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Modeling and Characterization of Ultrasound Contrast Agents

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INTRODUCTION

Contrast agent imaging is based on exciting small gas-filled microbubbles by an ultrasonic pulse, and receiving the sound radiated from these microbubbles. The bubbles' response to ultrasound can be highly nonlinear, causing complicated but interesting effects. Examples are echoes at the harmonics of the transmitted frequency, differences between positive and negative pressure half-cycles, and subharmonics.

This presentation will review some of the physics involved in bubble-ultrasound interactions. It starts with an overview over various bubble models, adds the effect of an encapsulating shell, and finishes by describing a computer simulation program that models the response of contrast agent bubbles to ultrasound pulses.

BUBBLE MODELS

Several models have been proposed for the response of a bubble to a driving ultrasound pulse. The first studies date back to Lord Rayleigh [1], who in 1917 looked at cavitation around ship propellers. Later, in 1933, Minnaert [2] published a combined experimental and theoretical study of the sound emitted from bubbles, explaining their characteristic resonance frequency. Studies from the 1940s until today have introduced more sophisticated models for oscillating bubbles.

A bubble in a sound field is a highly nonlinear system. The bubble oscillation depends on the driving sound field in a complicated manner, where a change in the sound amplitude not only changes the amplitude of the oscillations, it also changes their shape. The high nonlinearity makes modeling of bubble responses more difficult than what should first be expected from such a simple system. However, the strong nonlinearity also opens possibilities for new imaging methods, methods that enhance the contrast agent echoes above the echoes from tissue. *Harmonic imaging* and *Pulse Inversion Imaging* are probably only the first of a number of imaging methods utilizing the strong nonlinearity of the bubble.

The most commonly used model for sound-bubble interaction is the *Rayleigh-Plesset* equation, describing a bubble in an incompressible liquid. The Rayleigh-Plesset model works very well in most situations, but the assumption of incompressibility causes damping from sound radiation to be ignored. This is compensated for in the models by Trilling [3] and Keller et al. [4,5], who included liquid compressibility to the first order in the acoustic Mach-number M. However, these models cause problems for high Mach-numbers, i.e. $M \geq 0.5$. Here, these models over-compensate for liquid compressibility, giving negative inertia terms and causing the equations to become computationally unstable. It may be commented that at such high Mach-numbers, these models are invalid anyway. However, a bubble will often experience a high wall velocity in the short compressional phase of the oscillation, which constitutes a very small fraction of the total bubble oscillation period. A model that is inaccurate only during this short fraction of the oscillation may still be useful. A model for large amplitude bubble oscillations that includes nonlinear effects in the liquid is due to Gilmore [6].

A compromise between these approaches is using a modified Rayleigh-Plesset model that includes the radiation damping term from the Trilling and Keller models, but omits the correction terms of first-order in the Mach-number. This model includes damping from sound radiation, but avoids the unphysical negative inertia and associated numerical instability problems of the Trilling or Keller models. This modified Rayleigh Plesset equation is able to model the bubble-sound interaction for most realistic situations in ultrasound contrast agent imaging, and the resulting equations are numerically stable and easy to implement using standard numerical software packages.

SHELL MODELS

Most contrast agent bubbles are encapsulated in a shell. The shell has two major effects on the oscillation and scatter of sound from the bubble. First, the shell makes the bubble stiffer than a free gas bubble of equal size. This causes the resonance frequency of the shell-encapsulated bubble to be higher than for the free bubble, and it limits the oscillation amplitude, possibly reducing nonlinear effects. Secondly, the shell makes the bubble more viscous. This causes more of the absorbed sound energy to be converted to heat instead of being reradiated, thereby reducing the scatter to attenuation ratio of the bubble.

Our studies indicate that for most contrast agents, the shell has major influence on the acoustic properties of the microbubbles, the acoustic properties of the agent are in fact dominated by the shell.

