Introduction to the Special Issue on Ultrasound Contrast Agents and Targeted Drug Delivery

Targeted drug delivery (delivery of a drug to a spatially localized site in the human body) is one of the most ambitious goals of modern therapy. The strict localization of the pharmacological activity of a drug to the site of pathology would result in a significant reduction in systemic drug toxicity. This would enable the ability to deliver increased doses of drug to desired tissue, and thus would result in an increase in treatment efficacy and safety. Although a great amount of work is conducted worldwide on the research of various targeted drug delivery systems, clinical applications of site-targeted delivery are still very limited. In recent years, new promising possibilities for targeted drug delivery have been discovered based on the combination of ultrasound and microbubbles.

Ultrasound contrast agents are micrometer-sized encapsulated gas bubbles utilized for improved medical diagnosis. They are routinely injected into the bloodstream of the patient in order to increase blood–tissue contrast during an ultrasonic examination and thereby to improve the quality of ultrasonic images and the diagnostic confidence. The gas microbubbles are encapsulated to prevent them from coalescing and to prolong their circulation lifetime by reducing dissolution. Although microbubbles are used currently in clinical medicine as contrast agents, their potential extends far beyond imaging.

Part of the utility of microbubbles is that they can be readily modified for additional functionality. These spheres can be designed to carry drugs which can be released upon excitation with acoustic energy, or can be targeted by incorporation of ligands into the shell which can selectively adhere to specific sites in the human body. These capabilities, in combination with the effect known as sonoporation, provide great possibilities for localized drug delivery. Sonoporation is a process in which ultrasonically activated microbubbles, pulsating near biological barriers (cell membrane or endothelial layer), increase the barriers' permeability and thereby boost the penetration of external substances. In this way, drugs and genes can be delivered inside individual cells without serious consequences for the cell viability. Such a delivery system would likely be low-cost and portable, similar to other ultrasound technologies. Nevertheless, many questions remain regarding the fundamental understanding of the interaction between ultrasound waves, microbubbles, and biological entities (cells), and thus research in this field is still ongoing.

With this in mind, this special issue of the *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control* (UFFC) presents an opportune consideration of the research area in drug delivery using ultrasound and microbubbles.

The main objective of this special issue is to provide the ultrasound research community with a view on the latest research progress in the field of ultrasound contrast agents and targeted drug delivery. The first paper, from a renowned group (Erasmus University, Rotterdam, The Netherlands) in the field of microbubbles discusses a long history of theoretical modeling of the dynamics of contrast microbubbles. We believe that such a survey is a timely assessment of theoretical investigations in the field of contrast microbubble dynamics.

The second group of 4 papers discusses the mechanisms of drug release and uptake into cells and the underlying processes of ultrasound, microbubble, and cell interaction.

The following 3 papers provide concrete examples of drug delivery using ultrasound and microbubbles.

The last 2 papers concern the behavior of microbubbles in a confined space in the context of applications in therapy (sonothrombolysis) and imaging.

In closing, we would like to thank all the participants who have made this special issue possible. We are deeply grateful to the authors for their contributions and to the reviewers for their insightful and constructive comments. We thank IEEE TUFFC editors-in-chief Dr. Marjorie Yuhas and Dr. Steven Freear, who encouraged and guided us for this special issue. We also thank the editorial staff of the TUFFC for their efforts in editing and assembling this issue.

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Paul Dayton received his B.S. degree in physics from Villanova University in 2005, his M.E. degree in electrical engineering from the University of Virginia in 1998, and his Ph.D. degree in biomedical engineering in 2001, also from the University of Virginia. He pursued postdoctoral research and was later research faculty at the University of California, Davis. Much of Dr. Dayton's training was under the mentorship of Dr. Katherine Ferrara, where his initial studies involved high-speed optical and acoustical analysis of individual contrast-agent microbubbles. In 2007, Dr. Dayton moved to the Joint Department of Biomedical Engineering at UNC Chapel Hill and NC State University, Raleigh, where he is now Associate Professor and Associate Department Chair. Dr. Dayton is currently Associate Director for Education for the Biomedical Imaging Research Center, and his research interests involve ultrasound contrast imaging, ultrasound-mediated therapies, and medical devices. Dr. Dayton is a member of the technical program committee for IEEE UFFC, and a member of the editorial boards for the journals *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control* as well as *Molecular Imaging* and *Bubble Science, Engineering, and Technology*.