Models of Ultrasound Contrast Agents

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Abstract

Traditional medical ultrasonography uses the backscattering of acoustic signals from tissue to investigate an object of interest. Microbubble contrast agents, which are usually administered intravenously into a patient’s circulatory system, were first approved for clinical studies in 1991. Modern contrast agents are a gas filled microbubble, which may be preformed with a shell of, for example, lipid, polymer or albumin. Contrast agents enhance backscatter, due to the high compressibility of the gas, relative to body tissue.

The oscillatory response of a microbubble to an applied ultrasound field is complicated and frequency dependent. The bubble has a size dependent linear resonance frequency. Typically the contrast agent diameter is 1-10 µm and resonant frequencies are in the 2-15 MHz range, which is the range used for clinical applications. As the amplitude of the driving pressure field is increased, the bubble response is nonlinear, which leads to sub and higher harmonic generation. New techniques for specialised clinical applications have been developed to utilise this phenomenon.

In this project models are derived for the radius of the bubble as a function of time in response to a time dependent driving pressure. The most fundamental of the nonlinear models is a second order, ordinary differential equation, called the Rayleigh-Plesset (RP) equation. This applies to a bubble in a simplified liquid, assumed infinite in domain, inviscid, incompressible (uniform density) and with zero surface tension. For small changes in radius the RP equation reduces to a linear oscillator equation. The RP equation may be modified by allowing non-zero surface tension and viscosity, resulting in an equation referred to as the RPNNP equation. This is the first step to constructing a shelled bubble model. In the RP equation the fluid is assumed incompressible, and this implies an infinite sound speed. This limits the accuracy of the RP equation to moderate amplitude oscillations. The RP model was extended by Herring and Trilling, by allowing for a constant sound speed, assuming the fluid disturbance was a diverging spherical wave.

Models of shelled contrast agents are of the utmost importance to understand biomedical signals. The behaviour of the encapsulating shell is dependent on the thickness, shear modulus and viscosity of the shell medium. Several models exist for the encapsulating shell. This thesis reviews the models derived by Church. The encapsulating shell is modelled as a Newtonian fluid, or as a viscoelastic material with a constant shear modulus and viscosity. The equation of motion obtained is an extension of the RP equation.

The models including radiation damping and shell layers, all have a persistent form, which is the same as the fundamental Rayleigh-Plesset equation.
CHAPTER 1

Introduction

1.1. Medical ultrasonography

For diagnostic medical ultrasonography (ultrasound) an acoustic pulse, typically an enveloped sinusoid, with a centre frequency in the 2-15 MHz range is generated by a device called a transducer. The signal is transmitted through the patient and directed at the object of interest. The ultrasound wave is reflected, scattered, dispersed and attenuated by the body tissue. The signal that is returned to the transducer is detected and interpreted, typically to form an image.

The reflected signal from blood is 30-60 dB less than the signal from body tissue. Contrast enhancement makes images of the heart chambers and blood vessels much easier to interpret. For example, it may be required to monitor the tissue perfusion, which is the blood flow through tissue. The tissue perfusion is an indication of the state of health of the tissue, since blood flow is vital for transporting nutrients and waste products to and from tissue.

Contrast agent ultrasonography involves the intravenous injection of contrast agents. Microbubble contrast agents are gas filled microbubbles, typically with lipid, polymer or albumin encapsulating shells. The microbubbles, due to their high compressibility and low density, enhance the backscatter of the ultrasound signal. The enhanced backscatter allows blood vessels to be imaged, thereby allowing tissue perfusion to be observed.

Figure 1.1. Image of the heart with (right) and without (left) contrast enhancement. The endocardial border and tissue perfusion is clearly shown in the right image. From http://people.maths.ox.ac.uk/~mcburnie/research.html

Figure 1.1 shows a typical medical ultrasound image of the left ventricle of the human heart (left part of the figure) and the same area imaged with using EchoGen microbubble contrast
agents (right of the figure). In the non-contrast enhanced image, the left ventricle appears as a dark cavity. In the contrast enhanced image it is possible to observe the endocardial border (the heart chamber wall). The tissue perfusion of the endocardial border may also be observed. Healthy tissue, with blood flow, will appear as a bright part of the image. The unhealthy tissue has little or no blood flow and the image of that region will be considerably darker. This can be seen in the extreme right of the right hand image.

1.2. History

1.2.1. Observation of contrast phenomena and modern application. Contrast agent phenomena were serendipitously observed in around 1968, when Gramiak and Shah reported a personal communication with Joyner, who observed clouds of echos from intracardiac saline injection using a catheter in the left ventricle. Gramiak and Shah proposed that the observed echos arose from microbubbles introduced by the rapid injection of the saline (Gramiak & Shah 1968). The microbubbles were unstable and would not persist for a long time period. Experimentally, it was found that a more stable microbubble was formed by premixing the saline solution with the blood product albumin. This approach lead to the first clinical microbubble contrast agent, Albunex. Albunex was manufactured by the sonation of a 5% solution of human albumin, generating an air bubble with an aggregated albumin shell. The shell thickness is of the order of 15 nm and the bubble diameter is distributed between 1-10 µm, so that they may pass through capillary blood vessels. The contrast agent exhibits similar behaviour, in response to an ultrasonic pulse, to air microbubbles in water. Albunex has been documented as clinically safe and is stable enough to undergo transpulmonary passage. (Sponheim et al. 1993).

1.2.2. Mathematical models. The basic mathematical models now applied to contrast agents were originally developed for modelling cavitation bubbles. Cavitation bubbles are formed when the local liquid pressure drops below its vapour pressure. The rapid collapse of these cavitation bubbles forms a shock wave. The resulting liquid jet may damage nearby boundary surfaces. The classical example of cavitation damage is the pitting observed on ship’s propellers. Bubbles are generated in the low pressure wake of the propeller. The bubbles then collapse causing the pitting.

In 1917 Lord Rayleigh studied the cavitation phenomenon and proposed an ODE model, now referred to as the Rayleigh-Plesset equation. The work of Noltingk and Neppiras and Poritsky modified the Rayleigh-Plesset model to include fluid viscosity and surface tension. Damping of bubble oscillations, due to a pressure wave in the surrounding liquid, caused by the bubble oscillation was studied by many including Herring, Trilling, Keller, Miksis and Gilmore. Initially this radiation damping phenomena was modelled as a diverging spherical wave with constant speed by Herring and later (independently) by Trilling. Keller and Miksis extended the model to include a full spherical wave in the liquid surrounding the bubble. Gilmore’s model allows the sound speed to vary as a function of pressure.

Models of bubbles with encapsulating shells were considered in the context of cavitation (Fox & Herzfeld 1954). The experimental development of ultrasound contrast agents requires
more extensive modelling of the shell layer. Initially the cavitation models were used as basic models for the oscillatory response of the bubble wall to a driving pressure. Work by Church specifically developed the model of a shelled microbubble contrast agent.

1.3. Outline

This thesis presents a review of basic fluid mechanics, together with the assumptions and simplifications required to derive of the models of ultrasound contrast agents. From the governing equations of the fluid, ODE models for the time evolution of the bubble wall will be derived. This project starts with the derivation of the fundamental and much idealised, Rayleigh-Plesset model, before progressing to modified models including surface tension and fluid viscosity. The models for radiation damped bubble oscillations are also derived. Gilmore’s model for microbubbles in a fluid with non constant sound speed is discussed but not derived. Church’s model for microbubbles with encapsulating shells is derived. Brief consideration is given to the different models of the shell, here two models, a Newtonian fluid and a viscoelastic material, will be discussed. The viscoelastic model will then be simplified, assuming a thin shell.