Various shell models have been proposed. Fox and Herzfeld [7] studied bubbles in sea water, and came up with a model for the influence of organic shells on the oscillations of such bubbles. De Jong et al. [8,9] have published empirical models for the influence of the shell on oscillations of Albunex. In 1995, Church [10] published a more well-founded model for the shell, based on a visco-elastic model. The nonlinear response of the shell is not known. Church's model assumes linear material properties but includes nonlinear geometry effects. Angelsen et al.[11] proposed an exponential stress-strain relationship for the shell. The stress-strain relationship of the shell may also be assumed to be linear. A discussion of these shell models, together with the resulting equations, is given by Hoff [12].

ESTIMATION OF SHELL MATERIAL PROPERTIES

The material properties of the shell are in general not known, and must be determined from experiments. The models used here describe the shell as an incompressible solid, as proposed by Church. Hence, the shell is characterized by two material parameters: The shear modulus G_S and the shear viscosity h_S. The values of G_S and h_S have been estimated from ultrasound attenuation measurements. The parameters can in general be frequency dependent, and the estimation is done in the frequency range used in medical ultrasound imaging, i.e. between approximately 2 and 8 MHz. The method used is due to de Jong et al. [8,9], as described by Hoff et al. [12]. Short ultrasound pulses are transmitted through a suspension of contrast agent, and the resulting attenuation spectra are calculated by Fourier Transform. The attenuation spectra are also calculated theoretically from size-distributions measured with a Coulter Multisizer. Values of the shear modulus G_S and the shear viscosity h_S are then estimated by varying these parameters to a best fit between measured and calculated spectra is obtained.

We have investigated several contrast agents by this method, including *Albunex* and *Sonazoid*. All the agents have a resonance frequency that is higher than predicted for gas bubbles of the same size. The increased resonance frequency is caused by the increased bubble stiffness due to the shell, and this effect is the basis for estimating the shell material properties. We have found large variations in shell stiffness between different contrast agents.

The described method gives estimates for the shell stiffness in the linear oscillation range, i.e. for small amplitude oscillations. It does not give any information about the nonlinear stress-strain relationship of the shell, this must be added using an *ad hoc* model. In the following, the exponential shell model of Angelsen et al. [11] is used.

IMPLEMENTATION OF BUBBLE OSCILLATION MODELS

The bubble and shell models are combined to give a nonlinear ordinary differential equation, ODE, for the gas-shell-liquid system that makes up one contrast agent bubble. The driving sound field is modeled as a typical imaging ultrasound pulse, described by frequency, amplitude, and pulse length and shape. An expression for the pressure radiated from the bubble is found from the basic equations of motion.

The resulting set of equations has been implemented as a simulation model using *Matlab* (The Math Works Inc.). The aim of this is to provide an easy to use software package that can rapidly and reliably predict the contrast bubble's oscillation and the resulting echo, for a specified driving ultrasound pulse. The simulation program is operated from a graphical user interface where properties of the bubble and of the ultrasound pulse are specified. The contrast agent bubble is described by its diameter and shell properties. The ultrasound pulse is described by its frequency, amplitude, shape, and length. For the selected bubble and pulse, the oscillation radius is simulated numerically using a standard ODE solver, and the echo is then calculated from the oscillation. Results are plotted graphically, or stored as *Matlab* vectors for later analysis. Using a modern personal computer, i.e. a 500 MHz Pentium III, the required calculation time is typically less than one minute for standard ultrasound pulses. However, this time depends greatly on the pulse length and amplitude. The programs may also be run from a batch-file. This is useful for larger studies, investigating several bubble diameters and pulse parameters.

The simulation program has been used to simulate a wide range of effects present in contrast agent imaging, such as harmonics of the driving frequency (*Harmonic Imaging*), pulses with inverted polarity (*Pulse Inversion Imaging*), amplitude dependence in the received echoes, and sub- and ultraharmonics. The simulations show good agreement with experimental observations.

SUMMARY

Various bubble models are reviewed. A Rayleigh-Plesset equation modified to include radiation damping is chosen, as this gives realistic physics while being computationally simple and stable. The shell is described using Church's visco-elastic model, with the exponential stress-strain relationship proposed by Angelsen et al.. Shell material parameters are estimated using the methods by de Jong et al. and Hoff et al.. The resulting equations have been implemented in a simulation program. This program calculates the oscillation and scattered echoes for specified contrast agent bubbles and driving ultrasound pulses, using easy to operate graphical user interfaces.

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