

# Acoustic Characterization of Contrast Agents for Medical Ultrasound Imaging

by

Lars Hoff

Contrast agents for medical ultrasound imaging is a field of growing interest. A large amount of literature has been published on the medical applications of such contrast agents. However, there is no textbook giving a broad overview of the physics and acoustics of the agents. This monograph aims to fill this gap.

The book is written by a physicist, from a physics point of view and it tries to draw links from physics and acoustics into the medical imaging methods, but medical applications are mainly included for background information.

The book consists of nine chapters. The first 3 chapters give a broad overview of the acoustic theory for bubble-sound interaction, both linear and nonlinear. Most contrast agents are stabilized in a shell, and this shell can have a strong influence on the interaction between the bubbles and the ultrasound. The effect of the shell is given special attention, as this is not easily found in other bubble literature. Chapters 4, 5, 6 and 7 describe experimental and theoretical methods used to characterize the acoustic properties of the agents, and results of studies on some agents. Chapter 8 shows how the theory and the experimental results can be combined and used to model various phenomena by means of computer simulations. The main purpose of the simulations is to get insight into the mechanisms behind the described phenomena, not to get accurate predictions and values.

The book is aimed at both newcomers into the field, as well as those who are more experienced, but want better insight into the acoustics of the contrast bubbles.

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**L. Hoff**



## **Acoustic Characterization Of Contrast Agents For Medical Ultrasound Imaging:**

*Acoustic Characterization of Contrast Agents for Medical Ultrasound Imaging* L. Hoff, 2013-06-29 Contrast agents for medical ultrasound imaging is a field of growing interest A large amount of literature has been published on the medical applications of such contrast agents However there is no textbook giving a broad overview of the physics and acoustics of the agents This monograph aims to fill this gap The book is written by a physicist from a physics point of view and it tries to draw links from the physics and acoustics to the medical imaging methods but medical applications are mainly included for background information The book consists of nine chapters The first three chapters give a broad overview of the acoustic theory for bubble sound interaction both linear and nonlinear Most contrast agents are stabilized in a shell and this shell can have a strong influence on the interaction between the bubbles and the ultrasound The effect of the shell is given special attention as this is not easily found in other bubble literature The following chapters 4 5 6 and 7 describe experimental and theoretical methods used to characterize the acoustic properties of the agents and results of studies on some agents Chapter 8 shows how the theory and the experimental results can be combined and used to model various phenomena by means of computer simulations The main purpose of the simulations is to get insight into the mechanisms behind the described phenomena not to get accurate predictions and values The book is aimed at both newcomers into the field as well as those who are more experienced but want better insight into the acoustics of the contrast bubbles

**Ultrasound Contrast Agents** Peter Johan Anton Frinking, 1999 *Acoustic Characterization of Ultrasound Contrast Agents with Lipid-coated Monodisperse Microbubbles* Yanjun Gong, 2013 Abstract Lipid coated microbubbles which have been widely used in diagnostic ultrasound as contrast agents also show promising applications in medical therapy The knowledge of acoustic behaviors and shell properties with respect to Ultrasound Contrast Agents UCA microbubbles can greatly enhance and extend their clinical applications A polydimethylsiloxane PDMS based microfluidic flow focusing device was fabricated to produce lipid coated microbubbles with narrow size distribution and controllable mean diameters 3 12 $\mu$ m These monodisperse microbubbles show unique acoustic properties compared with commercial UCA microbubbles with wide size distribution which makes it possible to investigate the relationship between microbubble size and attenuation coefficient resonance frequency or backscattering experimentally Our studies show that monodisperse microbubbles can be tailored for optimal contrast enhancement in ultrasound imaging By using an ultrasound spectroscopy method the frequency dependent attenuation coefficient for monodisperse microbubbles and polydisperse microbubbles were measured and compared The results showed that decreasing the width of the microbubble size distribution would lead to a reduction in the bandwidth and an increase in the magnitude of the attenuation spectrum The resonance frequency determined by the attenuation coefficient peak was inversely proportional to the mean diameter of the monodisperse microbubble suspension These conclusions corroborated the theoretical predications The dependence of resonance frequency on acoustic pressure and lipid composition