The models derived are all highly nonlinear but may be linearised for small amplitude driving pressures. Linearisation and calculation of the resonant frequencies is performed. Since the models are highly nonlinear, numerical solutions are required. Numerical solutions for a range of different behaviours and bubble models are presented and discussed. In the case of the Rayleigh-Plesset equation, the only known analytical solution for step function pressure changes, is presented in Appendix [A].

Finally the assumptions and limitations of the models are discussed. The applications and further developments for ultrasound contrast agents are briefly discussed.
Mathematical models for microbubbles without a shell

A model for microbubble contrast agents requires consideration of the gas inside the bubble, the shell of the bubble (if any) and the fluid surrounding the bubble. The gas will be modeled as ideal. The bubble will be initially modelled only as a cavity within the fluid.

It is assumed that the bubble is spherically symmetric and it is also assumed that the bubble oscillations preserve this symmetry. This is the case for a single bubble far from any boundaries, in a low amplitude driving field. In practice the contrast agents are free to move around in the bloodstream. In these models the centre point of the bubble remains stationary at the origin, by the assumption of spherical symmetry about the origin. The low amplitude field and the persistant spherical symmetry also implies the assumption that the bubble does not collapse.

2.1. Fluid mechanics

A fluid flow at a spatial point $x$ is described by the velocity field $u(x, t) = (u, v, w)$ and time $t$. The velocity field $u$ is considered fixed at a spatial point $x$ and the individual fluid elements vary in velocity as they move through the velocity field. A fluid flow is called steady if $\frac{\partial}{\partial t} u(x, t) = 0$, note that a fluid element may accelerate in a steady flow.

2.1.1. Acceleration of fluid element. Consider the acceleration of a fluid element, following the fluid, which was initially at point $u(x, 0) = u(q, 0)$. The acceleration of the fluid element is

$$\left( \frac{\partial}{\partial t} u \right)_q = \frac{\partial u}{\partial t} + (u \cdot \nabla) u := \frac{Du}{Dt}. \quad (2.1)$$

The derivative $\frac{Du}{Dt}$ is called the convective or material derivative.

2.1.2. Continuity equation. In a physical fluid mass is conserved. This places a restriction on the velocity field of the fluid. Assume the fluid has density $\rho(x, t)$ and consider some volume $V$ enclosed by a surface of area $A$, fixed within the body of fluid. The mass of fluid enclosed at any $t$ is $\int \rho \, dV$ and the net flow across the surface is $\int \rho u \cdot n \, dA$.

The conservation of mass flow in and out of the volume implies:

$$\frac{d}{dt} \int_V \rho \, dV = - \int_A \rho u \cdot n \, dA. \quad (2.2)$$
Assuming the order of differentiation and integration can be interchanged and rewriting the surface integral with the divergence theorem, gives:

\[ \int_V \left( \frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{u}) \right) dV = 0. \] (2.3)

Since this is true for all \( V \) the integrand is identically zero:

\[ \frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{u}) = 0. \] (2.4)

Equation (2.4) is called the continuity, or conservation of mass, equation.

2.1.3. Stress and strain. Stress is defined as the average force per unit area. In a continuum body which is acted upon by internal and external forces, the state of stress at a point may be described by a second rank Cartesian tensor. The tensor is referred to as the Cauchy Stress tensor. The Cauchy stress tensor for fluids \( \sigma_{ij} \) may be written as \( \sigma_{ij} = -p \delta_{ij} + \tau_{ij} \). Here \( p \) is the fluid pressure, defined as positive inwards upon the element, and \( \tau_{ij} \) is the deviatoric stress tensor. \( \delta_{ij} \) is the Kroneker delta.

The deformation of a body under stress is called strain. A Newtonian fluid has a linear relation between the stress and rate of strain, where the constant of proportionality is called dynamic viscosity (hereafter, referred to as viscosity). The rate of strain is described by a second rank symmetric Cartesian tensor denoted \( \epsilon_{ij} \).

The stress tensor is symmetric for a incompressible Newtonian fluid. The components of the stress tensor of an incompressible Newtonian fluid, with viscosity \( \mu \) are derived in Landau & Lifshitz (1987). The radial component is

\[ \sigma_{rr} = -p + 2\mu \frac{\partial u}{\partial r}. \] (2.5)

2.1.4. Surface tension effects. In this project, it will be required to understand the pressure difference across an interface of two continuous media. If the interface is curved, such as a bubble surface, there will be a pressure difference across a thin transitional region, due to the surface tension effect. By considering the surface layer, with inner and outer radii of curvature \( R_1 \) and \( R_2 \), in thermodynamic equilibrium it is possible to derive Laplace’s formula for the pressure difference \( p_1 - p_2 \) across the surface layer (Landau & Lifshitz 1987). Here the surface tension \( \sigma \) is assumed constant.

\[ p_1 - p_2 = \sigma \left( \frac{1}{R_1} + \frac{1}{R_2} \right). \] (2.6)

If the layer becomes infinitely thin, \( R_1 = R_2 = R \):

\[ p_1 - p_2 = \frac{2\sigma}{R}. \] (2.7)
2.1.5. **Navier-Stokes or Momentum equation.** The Navier-Stokes (NS) equation is a second order PDE describing the momentum of a fluid element. In the Navier-Stokes equation the fluid is required to be Newtonian. For a derivation of the Navier-Stokes equation see Batchelor (1967) or Landau & Lifshitz (1987). The form of the NS equation quoted here is for an incompressible fluid with viscosity $\mu$. This form also assumes $\nabla \times \mathbf{u} = 0$.

$$
\rho \frac{D\mathbf{u}}{Dt} = \rho \mathbf{F} - \nabla p + \frac{4\mu}{3} \nabla^2 \mathbf{u}.
$$

(2.8)

The $\mathbf{F}$ term is an external body force such as gravity. In the models of contrast agents gravitational force is neglected due to the small mass of the contrast agent.

In spherical polar coordinates, with no body forces and the assumption of spherical symmetry the NS equation becomes:

$$
\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \frac{\partial \mathbf{u}}{\partial r} = -\frac{1}{\rho} \frac{\partial p}{\partial r} + \frac{\mu}{\rho} \left( \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial \mathbf{u}}{\partial r} \right) - \frac{2\mathbf{u}}{r^2} \right).
$$

(2.9)

2.1.6. **Simplifications and assumptions.** There are assumptions that can be made about the fluid and the fluid flow which simplify the momentum equation. A fluid is incompressible if $\frac{D\rho}{Dt} = 0$ and gives $\nabla \cdot \mathbf{u} = 0$. A fluid is irrotational if $\nabla \times \mathbf{u} = 0$, $\implies \mathbf{u} = \nabla \Phi$.

$\Phi$ is a scalar function, called the *velocity potential*. Irrotational means the local angular rate of rotation is zero, this does not imply that the angular velocity is everywhere zero. Also note that from the definitions, a spherically symmetric fluid must be irrotational.

