TECHNICAL COMMITTEE REPORT

Biomedical Acoustics

Nathan McDannold

Postal:
Department of Radiology
Brigham and Women's Hospital
221 Longwood Avenue, Room 521
Boston, Massachusetts 02130
USA

Email:
njm@bwh.harvard.edu

The Technical Committee (TC) on Biomedical Acoustics (BA), one of the most diverse groups in the Acoustical Society of America (ASA), is composed of individuals whose interests cover a broad range of diagnostic and therapeutic applications or, more generally, the interaction of sound with biological materials. BA was formerly known as Biomedical Ultrasound/Bioresponse to Vibration. The BATC is concerned with the study of the interactions of acoustic waves with biological materials, including cells, tissues, organ systems, and entire organisms.

The areas of interest of members of the BATC include the diagnostic and therapeutic applications of acoustics in medicine, the biological effects of exposure to mechanical vibration and acoustic waves, acoustic propagation in biological materials, instrumentation, ultrasound field calibration, exposimetry and dosimetry, ultrasound contrast agents, medical image and signal processing, the characterization and processing of biological materials, ultrasonic characterization of bones, and acoustic-based physiological measurements. Acoustics-based imaging methods and therapies have potential applications, many of them only emerging in the last decade, that touch every conceivable medical condition, and it would be impossible to review all of them.

Topics discussed during BATC sessions include nonlinear acoustic propagation through different tissue structures, the design of phased-array transducers and driving electronics, the use of MRI to measure temperature during ultrasonic surgery, the use of lasers to generate acoustic waves, the delivery of genes or stem cells to the brain or heart, and the use of focused ultrasound to push around kidney stones. These diverse topics reflect the multidisciplinary makeup of the scientists and students who work in this area. Although the BATC is not the largest TC within the ASA and the associated areas of research are often represented in many other conferences, it remains a community for researchers who are interested in technically rigorous explorations of the application of acoustics in medicine. This core of acousticians makes the ASA a unique venue for scientists, students, and others who are interested in learning not only the newest applications but also the detailed acoustical principles that govern them. This aspect is sometimes missing in other conferences.

Imaging is one of the major general areas that is encountered at the BATC. Although ultrasound imaging has been a medical staple for decades, it is still a very active area of research and there are a growing number of different approaches that are advancing rapidly. One example is photoacoustics, where laser pulses are applied into the tissue and the resulting thermal expansion creates an acoustic wave that can be detected using a transducer or transducer array (Wang and Yao, 2016). Thus one can produce images using optical contrast with ultrasound, with the ability to penetrate deeper into the tissue than other approaches. This field has advanced greatly in recent years and is often represented in BATC sessions at ASA conferences. The use of acoustics to probe tissue elasticity is also an active area of research (Garra, 2015). Through cross-correlation of speckle patterns, one can measure minute displacements in the tissue produced by an external force. Recently, ultrafast ultrasound imaging has been employed to map shear waves in tis-

©2016 Acoustical Society of America. All rights reserved.

sues, giving clinicians new diagnostic information. The use of novel imaging methods with ultrasound contrast agents, e.g., preformed, shelled microbubbles that are injected intravenously, is also studied by several BATC members. In particular, novel uses of the inherent nonlinear response of microbubbles to acoustic waves are an evolving research topic.

The therapeutic use of ultrasound is another major area being explored by many BATC members. These devices focus high-intensity ultrasound into soft tissue to induce biological effects that arise from heating or mechanical effects that are primarily related to cavitation. Although this use of ultrasound has been investigated for more than 60 years, improvements in medical imaging have led to increased interest and visibility of this noninvasive technology in the last decade. It is a rapidly growing field, with several companies that have developed devices to treat practically every part of the body. Beyond the ASA, the field now supports an international society and an active nonprofit foundation (the Focused Ultrasound Surgery Foundation) that both hold well-attended meetings, with attendance that is growing every year.

