MODELLING THE EFFECT OF SHELL THICKNESS ON HIGH FREQUENCY ULTRASOUND SCATTERING FROM ULTRASOUND CONTRAST AGENTS

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1. INTRODUCTION

Ultrasound contrast agents (UCAs) are gas-filled, encapsulated bubbles that are administered intravenously to the venous system. They are very small (< 8 microns) which enables them to pass through capillaries. UCAs have a high degree of echogenicity compared to a cell, and therefore they enable contrast between the blood vessels and the surrounding tissue.

Few studies (Moran et al. 2002; Goertz et al. 2005; Ketterling et al. 2007) have looked at the dynamic response and backscatter of UCAs at high frequency ultrasound (HFUS). While some authors reported backscatter from UCAs with no harmonic components when insonicated at a transducer central frequency equal to the resonance frequency of the UCA (Moran et al. 2002), others (Goertz et al. 2005) observed the presence of harmonics in the backscatter of a lipid-shelled UCA, Definity (Bristol-Myers Squibb, North Billerica, MA), at low pressure (0.49 MPa). The results reported by Goertz et al. (2005) are unanticipated since high pressure is required to produce a non-linear response from UCA and generate harmonics in the backscatter. Ketterling et al. (2007) reported the presence of subharmonics in the response of a polymer-shelled UCA, Point (POINT Biomedical, San Carlos, CA), at high pressure (5.9 MPa). However, the experimental subharmonic response occurs at somewhat lower pressure amplitude than the theoretical response.

Analytical solutions to the problem of wave scattering from spherical objects such as ultrasound contrast agents have been studied extensively in the past (De Jong et al. 1993; Church 1995). These solutions are based on the Rayleigh-Plesset equation or variants and can only predict resonance frequencies at which the UCAs undergo radially symmetric oscillations. They cannot easily account for features such as asymmetric bubble oscillations and the interactions of bubbles with their surroundings.

Finite-element analysis (FEA) combined with other numerical techniques, such as the boundary element method, infinite elements, T-matrix method, etc. have been used in the past to model acoustic scattering from various objects submerged in a fluid (Hunt et al. 1975). The scatterer was typically modeled using finite elements while other techniques were used to find the solution in the surrounding medium. Most of these studies concentrated on scattering from rigid objects (Hunt et al. 1975).

In this work, we introduce a 2-D axi-symmetric finite element scattering model that allows asymmetric bubble oscillations and models the interaction of the bubble shell with the incident pressure wave using the constitutive stress-strain relationship coupled to the Helmholtz equation.

2. METHODS

The COMSOL Multiphysics package (COMSOL, Inc., Burlington, MA) was used to develop a 2D axi-symmetric finite element model to study scattering from contrast agents subject to high frequency ultrasound. The UCA was located in the centre of the computational domain with different acoustic properties than those of the surrounding fluid. The scatterer is insonified by a plane wave travelling is the $+z$ direction. Due to the symmetric nature of the problem, the 3-D model can be simplified by a 2-D axi-symmetric, with the z-axis being the axis of the symmetry. This simplification was used since 2-D models require less computational resource and execution times when compared to 3-D models (Falou et al. 2005). The Helmholtz equation was used to describe the propagation of sound waves in the UCA gas core and the surrounding fluid medium. The constitutive equation for the elastic material was used to describe the stress-strain relationship in the UCA shell.

Table 1. Physical properties of the BR14 ultrasound contrast agent (Dollet et al. 2008)

Property	Value
Shell density	1100 Kg/m^3
Shell's Young's modulus	177.6 MPa
Shell's shear modulus	60 MPa
Shell's Poisson's ratio	0.48
Perfluorocarbon density	11.21 Kg/m^3
Perfluorocarbon speed of sound	100 m/s

A perfluorocarbon phospholipid-coated contrast agent known as BR14 (Bracco Research SA, Geneva, Switzerland) surrounded by water was used to validate the finite element model by comparing the resonance frequency predicted by both the finite element model and the analytical Church formulation (Church 1995). This contrast agent was chosen it since it is widely used and has been the subject of research by many investigators (Goertz et al. 2003). Table 1 gives the physical the physical properties of BR14 used in the Church and finite element model. The surface tensions at both the shell-gas and the shell-liquid interfaces were assumed to be negligible. For simplicity, the finite element model does not take into account the viscosity of the shell and the surrounding medium. Initially, the far-field backscatter response of a 5 μm BR-14 having a 3 nm phospholipid shell thickness was considered. Then scattering from 25 nm, 125 nm, and 250 nm shelled UCAs were studied at 1 – 70 MHz.