For an incompressible, irrotational, inviscid fluid the Navier-Stokes and continuity equations reduce to *Euler’s equations*:

Momentum equation

$$
\frac{D\mathbf{u}}{Dt} = -\frac{\nabla p}{\rho}.
$$

Incompressibility

$$
\nabla \cdot \mathbf{u} = 0.
$$

2.1.7. **Bernoulli’s equation.** From the Euler equations, with no body forces, for an irrotational, steady fluid it is possible to derive *Bernoulli’s equation* for the velocity potential $\Phi(r,t)$ by integrating the momentum equation. The momentum equation is:

$$
\frac{\partial u}{\partial t} = -\frac{1}{\rho} \frac{\partial p}{\partial r},
$$

(2.10)

$$
\implies \frac{\partial \Phi}{\partial r} \frac{\partial^2 \Phi}{\partial r^2} = -\frac{1}{\rho} \frac{\partial p}{\partial r}.
$$

(2.11)
2.2. Microbubbles in an inviscid, incompressible fluid

2.2.1. The Rayleigh-Plesset equation. The Rayleigh-Plesset (RP) equation is a second-order nonlinear ODE for the radius of a bubble oscillating in a fluid. The RP equation models a bubble in an inviscid and incompressible fluid of constant density \( \rho \). The RP equation is derived
from the momentum equation and the continuity equation by considering a persistent spherical bubble in the fluid. The gas within the bubble is simplified to a polytropic gas.

It is assumed that far from the bubble the fluid pressure is $p_\infty$. If there is some driving sound field $P(t)$ the fluid pressure far from the bubble is $p_\infty = p_0 + P(t)$, where $p_0$ is constant.

The ODE for the bubble radius $R(t)$ is

$$\ddot{R} R + \frac{3}{2} \dot{R}^2 = \frac{p_L(t) - p_\infty}{\rho},$$

(2.15)

where $p_L$ is the liquid pressure on the surface of the bubble.

The RP equation has an analytical solution for step function driving pressures, presented in Appendix A.

The driving pressure in medical ultrasound is oscillatory and pulsed, for example the driving pressure may be a sinusoidal wave with a window function, which may be approximately Gaussian or approximately rectangular. Numerical solutions of the RP equation are required in this case.

For small changes in the radius, the RP equation reduces to a driven linear oscillator equation. It is also possible to gain further insight into the full RP equation using perturbation techniques. This can yield second order solutions, although this will not be considered in this thesis. See for example Prosperetti (1974).

### 2.2.2. Derivation.

(The RP equation was first derived by Lord Rayleigh (1917) using an energy argument, different to the approach here.) Consider a spherically symmetric persistent bubble of radius $R(t)$ as sketched in Figure (2.1) with the bubble centre located at the origin, in an infinite domain of inviscid, incompressible, constant density fluid.

With spherical symmetry, the continuity equation (2.4) becomes:

$$\frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 u(r, t) \right) = 0,$$

(2.16)

$$\Rightarrow u(r, t) = \frac{1}{r^2} F(t),$$

(2.17)

where $F(t)$ is some function of time alone. If there is no mass transport across the boundary, the wall velocity at the boundary is simply the time rate of change of the radius. Thus at the cavity boundary:

$$u(R, t) = \frac{dR}{dt},$$

(2.18)

$$\Rightarrow F(t) = R^2 \frac{dR}{dt},$$

(2.19)

$$\Rightarrow u(r, t) = \left( \frac{R}{r} \right)^2 \dot{R},$$

(2.20)
2.3. Microbubbles in a viscous, incompressible, Newtonian fluid

where \( \dot{R} = \frac{dR}{dt} \). Then, from the spherical symmetric momentum equation and the ideal fluid considered:

\[
- \frac{1}{\rho} \frac{\partial p(r, t)}{\partial r} = \frac{\partial u}{\partial t} + u \frac{\partial u}{\partial r}.
\]

(2.21)

Substituting (2.20) into (2.21):

\[
- \frac{1}{\rho} \frac{\partial p(r, t)}{\partial r} = \left( \frac{2R\dot{R}^2 + R^2 \ddot{R}}{r^2} - \frac{2R^4 \dddot{R}^2}{r^5} \right).
\]

(2.22)

Equation (2.22) is then integrated with respect to \( r \) from \( R \) to \( \infty \), to give equation (2.24).

Therefore boundary conditions are required to specify the liquid pressure on the bubble surface \( p_L(R, t) \). The pressure far from the cavity, is assumed to be the sum of a time varying driving pressure \( P(t) \) and a constant reference pressure, \( p_0 \).

For convenience assume that the driving field is only applied at \( t = 0 \), with \( P(0) = 0 \), and assume that the bubble is initially stationary.

The gas within the bubble is modelled as a polytropic gas. The pressure at the bubble wall will be

\[
p(R, t) = p_L(R) = p_G(0) \left( \frac{R_0}{R} \right)^{3\gamma},
\]

(2.23)

where \( R_0 \) is the initial bubble radius and \( p_G(0) \) the initial gas pressure. Since the bubble is initially in equilibrium, \( p_G(0) = p_0 \).

Finally upon integrating and applying the boundary conditions:

\[
\dddot{R}R + \frac{3}{2} \ddot{R}^2 = \frac{p_0 \left( \frac{R_0}{R} \right)^{3\gamma} - p_0 - P(t)}{\rho}.
\]

(2.24)

2.3. Microbubbles in a viscous, incompressible, Newtonian fluid

2.3.1. The RPNNP equation. The effects of the fluid viscosity, \( \mu \), and surface tension, \( \sigma \), are included. The equation derived is called the RPNNP equation (to acknowledge contributions to the RP equation from Noltingk and Neppiras and Poritsky):

\[
R\ddot{R} + \frac{3}{2} \dot{R}^2 = \frac{1}{\rho} \left( p_0 + \frac{2\sigma}{R_0} \left( \frac{R_0}{R} \right)^{3\gamma} - p_0 - P(t) - \frac{4\mu \dot{R}}{R} - \frac{2\sigma}{R} \right).
\]

The surface tension and viscosity modify the boundary condition, resulting in the modified right hand side of the equation. The viscous terms only appear as a contribution to the liquid pressure at the bubble surface. The viscous components of the momentum will cancel due to spherical symmetry.
2.3.2. Derivation. (This derivation follows Brennen (1995)). The problem is formulated in the same manner as the Rayleigh-Plesset equation. There exists a persistent spherically symmetric cavity of radius \( R(t) \) in an infinite, incompressible, Newtonian fluid, of constant density \( \rho \). The derivation proceeds in the same manner as before. The expression for velocity follows exactly the same reasoning as in equation (2.20), so

\[
\frac{\partial \rho}{\partial t} = \left( \frac{R}{r} \right)^2 \dot{R}. \tag{2.25}
\]

The radial component of the NS equation, including viscosity is:

\[
- \frac{1}{\rho} \frac{\partial \rho}{\partial r} = \frac{\partial u}{\partial t} + u \frac{\partial u}{\partial r} + \mu \left[ \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial u}{\partial r} \right) - \frac{2u}{r^2} \right]. \tag{2.26}
\]

Upon substitution of (2.25) into (2.26), the viscous terms vanish:

\[
- \frac{1}{\rho} \frac{\partial \rho}{\partial r} = \left( \frac{2R\dot{R}^2 + R^2 \ddot{R}}{r^2} - \frac{2R^4 \dot{R}^2}{r^5} \right) + \mu \left[ \frac{2R^2 \dot{R}}{r^4} - \frac{2R^2 \dot{R}^3}{r^4} \right]. \tag{2.27}
\]

This is the same equation as (2.22). As before the problem requires boundary conditions. The pressure far from the cavity is the same as for the Rayleigh-Plesset equation. \( p_\infty = P(t) + p_0 \). The consideration of surface tension and viscosity modifies the pressure in the liquid at the bubble wall \( p_L(R, t) \).