have also been examined and compared with theoretical calculations. The results demonstrated that the lipid shell of microbubbles behaves nonlinearly even at low pressure, which results in a decrease of resonance frequency as incident pressure is increased, approaching the resonance frequency of uncoated bubbles. Moreover, the length of the lipid hydrocarbon chain impacts the dependences of shell stiffness, attenuation coefficient, and resonance frequency on the excitation pressure. The frequency-dependent backscattering coefficients for monodisperse microbubbles have been investigated using a broadband pulses technique over different sizes, concentrations, and pressures. The experimental results showed the same size-dependent resonance peaks as the attenuation coefficient. It demonstrated that increasing the acoustic pressure caused a frequency shift of the resonance peak but no significant changes in magnitude. A linear dependence on microbubble concentration for the backscatter coefficient was confirmed. In addition, the pressure-dependent backscattering coefficients at 2.25 MHz were studied. It is interesting to note that with the increase of incident pressure, the change of backscattering coefficients values (increase or decrease) were strongly dependent on the mean size of microbubbles.

*Acoustic Characterization of Ultrasound Contrast Microbubbles and Echogenic Liposomes* Shirshendu Paul, 2014. Micron to nanometer-sized ultrasound agents like encapsulated microbubbles and echogenic liposomes are being actively developed for possible clinical implementations in diagnostic imaging and ultrasound-mediated drug/gene delivery. Contrast microbubbles (1–10 µm in diameter) contain a low-solubility gaseous core stabilized by an encapsulation made of lipids, proteins, polymers, and surfactants. Echogenic liposomes (ELIPs), which combine the advantages of liposomes such as biocompatibility and ability to encapsulate both hydrophobic and hydrophilic drugs with a strong reflection of ultrasound, are also excellent candidates for concurrent ultrasound imaging and drug delivery applications. The primary objective of this thesis is to characterize the acoustic behavior and the ultrasound-mediated content release of these contrast agents for developing multi-functional ultrasound contrast agents. The first part of this thesis reports the investigation of encapsulated microbubbles utilized as ultrasound contrast agents, whereas the second part reports the experimental characterizations of echogenic liposomes (ELIPs) and echogenic polymersomes. Contrast microbubbles are nonlinear systems capable of generating a subharmonic response (i.e., response at half the excitation frequency), which can improve image quality by providing a higher signal-to-noise ratio. However, design and development of contrast microbubbles with favorable subharmonic behavior requires accurate mathematical models capable of predicting their nonlinear dynamics. To this goal, strain-softening viscoelastic interfacial models of the encapsulation were developed and subsequently utilized to formulate a modified form of the Rayleigh-Plesset equation to model the nonlinear dynamics of these encapsulated microbubbles. A hierarchical two-pronged approach of modeling a model is applied to one set of experimental data to obtain the model parameters (material characterization), and then the model is validated against a second independent experiment, as demonstrated in this thesis for two lipid-coated Sonazoid and Definity and a few polymer (polylactide) encapsulated microbubbles. We performed in vitro