Currently approved treatments use focused ultrasound to thermally ablate tumors or other tissues as alternatives to surgery or ionizing radiation. In the United States, treatments that ablate prostate tissue, uterine fibroids, and bone metastases are now approved for commercial use. In July 2016, ablation of a target in the brain to treat essential tremor was approved by the Food and Drug Administration. Multiple other treatments are currently being tested clinically with focused ultrasound ablation, including treatments for cancer in the breast, pancreas, and brain. The reader is pointed to the Web site of the Focused Ultrasound Surgery Foundation (www.fusfoundation.org) that has compiled an extensive list of hundreds of different applications of therapeutic ultrasound.

A new range of treatments is emerging that uses cavitation, the interaction of microbubbles and the acoustic field. These microbubbles can be created from gas nuclei present in tissues or are introduced systemically with the administration of microbubble-based ultrasound contrast agents. Because, unlike fluids, gas is strongly compressible, these microbubbles have an outsized response to even moderate acoustic intensities and can be used to enhance ultrasound therapies and to produce completely new applications. A particularly promising application of cavitation is the use of short ultrasound bursts at pressure amplitudes exceeding 10 MPa to disintegrate tissue. This treatment, termed "histotripsy," offers a significant reduction in treatment time, a current issue with thermal ablation, and improves the ability of using ultrasound imaging to monitor the procedure (e.g., Xu et al., 2007). Recent work has explored pressure amplitudes above the intrinsic threshold of water to induce cavitation with a single acoustic cycle. This approach leads to highly reproducible cavitation generation on a submillimeter scale (e.g., Vlaisavljevich et al., 2015).

Another exciting area in therapeutic ultrasound is the use of microbubbles or heat to enhance or trigger the delivery of therapeutic agents in the body (Kooiman et al., 2014). These approaches can direct the delivery of therapeutic agents to only the desired tissue targets or they can enable drugs to be delivered where they are currently restricted, such as in many tumors or in the central nervous system. Two approaches are used for ultrasound-induced drug delivery. One approach uses ultrasound to modify cellular membranes or vascular permeability to facilitate drug penetration. "Sonoporation," an alternative to the better known electropora-

- *Variable acoustics including low frequencies*
- *Bass frequency control is crucial for amplified music concerts*
- *Mobile solution available: aQtube®*

Flex Acoustics™
Any kind of acoustics at any time

aQflex™ : Revolutionary on/off sound absorption system

- Lowers RT (63 – 1000 Hz) by up to 45% at the push of a button
- a_{on} = app. 0.5 (63 – 1000 Hz) in entire ceiling area. a_{off} = app. 0.0
- Obtain sought-after low frequency control
- For music education, multipurpose concert halls, theatres etc.
- Complies with safety and fire regulations (B,s1 – d0 standard)
- Projects in Dubai, Germany, Finland, Denmark, Kuwait, Norway etc.
- Patents: EP 1 779375 B1, JP 2008 510408, US 7905323 etc.
- Engineered by Gerriets Germany

For more information please visit our website: www.flexac.com

tion, uses ultrasound and microbubbles to produce transient pores in cell membranes to enable the uptake of drugs or genes (Bouakaz et al., 2016). When preformed microbubbles (ultrasound contrast agents) are injected systemically, the microbubble-ultrasound interactions are focused on the blood vessels. This approach can be used to enhance the delivery of a thrombolytic agent into a blood clot or to directly break it up (Bader et al., 2016). In the central nervous system, microbubble-enhanced sonication can result in a temporary opening of the blood-brain barrier, which normally prevents most drugs from leaking out of the blood vessels (Burgess and Hynynen, 2016). At the May 2016 ASA meeting in Salt Lake City, we heard from a group in Norway who used a commercial ultrasound imaging system and a commercial ultrasound contrast agent to enhance the delivery of chemotherapy in patients with pancreatic cancer (Kotopoulis et al., 2013). In tumors, hyperthermia can increase blood flow and drug delivery.