3. RESULTS

Table 2 shows a comparison between the resonance frequencies predicted by the Church and the finite element models for 3, 25, 125, and 250 *n*m shell UCAs. Fig 1 illustrates the effect of changing the shell thickness on the backscatter response from the UCAs.

Table 2. Comparison between the resonance frequencies predicted by the Church and the FEA models.

Shell thickness (nm)	Church Model (MHz)	FEA Model (MHz)	% error
3	2.3	2.2	4.4
25	5.6	5.4	3.6
125	12.4	12.1	2.4
250	18	17.6	2.2

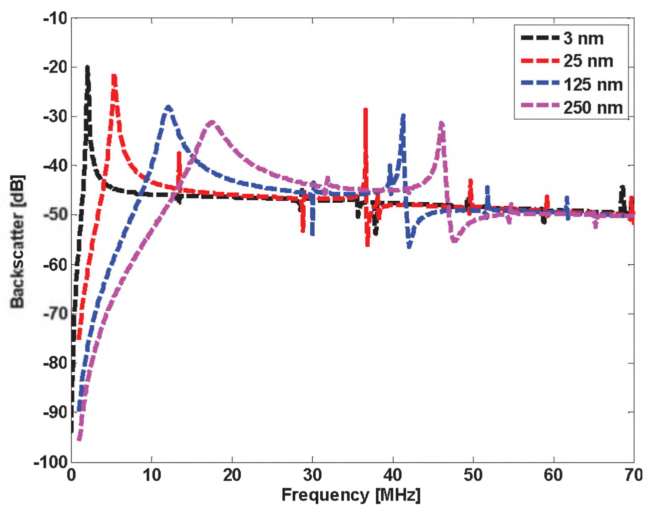

Fig. 1. Backscatter [dB] vs. Frequency [MHz]: effect of changing the shell thickness.

4. DISCUSSION AND CONCLUSIONS

The developed 2-D model has several advantages over conventional 3-D models we have previously developed for studying UCAs behaviour. It requires much less computational resources and execution times and can be used to calculate all quantities of interest, such as stresses and strains at the surface of the UCA, surface modes, etc.

A good agreement (error < 5%) was found between the finite element and analytical solutions (Church model) of the UCA resonance frequencies (the radially symmetric monopole resonance, the first peak in figure 1). Increasing the shell thickness increased the monopole resonance frequency (5.4 MHz, 12.1 MHz, and 17.6 MHz for the 25 nm, 125 nm, and 250 nm shelled UCAs, respectively) and broadened the resonant peaks. The finite element model revealed the presence of a second resonant peak of comparable magnitudes for the BR14 UCA. The frequency of the second peak also increased with shell thickness. Only one dominant resonant peak was found for the 3 nm shell thickness UCA within the studied frequency range. The presence of other resonant peaks in the backscatter from the 25 nm, 125 nm, and 250 shelled UCAs may be used to enhance the effectiveness of the ultrasonic imaging systems at high frequencies. It may also contribute to the generation of harmonics. This may provide an explanation to the presence of harmonics in the backscatter of the Definity UCA at low pressure (Goertz et al. 2005), where non-linear behaviour of the contrast agent is unlikely to occur. This study also shows that more careful design approaches may be taken to maximize the backscatter response from UCAs at high frequencies. This can be achieved by using the developed finite element model to optimize the UCA parameters in order to obtain the desired results. Future work includes the use of the developed model for the optimization of UCAs for high frequency ultrasound imaging.

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