acoustic characterization with these contrast microbubbles i.e. determined the material properties of their encapsulations and compared model predictions with experimental observations. The nonlinear elastic models developed were successful in predicting several experimentally observed behaviors e.g. low subharmonic thresholds and compression only radial oscillations. Results indicate that neglecting the polydisperse size distribution of contrast agent suspensions a common practice in the literature can lead to inaccurate predictions and unsatisfactory results. Recent numerical investigations of the nonlinear dynamics of encapsulated microbubbles from our group contradicted previously published experimental results on the dependence of subharmonic behaviors on ambient pressure. We wanted to investigate this issue through new in vitro acoustic experiments by designing a modified experimental setup. Preliminary results indicate that the previously published conclusion that subharmonic response from contrast microbubbles linearly decreases with increasing ambient pressure might not be correct under all excitation conditions it may both increase or decrease under appropriate excitations in conformity with the results of numerical investigations. Experimental characterization of the ELIPs and polymersomes was performed with the goal of demonstrating their potential as ultrasound agents with simultaneous imaging and drug gene delivery applications dual purpose contrast agents. Carefully performed experiments conclusively demonstrate the ultrasound reflectivity echogenicity of the liposomes prepared using an established protocol. Although no subharmonic response from these ELIPs was observed altering the constituents of the lipid bilayer and polymerizing it generated a subharmonic response indicating that the echogenic properties of ELIPs can be controlled by altering the preparation protocol. Our results indicate that the freeze thaw cycle and lyophilization in presence of mannitol followed by reconstitution in a buffer was critical for generating echogenic response from these liposomes. A finite amount of mannitol above 100 mM proved critical for echogenicity but increasing the mannitol concentration above that amount did not change the echogenicity. Lyophilized powders create a polydisperse suspension of liposomes upon reconstitution which in turn results in a response without a distinct resonance peak. We believe that the echogenicity of the liposomes results from the larger diameter liposomes present in this polydisperse suspension. In spite of the conclusive experimental evidence of echogenicity the underlying mechanisms are not completely understood primarily due to the uncertainty regarding the exact location of the gas pockets. An accurate knowledge of the locations and dimensions of the gas pockets is critical for developing improved mathematical models of their acoustic behaviors. For the experimental validation of the concept of dual purpose contrast agents four novel formulations were investigated a lipopeptide conjugated ELIP formulation that can be triggered by the extracellular enzyme matrix metalloproteinase 9 MMP 9 a polymer coated redox triggered ELIP formulation for cytosolic drug delivery pH sensitive liposomes with tunable echogenicity capable of drug release in mildly acidic micro environment and redox sensitive echogenic polymersomes. Both in vitro acoustic studies and ultrasound imaging the latter performed in NDSU by our collaborators demonstrated the echogenicity of each of these formulations. Although ultrasound excitation

*Biomechanical*

*Systems Technology (A 4-volume Set): (2) Cardiovascular Systems* Cornelius T Leondes, 2007-11-12 Because of rapid developments in computer technology and computational techniques advances in a wide spectrum of technologies coupled with cross disciplinary pursuits between technology and its application to human body processes the field of biomechanics continues to evolve Many areas of significant progress include dynamics of musculoskeletal systems mechanics of hard and soft tissues mechanics of bone remodeling mechanics of blood and air flow flow prosthesis interfaces mechanics of impact dynamics of man machine interaction and more Thus the great breadth and significance of the field in the international scene require a well integrated set of volumes to provide a complete coverage of the exciting subject of biomechanical systems technology World renowned contributors tackle the latest technologies in an in depth and readable manner **Ultrasound contrast agents** Gaio Paradossi, Paolo Pellegrini, Andrea Trucco, 2010-07-16 Recent advancements in nano micro materials and related characterization approaches allow the design of a new type of ultrasound contrast agents UCAs with enhanced multifunctional behaviour This is chance is also supported by the recent achievements in modelling and signal processing This book provides the state of art of the research activity of two successful European projects TAMIRUT and SIGHT addressing an integrated system encompassing the contrast agent the hardware equipment and the processing strategies as a key tool for a combined diagnostic and therapeutic approaches theranostics in medical ultrasound The work provides a highlight of the state of art in the research of novel ultrasound contrast agents UCAs Main progresses on the multifunctional aspects of next generation UCAs concern targeting and drug release properties perfusion and biointerface behaviour ultrasound scattering performance signal processing electronic equipment *Biomechanical Systems Technology* Cornelius T. Leondes, 2007 Dealing with the field of biomechanics this book covers topics including dynamics of musculoskeletal systems mechanics of hard and soft tissues mechanics of bone remodeling mechanics of blood and air flow flow prosthesis interfaces mechanics of impact and dynamics of man machine interaction *Cavitation in Biomedicine* Mingxi Wan, Yi Feng, Gail ter Haar, 2015-08-29 This book offers a systematic introduction to the engineering principles and techniques of cavitation in biomedicine on the basis of its physics and mechanism Adopting an interdisciplinary approach it covers areas of interest ranging from physics and engineering to the biological and medical sciences Individual chapters introduce the fundamentals of cavitation describe its characterization control and imaging techniques and present cavitation enhanced thermal and mechanical effects and their applications Intended as both a reference work for graduate students and as a guide for scientists and engineers who work with cavitation in biomedicine it provides a broad and solid foundation of knowledge The aim is to bridge the different disciplines involved and to promote cross discipline research thus encouraging innovations in the scientific research and engineering applications alike Dr Mingxi Wan is a professor at Department of Biomedical Engineering Xi an Jiao Tong University Xi an Shaanxi China Dr Yi Feng works at Department of Biomedical Engineering Xi an Jiao Tong University Xi an Shaanxi China Dr Gail ter Haar is a professor at The Institute of Cancer

