provides an example of methods for preventing the adverse effects of cavitation.

As we move forward in developing therapeutic applications of HIFU, we need to improve our understanding of the dynamics of lesion formation for a given HIFU or pHIFU protocol design. This requires the development of computational models for generating and predicting HIFU beam patterns. While this has been addressed before [20], it continues to be an important area with continued increase in the control of HIFU beam patterns (both arrays and drivers). The paper by Heikkilä et al. describes a multiphysics computational model for local harmonic motion (LHM) imaging-based monitoring of high intensity focused ultrasound surgery (FUS). In addition to computational methods, quality assurance phantoms suitable for visualization of the lesion formation process are necessary [21]. The paper by Park et al. describes a new reusable phantom for visualization of thermally induced HIFU lesions with settable temperature threshold for lesion boundaries.

Finally, no single special issue can capture all the research activities in an active field like Therapeutic Ultrasound. There is currently a significant body of publications in this area in other well respected journals. Recent publications as well as others currently in press describe methods and applications not addressed in this special issue, but are highly relevant. The interested reader is encouraged to survey the recent literature to assess the full scope of challenges and opportunities in the field of Therapeutic Ultrasound and its wide array of clinical applications.

C. Future Directions

The special issue papers represent a snapshot of the current status of therapeutic ultrasound research with contributions from a number of leading laboratories in the field. These contributions also provide a glimpse of the future directions toward the clinical deployment of image-guided therapeutic ultrasound systems for a variety of oncological, cardiovascular, and neurological applications.

The key to the widespread acceptance of noninvasive FUS will continue to be the improved imaging technology for the guidance, monitoring, and control of the therapeutic HIFU beam. Equally important is the development of HIFU and pHIFU protocols to manipulate tissue structures to achieve transient or permanent changes suitable to achieve the desired therapeutic end point, including ultrasound-mediated drug delivery. The accompanying issue of the IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING LETTERS contains some interesting contributions that point the way forward in therapeutic ultrasound research.

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to combine the regular papers and the letters in a single issue as this clearly increases the value of this special issue for years to come.

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REFERENCES