Consider the pressure acting on the bubble wall as shown in Figure (2.2), taking the positive radial direction to be outwards from the cavity. The gas pressure inside the bubble is \( p_G \left( \frac{R_0}{R} \right)^{3\gamma} \) and acts outwards. The pressure due to surface tension acts inwards and may be found from Laplace’s formula to be \(- \frac{2\sigma}{R}\). The fluid exerts stress inwards on the bubble wall due to viscosity. Recall that for a Newtonian fluid, the stress is proportional to the rate of strain, which is the
velocity gradient of the fluid. The velocity gradient may be found from equation (2.25). Thus the stress is:

\[ 2\mu \frac{\partial u}{\partial r} = -\frac{4\mu \dot{R}}{R}. \]  

(2.28)

Summing the contributions:

\[ p(R) = p_G \left( \frac{R_0}{R} \right)^{3\gamma} - 2\sigma - 4\mu \frac{\dot{R}}{R}. \]  

(2.29)

Assuming that the bubble was initially in equilibrium \( \dot{R} = 0 \) and assume that \( P(0) = 0 \)

\[ p_\infty = p_0, \]  

(2.30)

\[ \implies p_G(0) = p_0 + \frac{2\sigma}{R_0}. \]  

(2.31)

Integrating (2.27) applying the boundary conditions:

\[
R \ddot{R} + \frac{3}{2} \dot{R}^2 = \frac{1}{\rho} \left( (p_0 + \frac{2\sigma}{R_0}) \left( \frac{R_0}{R} \right)^{3\gamma} - p_0 - P(t) - \frac{4\mu \dot{R}}{R} - \frac{2\sigma}{R} \right).
\]  

(2.32)

### 2.4. Microbubbles in a compressible fluid.

If the bubble oscillates in a compressible fluid, it will act as a source, generating a sound wave in the fluid. It is therefore necessary to consider the propagation of sound in the fluid medium. The acoustic approximation will be used to simplify the modeling. The acoustic approximation assumes that the acoustic wave is a small pressure disturbance on a much larger acoustic background pressure. The Mach number, \( M \), is the ratio of the velocity of an object to the sound speed in the fluid. In the case of contrast agents, the object is the cavity wall and \( M = \frac{\dot{R}}{c} \).

The acoustic approximation is equivalent to \( M \ll 1 \), this is typically valid in the case of microbubble contrast agents, since, for example, the sound speed is water is \( c \approx 1480 \text{ ms}^{-1} \) and the bubble wall velocity is typically \( \dot{R} \approx 1 \text{ ms}^{-1} \).

The wave or acoustic equation for a spherically symmetrically velocity potential is:

\[
\left( \frac{\partial^2}{\partial t^2} - c^2 \frac{\partial^2}{\partial r^2} \right) (r\Phi) = 0,
\]  

(2.33)

which may be written as:

\[
\left( \frac{\partial}{\partial t} - c \frac{\partial}{\partial r} \right) \left( \frac{\partial}{\partial t} + c \frac{\partial}{\partial r} \right) (r\Phi) = 0.
\]  

(2.34)

The general solution due to, d’Alembert, is:

\[ \Phi = \frac{f(t - r/c) + g(t + r/c)}{r}, \]  

(2.35)
where \( f \) and \( g \) are arbitrary functions. The solution corresponds to an inwards moving wave \( f \) with wavespeed \( c \) and an outward moving wave \( g \) with wavespeed \( c \).

2.5. Equations of state

This section follows Hoff (2001). The presence of sound waves in the fluid means that the density cannot be assumed constant. The density becomes a function of pressure, \( \rho = \rho(p) \). The motion of the fluid is assumed isentropic (constant entropy). It will be shown the density may be approximated by the constant density far from the bubble.

If the oscillations of the bubble do not change the entropy of the system, then it is possible to define the enthalpy, \( h = h(p) \). The enthalpy is a measure of the thermodynamic potential of the system, and allows the calculation of the useful work that may be obtained from the system.

It is known from thermodynamics that:

\[
\left( \frac{\partial \rho}{\partial p} \right)_s = \frac{1}{c^2},
\]

(2.36)

\[
\left( \frac{\partial h}{\partial p} \right)_s = \frac{1}{\rho},
\]

(2.37)

where \( c \) is the sound speed in the fluid. Clearly \( c = c(p) \). Far from the cavity, the density is assumed constant \( \rho \to \rho_\infty \), and the sound speed tends to a constant \( c \to c_\infty \).

The enthalpy may be expressed as an integral, which may be approximated by a Taylor expansion around \( \rho = \rho_\infty \).

\[
h(r) = \int_{p_\infty}^{\rho(r)} \frac{dp}{\rho(p)},
\]

(2.38)

\[
\Rightarrow h(r) = \int_{p_\infty}^{\rho(r)} \left( \frac{1}{\rho_\infty} - (x - x_\infty), \frac{1}{\rho_\infty^2} \frac{\partial \rho}{\partial x} \right) dx,
\]

(2.39)

\[
\approx \frac{p(r) - p_\infty}{\rho_\infty} + \mathcal{O}(c_\infty^{-2}).
\]

(2.40)

The terms proportional to \( \mathcal{O}(c_\infty^{-2}) \) are considered negligible, using the acoustic approximation. Similarly the sound speed \( c(p) \) may be found by a Taylor expansion around the constant value \( c_\infty \):

\[
\frac{1}{c^2} = \frac{1}{c_\infty^2} + (p - p_\infty) \frac{\partial c^{-2}}{\partial p} \bigg|_{r=\infty} + \cdots,
\]

(2.41)

\[
= \frac{1}{c_\infty^2} + \frac{(p - p_\infty) \partial c^2}{c_\infty^4} \bigg|_{r=\infty} + \cdots,
\]

(2.42)

\[
= \frac{1}{c_\infty^2} + \mathcal{O}(c_\infty^{-4}).
\]

(2.43)

Again by the acoustic approximation, the \( \mathcal{O}(c_\infty^{-4}) \) is negligible. The enthalpy \( h \) and sound speed \( c \) are always approximated by the first term in the above expansion.
2.6. Fluids with constant sound velocity

The RP and RPNNP equations do not include damping effects from acoustic radiation, due to the incompressibility assumption. The radiation damping becomes important when modelling large (> 10 µm) bubble diameters and high frequencies (> 10 MHz). The incompressibility assumption is relaxed in the Herring-Trilling (HT) and Keller-Miksis (KM) models, which will now be considered.

Radiation damping correction terms of a similar form are obtained in both the HT and KM models. In the HT model it is assumed that the velocity potential satisfies the diverging spherical wave equation, while the KM model relaxes this to the full spherically symmetric wave equation. The HT model neglects the effects of viscosity for simplicity, while the KM model does not.

Both models assume a compressible fluid and a constant (finite) speed of sound, denoted $c_\infty$. Spherical symmetry is assumed and therefore the fluid flow is irrotational with a velocity potential $\Phi(r, t)$. It is possible to write a modified Bernoulli equation for a viscous compressible fluid. This will be used in the derivations of both models.