Research Sutton Surry UK      **Molecular Imaging** Brian D. Ross, Sanjiv S. Gambhir, 2021-08-03 The detection and measurement of the dynamic regulation and interactions of cells and proteins within the living cell are critical to the understanding of cellular biology and pathophysiology The multidisciplinary field of molecular imaging of living subjects continues to expand with dramatic advances in chemistry molecular biology therapeutics engineering medical physics and biomedical applications **Molecular Imaging Principles and Practice Volumes 1 and 2 Second Edition** provides the first point of entry for physicians scientists and practitioners This authoritative reference book provides a comprehensible overview along with in depth presentation of molecular imaging concepts technologies and applications making it the foremost source for both established and new investigators collaborators students and anyone interested in this exciting and important field The most authoritative and comprehensive resource available in the molecular imaging field written by over 170 of the leading scientists from around the world who have evaluated and summarized the most important methods principles technologies and data Concepts illustrated with over 600 color figures and molecular imaging examples Chapters topics include artificial intelligence and machine learning use of online social media virtual and augmented reality optogenetics FDA regulatory process of imaging agents and devices emerging instrumentation MR elastography MR fingerprinting operational radiation safety multiscale imaging and uses in drug development This edition is packed with innovative science including theranostics light sheet fluorescence microscopy LSPM mass spectrometry imaging combining in vitro and in vivo diagnostics Raman imaging along with molecular and functional imaging applications Valuable applications of molecular imaging in pediatrics oncology autoimmune cardiovascular and CNS diseases are also presented This resource helps integrate diverse multidisciplinary concepts associated with molecular imaging to provide readers with an improved understanding of current and future applications      *Biomedical Index to PHS-supported Research* ,1988      *Biomedical Sensors* Deric P. Jones, 2010 Sensors are the eyes ears and more Of the modern engineered product or system including the living human organism This authoritative reference work part of Momentum Press s new Sensors Technology series edited by noted sensors expert Dr Joe Watson will offer a complete review of all sensors and their associated instrumentation systems now commonly used in modern medicine Readers will find invaluable data and guidance on a wide variety of sensors used in biomedical applications from fluid flow sensors To pressure sensors To chemical analysis sensors New developments in biomaterials based sensors that mimic natural bio systems will be covered as well Also featured will be ample references throughout along with a useful Glossary and symbols list As well as convenient conversion tables      *The Journal of the Acoustical Society of America* ,2009      *3rd International Symposium on Therapeutic Ultrasound* ,2003      [Comprehensive Biomedical Physics](#) ,2014-07-25 **Comprehensive Biomedical Physics Ten Volume Set** is a new reference work that provides the first point of entry to the literature for all scientists interested in biomedical physics It is of particularly use for graduate and postgraduate students in the areas of medical biophysics This Work is indispensable to all serious readers in this interdisciplinary area where physics

is applied in medicine and biology Written by leading scientists who have evaluated and summarized the most important methods principles technologies and data within the field Comprehensive Biomedical Physics is a vital addition to the reference libraries of those working within the areas of medical imaging radiation sources detectors biology safety and therapy physiology and pharmacology as well as in the treatment of different clinical conditions and bioinformatics This Work will be valuable to students working in all aspect of medical biophysics including medical imaging and biomedical radiation science and therapy physiology pharmacology and treatment of clinical conditions and bioinformatics The most comprehensive work on biomedical physics ever published Covers one of the fastest growing areas in the physical sciences including interdisciplinary areas ranging from advanced nuclear physics and quantum mechanics through mathematics to molecular biology and medicine Contains 1800 illustrations all in full color