Another approach for targeted drug delivery with ultrasound is to produce novel drugs or drug carriers to release a therapeutic payload on demand at specific targets (Sirsi and Borden, 2014). A number of researchers have developed drug-loaded microbubbles, echogenic liposomes, or perfluorocarbon emulsions that release their cargoes when sonicated. Others have developed agents that are heat sensitive. Thermosensitive liposomes are designed to undergo a phase change when a specific temperature is reached, enabling the rapid release of chemotherapy or other drugs to the desired targets.

Each of these treatments can have unique roles for acousticians and scientists in related fields at each stage of its development from concept to clinical use. For each treatment, we need to figure out how to safely deliver the acoustic energy into the tissue, how to select the parameters to ensure the correct bioresponse, how to monitor and control what we are doing, and how to ensure that the treatment is successful. BATC members bring expertise in theoretical and experimental acoustics, electrical engineering, imaging (ultrasound and otherwise), and control as well as in biology and drug development.

I hope that I have conveyed the breadth of research that is going on in relation to the biomedical applications of acoustics. My favorite part of the ASA and the BATC has been the supportive environment for students and young investigators. We all make an effort to be open and welcoming to students, providing an outlet for discussion and advice. We are an engaged and friendly group, and I encourage everyone to attend our open meetings that are held at every ASA conference.

Biosketch

Nathan McDannold is an associate professor in radiology at Harvard Medical School. He has been working in the Focused Ultrasound Laboratory at Brigham & Women's Hospital since 1996. His work has been primarily concerned with the development and implementation of ultrasound-based therapies, image-guidance methods, and clinical focused ultrasound treatments. In recent years, a main focus of his work has been studying the use of ultrasound for temporary disruption of the blood-brain barrier, which may allow for targeted drug delivery to the brain. Dr. McDannold received his PhD in physics from Tufts University in 2002.

References

Bader, K. B., Bouchoux, G., and Holland, C. K. (2016). Sonothrombolysis. *Advances in Experimental Medicine and Biology* 880, 339-364.

Bouakaz, A., Zeghimi, A., and Doinikov, A. A. (2016). Sonoporation: Concept and mechanisms. *Advances in Experimental Medicine and Biology* 880, 175-189.

Burgess, A., and Hynynen, K. (2016). Microbubble-assisted ultrasound for drug delivery in the brain and central nervous system. *Advances in Experimental Medicine and Biology* 880, 293-308.

Garra, B. S. (2015). Elastography: History, principles, and technique comparison. *Abdominal Imaging* 40, 680-697.

Kooiman, K., Vos, H. J., Versluis, M., and de Jong, N. (2014). Acoustic behavior of microbubbles and implications for drug delivery. *Advanced Drug Delivery Reviews* 72, 28-48.

Kotopoulis, S., Dimcevski, G., Gilja, O. H., Hoem, D., and Postema, M. (2013). Treatment of human pancreatic cancer using combined ultrasound, microbubbles, and gemcitabine: A clinical case study. *Medical Physics* 40, 072902.

Sirsi, S. R., and Borden, M. A. (2014). State-of-the-art materials for ultrasound-triggered drug delivery. *Advanced Drug Delivery Reviews* 72, 3-14.

Vlaisavljevich, E., Lin, K. W., Maxwell, A., Warnez, M. T., Mancia, L., Singh, R., Putnam, A. J., Fowlkes, B., Johnsen, E., Cain, C., and Xu, Z. (2015). Effects of ultrasound frequency and tissue stiffness on the histotripsy intrinsic threshold for cavitation. *Ultrasound in Medicine and Biology* 41, 1651-1667.

Wang, L. V., and Yao, J. (2016). A practical guide to photoacoustic tomography in the life sciences. *Nature Methods* 13, 627-638.

Xu, Z., Hall, T. L., Fowlkes, J. B., and Cain, C. A. (2007). Effects of acoustic parameters on bubble cloud dynamics in ultrasound tissue erosion (histotripsy). *The Journal of the Acoustical Society of America* 122, 229-236.