**2.6.1. Modified Bernoulli equation.** Start with the momentum equation for an irrotational, viscous fluid. Substituting the velocity potential:

$$
\rho_\infty \left( \frac{\partial^2 \Phi}{\partial r \partial t} + \frac{\partial \Phi}{\partial r} \frac{\partial^2 \Phi}{\partial r^2} \right) + \frac{\partial p}{\partial r} = \frac{4\mu}{3} \frac{\partial}{\partial r} \left( \frac{\partial^2 \Phi}{\partial r^2} \right),
$$

(2.44)

$$\Rightarrow \frac{\partial}{\partial r} \left( \frac{\partial \Phi}{\partial t} + \frac{1}{2} \left( \frac{\partial \Phi}{\partial r} \right)^2 \right) + \frac{1}{\rho_\infty} \frac{\partial p}{\partial r} = \frac{4\mu}{3\rho_\infty} \frac{\partial}{\partial r} \left( \frac{\partial^2 \Phi}{\partial r^2} \right).
$$

(2.45)

Assume constant density and integrate with respect to the radial coordinate from $r \rightarrow \infty$:

$$
\frac{\partial \Phi}{\partial t} + \frac{1}{2} \left( \frac{\partial \Phi}{\partial r} \right)^2 + \int_{p(\infty)}^{p(r)} \frac{dp}{\rho} = \frac{4\mu}{3\rho_\infty} \left( \frac{\partial^2 \Phi}{\partial r^2} \right).
$$

(2.46)

The assumption of constant density is valid for only a small acoustic wave, which is justified by the acoustic approximation.
2.7. Herring-Trilling model

2.7.1. Derivation. (This derivation follows Trilling (1951)). Recall the definition of the velocity potential $\Phi(r, t)$ and assume there are only diverging waves. The governing equations are:

Velocity potential:
\[ u = \frac{\partial \Phi}{\partial r}, \]  
(2.47)

Acoustic equation:
\[ \left( \frac{\partial}{\partial t} + c_\infty \frac{\partial}{\partial r} \right) (r\Phi) = 0, \]  
(2.48)

Momentum equation, inviscid liquid:
\[ \frac{\partial u}{\partial t} + u \frac{\partial u}{\partial r} + \frac{1}{\rho_\infty} \frac{\partial p}{\partial r} = 0, \]  
(2.49)

Modified Bernoulli equation:
\[ \frac{\partial \Phi}{\partial t} + \frac{1}{2} \left( \frac{\partial \Phi}{\partial r} \right)^2 + \int_{p(\infty)}^{p(r)} \frac{dp}{\rho} = 0. \]  
(2.50)

Start by expanding the acoustic equation (2.48):
\[ r \frac{\partial \Phi}{\partial t} + c_\infty r \frac{\partial \Phi}{\partial r} + c_\infty \Phi = 0. \]  
(2.51)

Substitute for $\frac{\partial \Phi}{\partial t}$ from the modified Bernoulli equation (2.50). This yields:
\[ \frac{r}{2} \left( \frac{\partial \Phi}{\partial r} \right)^2 + \frac{r}{\rho_\infty} \int_{p(\infty)}^{p(r)} \frac{dp}{\rho} - c_\infty r \frac{\partial \Phi}{\partial r} - c_\infty \Phi = 0. \]  
(2.52)

Take the time derivative of equation (2.52) and substitute $u = \frac{\partial \Phi}{\partial r}$:
\[ r \frac{\partial u}{\partial t} + \frac{r}{\rho_\infty} \frac{\partial p}{\partial t} - c_\infty r \frac{\partial u}{\partial t} - c_\infty \frac{\partial \Phi}{\partial t} = 0, \]  
(2.53)

\[ \Rightarrow r u \frac{\partial u}{\partial t} + \frac{r}{\rho_\infty} \frac{\partial p}{\partial t} - c_\infty r \frac{\partial u}{\partial t} + c_\infty \left[ \frac{u^2}{2} + \int_{p(\infty)}^{p(r)} \frac{dp}{\rho} \right] = 0, \]  
(2.54)

by substituting for $\frac{\partial \Phi}{\partial t}$ again.

Substitute for the $c_\infty r \frac{\partial u}{\partial t}$ term using the momentum equation (2.49) to obtain the equation of motion:
\[ r u \frac{\partial u}{\partial t} + \frac{r}{\rho_\infty} \frac{\partial p}{\partial t} + \frac{c_\infty u^2}{2} + c_\infty r \frac{\partial u}{\partial r} + \frac{c_\infty r}{\rho_\infty} \frac{\partial p}{\partial r} + c_\infty \int_{p(\infty)}^{p(r)} \frac{dp}{\rho} = 0. \]  
(2.55)

Equation (2.55) is a PDE that involves $\frac{\partial u}{\partial t}$, $\frac{\partial p}{\partial t}$, $\frac{\partial u}{\partial r}$, and $\frac{\partial p}{\partial r}$ at some point $(r, t)$ in the fluid. To find an ODE for the time varying radius of the bubble wall $R(t)$ it is required to find expressions for these partial derivatives at the bubble wall.
At the bubble wall \( r = R(t) \), \( u = \dot{R} \) and \( p = p_L(R,t) \). The rates of change of the pressure and velocity at the boundary are:

\[
\frac{dp_L}{dt} = \frac{\partial p}{\partial t} + \dot{R} \frac{\partial p}{\partial r}, \tag{2.56}
\]

\[
\frac{d\dot{R}}{dt} = \frac{\partial u}{\partial t} + \dot{R} \frac{\partial u}{\partial r}. \tag{2.57}
\]

Recall the continuity equation (2.4) and expand for an isentropic fluid, where \( c_\infty^2 = \frac{\partial p}{\partial \rho} \):

\[
\frac{1}{\rho_\infty c_\infty^2} \frac{\partial p}{\partial t} + \frac{u}{\rho_\infty c_\infty^2} \frac{\partial p}{\partial r} + \frac{\partial u}{\partial r} + 2 \frac{u}{r} = 0. \tag{2.58}
\]

The equations on the bubble surface, together with the momentum equation (2.49) and the continuity equation (2.58) form a set of four equations in the four unknowns: \( \frac{\partial u}{\partial t}, \frac{\partial u}{\partial r}, \frac{\partial p}{\partial r}, \frac{\partial p}{\partial t} \) and \( \frac{\partial p}{\partial r} \), all evaluated at \((R,t)\). The solution is:

\[
\frac{\partial u(R,t)}{\partial t} = \frac{d\dot{R}}{dt} + \frac{\dot{R}}{\rho_\infty c_\infty^2} \frac{dp_L}{dt} + \frac{2\dot{R}^2}{R}, \tag{2.59}
\]

\[
\frac{\partial u(R,t)}{\partial r} = -\frac{1}{\rho_\infty c_\infty^2} \frac{dp_L}{dt} - \frac{2\dot{R}}{R}, \tag{2.60}
\]

\[
\frac{\partial p(R,t)}{\partial t} = \frac{dp_L}{dt} + \frac{\dot{R}}{\rho_\infty} \frac{d\dot{R}}{dt}, \tag{2.61}
\]

\[
\frac{\partial p(R,t)}{\partial r} = -\rho_\infty \frac{d\dot{R}}{dt}. \tag{2.62}
\]