**Encyclopedia Of Medical Robotics, The (In 4 Volumes)** ,2018-08-28 The Encyclopedia of Medical Robotics combines contributions in four distinct areas of Medical robotics namely Minimally Invasive Surgical Robotics Micro and Nano Robotics in Medicine Image guided Surgical Procedures and Interventions and Rehabilitation Robotics The volume on Minimally Invasive Surgical Robotics focuses on robotic technologies geared towards challenges and opportunities in minimally invasive surgery and the research design implementation and clinical use of minimally invasive robotic systems The volume on Micro and Nano robotics in Medicine is dedicated to research activities in an area of emerging interdisciplinary technology that is raising new scientific challenges and promising revolutionary advancement in applications such as medicine and biology The size and range of these systems are at or below the micrometer scale and comprise assemblies of micro and nanoscale components The volume on Image guided Surgical Procedures and Interventions focuses primarily on the use of image guidance during surgical procedures and the challenges posed by various imaging environments and how they related to the design and development of robotic systems as well as their clinical applications This volume also has significant contributions from the clinical viewpoint on some of the challenges in the domain of image guided interventions Finally the volume on Rehabilitation Robotics is dedicated to the state of the art of an emerging interdisciplinary field where robotics sensors and feedback are used in novel ways to re learn improve or restore functional movements in humans Volume 1 Minimally Invasive Surgical Robotics focuses on an area of robotic applications that was established in the late 1990s after the first robotics assisted minimally invasive surgical procedure This area has since received significant attention from industry and researchers The teleoperated and ergonomic features of these robotic systems for minimally invasive surgery MIS have been able to reduce or eliminate most of the drawbacks of conventional laparoscopic MIS Robotics assisted MIS procedures have been conducted on over 3 million patients to date primarily in the areas of urology gynecology and general surgery using the FDA approved da Vinci surgical system The significant commercial and clinical success of the da Vinci system has resulted in substantial research activity in recent years to reduce invasiveness increase dexterity provide additional features such as image guidance and haptic

feedback reduce size and cost increase portability and address specific clinical procedures The area of robotic MIS is therefore in a state of rapid growth fueled by new developments in technologies such as continuum robotics smart materials sensing and actuation and haptics and teleoperation An important need arising from the incorporation of robotic technology for surgery is that of training in the appropriate use of the technology and in the assessment of acquired skills This volume covers the topics mentioned above in four sections The first section gives an overview of the evolution and current state the da Vinci system and clinical perspectives from three groups who use it on a regular basis The second focuses on the research and describes a number of new developments in surgical robotics that are likely to be the basis for the next generation of robotic MIS systems The third deals with two important aspects of surgical robotic systems teleoperation and haptics the sense of touch Technology for implementing the latter in a clinical setting is still very much at the research stage The fourth section focuses on surgical training and skills assessment necessitated by the novelty and complexity of the technologies involved and the need to provide reliable and efficient training and objective assessment in the use of robotic MIS systems In Volume 2 Micro and Nano Robotics in Medicine a brief historical overview of the field of medical nanorobotics as well as the state of the art in the field is presented in the introductory chapter It covers the various types of nanorobotic systems their applications and future directions in this field The volume is divided into three themes related to medical applications The first theme describes the main challenges of microrobotic design for propulsion in vascular media Such nanoscale robotic agents are envisioned to revolutionize medicine by enabling minimally invasive diagnostic and therapeutic procedures To be useful nanorobots must be operated in complex biological fluids and tissues which are often difficult to penetrate In this section a collection of four papers review the potential medical applications of motile nanorobots catalytic based propelling agents biologically inspired microrobots and nanoscale bacteria enabled autonomous drug delivery systems The second theme relates to the use of micro and nanorobots inside the body for drug delivery and surgical applications A collection of six chapters is presented in this segment The first chapter reviews the different robot structures for three different types of surgery namely laparoscopy catheterization and ophthalmic surgery It highlights the progress of surgical microrobotics toward intracorporeally navigated mechanisms for ultra minimally invasive interventions Then the design of different magnetic actuation platforms used in micro and nanorobotics are described An overview of magnetic actuation based control methods for microrobots with eventually biomedical applications is also covered in this segment The third theme discusses the various nanomanipulation strategies that are currently used in biomedicine for cell characterization injection fusion and engineering In vitro 3D cell culture has received increasing attention since it has been discovered to provide a better simulation environment of in vivo cell growth Nowadays the rapid progress of robotic technology paves a new path for the highly controllable and flexible 3D cell assembly One chapter in this segment discusses the applications of micro nano robotic techniques for 3D cell culture using engineering approaches Because cell fusion is important in numerous biological events