Substituting this into the equation of motion (2.55) at \( r = R \) and recalling \( p(R,t) = p_L \) gives:

\[
R \frac{d\dot{R}}{dt} \left( 1 - \frac{2\dot{R}}{c_\infty} \right) + \frac{3\dot{R}^2}{2} \left( 1 - \frac{4\dot{R}}{3c_\infty} \right) = \frac{R}{\rho_\infty c_\infty} \frac{dp_L}{dt} \left( \frac{\dot{R}}{c_\infty} - \frac{\dot{R}^2}{c_\infty^2} + \frac{\dot{R}^3}{c_\infty^3} \right) + \int_{p(\infty)}^{p_L} \frac{dp}{\rho}. \tag{2.63}
\]

For the acoustic approximation to be valid it is required that \( \dot{R} < c_\infty \), which implies the \( \frac{\dot{R}^3}{c_\infty^3} \) term is negligible. Writing \( \frac{d\dot{R}}{dt} = \ddot{R} \) gives the Herring-Trilling equation:

\[
R \ddot{R} \left( 1 - \frac{2\ddot{R}}{c_\infty} \right) + \frac{3\ddot{R}^2}{2} \left( 1 - \frac{4\ddot{R}}{3c_\infty} \right) = \frac{R}{c_\infty \rho_\infty} \frac{dp_L}{dt} \left( 1 - \frac{\ddot{R}}{c_\infty} \right) + \frac{p_L - p_\infty}{\rho_\infty}, \tag{2.64}
\]

note \( p_L \) can be expressed as before in section (2.2), equation (2.24). And the driving pressure is introduced by writing \( p_\infty = p_0 + P(t) \).
2.7.2. Modified Herring Model. The modified Herring model further simplifies the Herring-Trilling model by neglecting the correction terms of the form \( \frac{\dot{R}}{c_\infty} \), since \( M = \frac{\dot{R}}{c_\infty} \ll 1 \). This gives:

\[
\ddot{R} R + \frac{3}{2} \dot{R}^2 - \frac{R \dot{p}_L}{\rho_\infty c_\infty} = \frac{p_L - p_\infty}{\rho_\infty},
\]

This model includes the \( \dot{p}_L \) radiation damping term, which occurs in both the Herring-Trilling and Keller-Miksis model.

The modified Herring model eliminates certain problems associated with the Herring-Trilling and Keller-Miksis models. As the \( M \) increases, the terms of the form \( (1 - \alpha M) \), for \( \alpha = \text{constant} \), may become negative, and therefore unphysical. The \( (1 - \alpha M) \) can cause difficulties in numerical integration where simple integration schemes may not be suitable for solving the equation.

2.8. Keller-Miksis model

The Keller-Miksis model includes viscosity and a full spherical wave equation potential. The Keller-Miksis equation models the sound field in a different manner to the Herring-Trilling model. The acoustic field around the bubble is modelled by assuming that the velocity potential satisfies the spherical wave equation with constant wavespeed. Different to the Herring-Trilling model which assumed a time dependent driving pressure \( P(t) \) far from the bubble, a condition on the driving acoustic field is derived from the wave equation.

2.8.1. Derivation. (Following Keller & Miksis (1980)). The governing equations are the modified Bernoulli equation, including viscosity and the spherical wave equation with constant wavespeed \( c_\infty \):

Modified Bernoulli with viscosity

\[
\frac{\partial \Phi}{\partial t} + \frac{1}{2} \left( \frac{\partial \Phi}{\partial r} \right)^2 - \frac{4\mu}{3} \frac{\partial^2 \Phi}{\partial r^2} + \int_{p(\infty)}^{p(r)} \frac{dp}{\rho} = 0,
\]

Wave equation

\[
\frac{\partial^2 \Phi}{\partial r^2} - \frac{1}{c_\infty^2} \frac{\partial^2 \Phi}{\partial t^2} = 0.
\]

The wave equation has a well known solution. The solution for \( \Phi \) and the partial derivatives of \( \Phi \) are therefore:

\[
\Phi(r, t) = \frac{f(t - r/c_\infty) + g(t + r/c_\infty)}{r},
\]

\[
\frac{\partial \Phi}{\partial t} = \frac{f' + g'}{r},
\]

\[
\frac{\partial \Phi}{\partial r} = \frac{g' - f'}{rc_\infty} - \frac{f + g}{r^2},
\]
2.8. Keller-Miksis Model

where \( f \) and \( g \) are arbitrary functions and the prime denotes differentiation with respect to the argument. The enthalpy to leading order (from equation (2.40)) is

\[
\int_{p(\infty)}^{p(R)} \frac{dp}{\rho} = \frac{p_L - p_{\infty}}{\rho_{\infty}}.
\]

(2.71)

The boundary conditions at the bubble surface are:

**Velocity:**

\[
\dot{R} = \frac{\partial R}{\partial t} = \frac{\partial \Phi(R,t)}{\partial r}.
\]

(2.72)

**Internal gas pressure:**

\[
p_G(R,t) = p_L(R,t) + 2\sigma R - 4\mu R \left( \frac{\partial^2 \Phi(R,t)}{\partial r^2} - \frac{1}{R} \frac{\partial \Phi(R,t)}{\partial r} \right).
\]

(2.73)

The first condition on the radius states that the derivative of velocity potential evaluated at the bubble wall, is the velocity of the wall. The internal bubble pressure is derived by summing the contribution of the liquid pressure \( p_L \), the surface tension \( 2\sigma R \) and subtracting the radial component of viscous stress \( 4\mu R \left( \frac{\partial^2 \Phi(R,t)}{\partial r^2} - \frac{1}{R} \frac{\partial \Phi(R,t)}{\partial r} \right) \). This is derived in a similar manner to the section (2.3) derivation of the internal pressure for the RPNNP equation.

Substituting the pressure condition (2.73) into the Bernoulli equation (2.66) gives an expression for the pressure difference:

\[
\Delta(R) = \frac{p_G(R,t) - p_{\infty}}{\rho_{\infty}} = \frac{2\sigma}{\rho_{\infty} R} + \frac{4\mu}{\rho_{\infty} R} \frac{\partial \Phi(R,t)}{\partial r} - \frac{\partial \Phi(R,t)}{\partial t} - \frac{1}{2} \left( \frac{\partial \Phi(R,t)}{\partial r} \right)^2.
\]

(2.74)

It is possible to eliminate all the terms involving \( \Phi \) and its derivatives by using the solution of the wave equation (2.68), its derivatives, equations (2.69) and (2.70) and the definition of \( \dot{R} \), equation (2.72). Substituting into the pressure difference equation (2.74) yields:

\[
R \Delta(R) - c_{\infty} \dot{R} \dot{R} = c_{\infty} \frac{f + g}{R} - \frac{R \dot{R}^2}{2} + \frac{4\mu}{\rho_{\infty}} - \frac{2\sigma}{\rho_{\infty}} - 2g'(t - R/c_{\infty}).
\]

(2.75)

Recall that \( \Phi = \frac{f + g}{R} \). Taking the time derivative of (2.75) will give a \( \frac{d\Phi(R,t)}{dt} \) which may be substituted into (2.74). This yields:

\[
R \ddot{R} \left( 1 - \frac{\dot{R}}{c_{\infty}} \right) + \frac{3}{2} \dot{R}^2 \left( 1 - \frac{\dot{R}}{3c_{\infty}} \right) = \Delta(R) \left( 1 - \frac{\dot{R}}{c_{\infty}} \right) + \frac{R \Delta'(R)}{c_{\infty} - 4\mu R}{\rho_{\infty} c_{\infty}} - \frac{4\mu R}{\rho_{\infty} R} - \frac{2\sigma}{\rho_{\infty} R} + \frac{2}{c_{\infty}} \left( 1 + \frac{\dot{R}}{c_{\infty}} \right) g''(t - R/c_{\infty}).
\]

(2.76)

A condition on the function \( g \) is required to specify the model of the incident sound field. Keller argues that the bubble is centred in a spherically symmetric incident sound field with velocity potential \( P(r,t) \), that has the form:

\[
P(r,t) = \frac{g(t + r/c_{\infty}) + h(t - r/c_{\infty})}{r}.
\]

(2.77)
For this function to be well defined it must be nonsingular at the origin which implies $h = -g$. The limit at the origin may be computed with l'Hôpital’s rule.

$$P(r, t) = \frac{g(t + r/c_\infty) - g(t - r/c_\infty)}{r}, \quad (2.78)$$

l'Hôpital $\implies P(0, t) = \frac{2}{c_\infty} g'(t). \quad (2.79)$

Hence, upon differentiation with respect to time:

$$2g''(t - R/c_\infty) = c_\infty \frac{\partial}{\partial t} P(0, t - R/c_\infty), \quad (2.80)$$

which specifies the equation of the motion of the bubble radius:

$$\Delta(R) \left( 1 - \frac{\dot{R}}{c_\infty} \right) + \frac{R \Delta'(R)}{c_\infty} - \frac{4 \mu \dot{R}}{\rho_\infty c_\infty} - \frac{4 \mu \dot{R}}{\rho_\infty R} \frac{2\sigma}{\rho_\infty R} + \left( 1 + \frac{\dot{R}}{c_\infty} \right) \frac{\partial}{\partial t} P(0, t - R/c_\infty).$$

(2.81)

2.9. Gilmore’s non-constant sound speed model

The next progression is to admit a pressure dependent sound speed. It is not necessary to study the model in great detail since for microbubble contrast agents the acoustic approximation is valid.

In the model derived by Gilmore and reviewed by Vokurka (1986), the equation of state is assumed to be $\left( \frac{\rho}{\rho_\infty} \right)^n = \frac{(p + B)}{(p_\infty + B)}$, for $B, n$ constant. The fluid is also assumed isentropic. The equation is:

$$\ddot{R} R \left( 1 - \frac{\dot{R}}{c} \right) + \frac{3 R^2}{2} \left( 1 - \frac{\dot{R}}{3c} \right) \left( 1 + \frac{\dot{R}}{c} \right) + \frac{R}{c} \dot{h} \left( 1 - \frac{\dot{R}}{c} \right). \quad (2.82)$$

The quantity $h$ is the enthalpy difference at pressures $p$ and $p_\infty$ evaluated at the bubble wall. The Gilmore model is similar to the Herring and Keller models for small pressure variations, and reduces to the RP in the limit $c \to \infty$. The Gilmore model is suitable for large amplitude bubble oscillations with high Mach numbers.
Chapter 3

Models of contrast agents with stabilising shells

3.1. Shelled contrast agents

Modern contrast agents have a stabilising shell typically of some polymer or lipid material. The shell may be incorporated into a Rayleigh-Plesset like model. The model presented here is due to Church (1995).

The derivation of the model proceeds similarly to the derivation of the RP and RPNNP equations. As before, spherical symmetry is assumed at all times. Similarly it is assumed that the shell does not rupture. The behaviour of the encapsulating shell is dependent on the thickness, shear modulus and viscosity of the shell medium. Several rheological models exist for the shell. The models for the shell considered here are a Newtonian fluid and viscoelastic material. Radiation damping is not considered as part of the model directly. Corrections to model radiation damping may be added to Church’s model, although that is not done here.

3.2. Elastic materials

An elastic material deforms under stress but returns to its original shape when the stress is removed. A typical simplification in modelling elastic materials is the assumption of a linear relationship between stress and strain. Such a material may be called Hookean after Robert Hooke who first postulated the linear relationship in 1678.

The elastic modulus, defined to be the slope of the stress-strain curve, is one parameter used to measure the elastic deformation of a body. Several elastic moduli may be found in the literature, depending on the nature of the stresses. Hooke’s law may be parametrised, leading to the definition of Lamé’s first and second parameters. Lamé’s first parameter, denoted \( \lambda \), has no physical interpretation. It arises as a combination of the elastic modulus and Poisson’s ratio (a measure of the extension of a material in response to a force in another direction). The second Lamé parameter is the shear elastic modulus \( G_s \), which describes the deformation of the body at constant volume, under the action of opposing stresses.

A viscoelastic material exhibits both viscosity and elasticity. There exists several models for this type of material. The model of the viscoelastic material presented here supposes the elastic component of the material may be modelled by a Hookean spring. The viscous component is modelled by a Newtonian fluid. The viscous component and elastic component undergo equal strains. (Landau & Lifshitz 1959).
3.3. Momentum equation for elastic materials

The stress tensor of an incompressible elastic material is traceless, as for an incompressible Newtonian fluid. The tensor form of the momentum equation may be used to derive a model of a shelled bubble.

The rate of change of the momentum of the fluid element is due to the forces acting upon the element. The momentum equation, assuming spherical symmetry for a general form of the stress tensor $\tau$ is (Landau & Lifshitz 1987):

$$\rho(r) \left( \frac{\partial u}{\partial t} + u \frac{\partial u}{\partial r} \right) = -\frac{\partial p}{\partial r} + \frac{\partial \tau_{rr}(r)}{\partial r} + \frac{3\tau_{rr}(r)}{r}. \tag{3.1}$$

Note the density $\rho$ and stress tensor $\tau_{rr}$ are now functions of the radius. By using step changes at the inner and outer walls of the shell the model will incorporate the different densities and stress tensors of the fluid, the shell and the gas. The stresses within the gas are neglected.

The substitution of the expression for the stress tensor of a Newtonian fluid into equation (3.1) yields the Navier-Stokes equation.

The derivation of the model for a microbubble with an encapsulating shell is similar to the derivation of the Rayleigh-Plesset equation. Using the continuity equation to find the velocity of the bubble wall, and integrating equation (3.1) yields Church’s equation for the motion of the wall of a microbubble with encapsulating shell.