and applications such as tissue regeneration and cell reprogramming a chapter on robotic tweezers cell manipulation system to achieve precise laser induced cell fusion using optical trapping has been included in this volume Finally the segment ends with a chapter on the use of novel MEMS based characterization of micro scale tissues instead of mechanical characterization for cell lines studies Volume 3 Image guided Surgical Procedures and Interventions focuses on several aspects ranging from understanding the challenges and opportunities in this domain to imaging technologies to image guided robotic systems for clinical applications The volume includes several contributions in the area of imaging in the areas of X Ray fluoroscopy CT PET MR Imaging Ultrasound imaging and optical coherence tomography Ultrasound based diagnostics and therapeutics as well as ultrasound guided planning and navigation are also included in this volume in addition to multi modal imaging techniques and its applications to surgery and various interventions The application of multi modal imaging and fusion in the area of prostate biopsy is also covered Imaging modality compatible robotic systems sensors and actuator technologies for use in the MRI environment are also included in this work as is the development of the framework incorporating image guided modeling for surgery and intervention Finally there are several chapters in the clinical applications domain covering cochlear implant surgery neurosurgery breast biopsy prostate cancer treatment endovascular interventions neurovascular interventions robotic capsule endoscopy and MRI guided neurosurgical procedures and interventions Volume 4 Rehabilitation Robotics is dedicated to the state of the art of an emerging interdisciplinary field where robotics sensors and feedback are used in novel ways to relearn improve or restore functional movements in humans This volume attempts to cover a number of topics relevant to the field The first section addresses an important activity in our daily lives walking where the neuromuscular system orchestrates the gait posture and balance Conditions such as stroke vestibular deficits or old age impair this important activity Three chapters on robotic training gait rehabilitation and cooperative orthoses describe the current works in the field to address this issue The second section covers the significant advances in and novel designs of soft actuators and wearable systems that have emerged in the area of prosthetic lower limbs and ankles in recent years which offer potential for both rehabilitation and human augmentation These are described in two chapters The next section addresses an important emphasis in the field of medicine today that strives to bring rehabilitation out from the clinic into the home environment so that these medical aids are more readily available to users The current state of the art in this field is described in a chapter The last section focuses on rehab devices for the pediatric population Their impairments are life long and rehabilitation robotics can have an even bigger impact during their lifespan In recent years a number of new developments have been made to promote mobility socialization and rehabilitation among the very young the infants and toddlers These aspects are summarized in two chapters of this volume *Medical Imaging*, 2005

Encyclopedia of Medical Devices and Instrumentation, Radiotherapy, Heavy Ion X-Rays, Production of John G.

Webster, 2006-04-07 The articles in The Encyclopedia of Medical Devices and Instrumentation focus on what is currently

useful or is likely to be useful in future medicine They answer the question What are the branches of medicine and how does technology assist each of them Articles focus on the practice of medicine that is assisted by devices rather than including for example the use of drugs to treat disease The title is the only resource on the market dealing with the subject in encyclopedic detail Accessible to practitioners with a broad range of backgrounds from students to researchers and physicians Articles cover the latest developments such as nanotechnology fiber optics and signal processing **Therapeutic Ultrasound**  
Gregory T. Clement,Nathan J. McDannold,Kullervo Hynynen,2006-06-05 Boston Massachusetts 27 29 October 2005  
Chemical Abstracts ,2002 **Journal of Diagnostic Medical Sonography** ,2002

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