3.4. Model of a bubble with an encapsulating shell

3.4.1. Derivation. (Following Church(1995)). Let $R_1$ and $R_2$ be the inner and outer radii of the shell as shown in Figure (3.1). Denote the velocities of the walls by $u_1$ and $u_2$. Use the subscripts and superscripts $G$, $S$ and $L$ as to denote gas, shell and liquid, respectively. Assume that the shell layer and the fluid is incompressible. Since the shell volume is constant:

$$u_1 = u_2 = u,$$  \hspace{1cm} (3.2)

$$R_2^3 - R_1^3 = R_{20}^3 - R_{10}^3 = V_S; \hspace{1cm} (3.3)$$

where the second subscript 0 denotes initial positions. Since the shell is incompressible, the velocity $u_1$ follows as for the Rayleigh-Plesset equation.

$$\frac{1}{r^2} \left( \frac{\partial}{\partial r} \left( r^2 u(r, t) \right) \right) = 0,$$  \hspace{1cm} (3.4)

$$\Longrightarrow u(r, t) = \frac{R_1^2 \dot{R}_1}{r^2}. \hspace{1cm} (3.5)$$

The density is a step function of radius:

$$\rho(r) = \begin{cases} \rho_G & r < R_1 \\ \rho_S & R_1 \leq r \leq R_2 \\ \rho_L & r > R_2 \end{cases}. \hspace{1cm} (3.6)$$
From the velocity equation (3.5),

$$\frac{\partial u}{\partial r} = \frac{\partial}{\partial r} \left( \frac{R_2^2 \dot{R}_1}{r^2} \right),$$

$$= -\frac{2R_1^2 \dot{R}_1}{r^3}. \tag{3.8}$$

Substituting equation (3.8) into the momentum equation (3.1) gives:

$$\rho(r) \left( \frac{\partial}{\partial t} \left( \frac{R_2^2 \dot{R}_1}{r^2} \right) - \frac{R_1^2 \dot{R}_1}{r^2} \frac{2R_2^2 \dot{R}_1}{r^3} \right) = -\frac{\partial p}{\partial r} + \frac{\partial \tau_{rr}}{\partial r} + \frac{3 \tau_{rr}}{r}. \tag{3.9}$$

As for the RPNNP equation, the pressure at the interfaces are derived by considering the forces on the interfaces, when the bubble is in equilibrium. This forms the boundary condition for equation (3.9).

Consider the positive direction to be outwards. The forces on the shell interfaces are shown in Figure (3.1).

The gas pressure acts outwards and must balance with the pressure due to the shell, at the inner shell wall, $P_S(R_1, t)$, the contribution due to surface tension $\frac{2 \sigma_1}{R_1}$ and the stress in the shell, $\tau_{rr}^S(R_1, t)$. At the other boundary, $R_2$, the shell pressure $P_S(R_2, t)$ and the stress in the liquid $\tau_{rr}^L(R_2, t)$ are balanced by the stress in the shell $\tau_{rr}^S(R_1, t)$, the surface tension $\frac{2 \sigma_2}{R_2}$ and the liquid pressure $p_L(R_2, t)$. This gives:

![Diagram showing forces on the shell surfaces, with inner radius $R_1(t)$ and outer radius $R_2(t)$.](image-url)
Gas pressure: 
\[ p_G(R_1, t) = p_S(R_1, t) - \tau_{rr}^S(R_1, t) + \frac{2\sigma_1}{R_1}. \]  
(3.10)

Shell pressure: 
\[ p_S(R_2, t) = \tau_{rr}^S(R_2, t) + \frac{2\sigma_2}{R_2} + p_L(R_2, t) - \tau_{rr}^L(R_2, t). \]  
(3.11)

Integrating equation (3.9) with respect to \( r \) from \( R_1 \) to \( \infty \) and including the boundary conditions (3.10) and (3.11) yields:

\[
\rho_S \left( \frac{\partial}{\partial t} \left[ R_1 \dot{R}_1 - \frac{R_2^2 \dot{R}_1}{R_2} \right] + \frac{1}{2} \left[ \dot{R}_1^2 - \frac{R_1^4}{R_2^4} \dot{R}_1^2 \right] \right) + \rho_L \left( \frac{\partial}{\partial t} \left[ \frac{R_1^2 \dot{R}_1}{R_2} \right] + \frac{1}{2} \frac{R_1^4}{R_2^4} \dot{R}_1^2 \right) \\
= p_S(R_1, t) - p_S(R_2, t) + p_L(R_2, t) - p_L(t) + \tau_{rr}^S(R_2, t) \\
- \tau_{rr}^L(R_2, t) + \int_{R_1}^{R_2} \frac{3\tau_{rr}^L}{r} dr + \int_{R_2}^{\infty} \frac{3\tau_{rr}^S}{r} dr.
\]  
(3.12)

Simplifying, by performing the differentiation with respect to \( t \) and recalling that \( \dot{R}_1 \dot{R}_1 = \ddot{R}_2 \dot{R}_2 \), by incompressibility, gives:

\[
R_1 \ddot{R}_1 \left( 1 + \frac{\rho_L - \rho_S R_1}{\rho_S} \frac{1}{R_2} \right) + \dot{R}_1^2 \left( \frac{3}{2} + \frac{\rho_L - \rho_S 4R_2^3 - R_1^4}{\rho_S} \frac{1}{2R_2^4} \right) \\
= \frac{1}{\rho_S} \left( p_S(R_1, t) - p_S(R_2, t) + p_L(R_2, t) - p_L(t) \right) \\
+ \tau_{rr}^L(R_2, t) - \tau_{rr}^S(R_1, t) - \tau_{rr}^L(R_2, t) + \int_{R_1}^{R_2} \frac{3\tau_{rr}^L}{r} dr + \int_{R_2}^{\infty} \frac{3\tau_{rr}^S}{r} dr.
\]  
(3.13)

Applying the boundary conditions and assuming that the pressure \( p_L(t) = P(t) + p_0 \) yields:

\[
R_1 \ddot{R}_1 \left( 1 + \frac{\rho_L - \rho_S R_1}{\rho_S} \frac{1}{R_2} \right) + \dot{R}_1^2 \left( \frac{3}{2} + \frac{\rho_L - \rho_S 4R_2^3 - R_1^4}{\rho_S} \frac{1}{2R_2^4} \right) \\
= \frac{1}{\rho_S} \left( p_G(R_1, t) - P(t) - p_0 - \frac{2\sigma_1}{R_1} - \frac{2\sigma_2}{R_2} + \int_{R_1}^{R_2} \frac{3\tau_{rr}^L}{r} dr + \int_{R_2}^{\infty} \frac{3\tau_{rr}^S}{r} dr \right).
\]  
(3.14)

This equation requires the specification of the stress tensors for the fluid and the shell. The fluid will be considered Newtonian. For a Newtonian liquid and shell \( \tau_{rr} \) is known in terms of the velocity gradient and viscosity:

\[
\tau_{rr}^L = 2\mu_L \frac{\partial u}{\partial r},
\]  
(3.15)

\[
\Rightarrow \int_{R_2}^{\infty} \frac{3\tau_{rr}^L}{r} dr = -\frac{4\mu_L \dot{R}_1^2}{R_2}. \tag{3.16}
\]
3.5. Models of the shell

The model previously derived depends on the radial component of the deviatoric stress tensor that models the shell. Several models exist for specifying $\tau_{rr}^s$. In this project the Newtonian fluid and viscoelastic solid models will be considered. The viscoelastic model will be further reduced by a thin shell approximation and solved numerically.

### 3.5.1. Newtonian fluid.

The shell may be modelled as a Newtonian fluid. The shell model is:

$$\tau_{rr}^s = 2\mu_s \frac{\partial u}{\partial r},$$

$$\Rightarrow \int_{R_1}^{R_2} \frac{2\tau_{rr}^s}{r} \, dr = -4\mu_s \frac{\dot{R}_1}{R_2} \left( \frac{V_S}{R_2^3 R_1} \right).$$

The equation (3.14) is therefore:

$$R_1 \ddot{R}_1 \left( 1 + \frac{\rho_L - \rho_S}{\rho_S} \frac{R_1}{R_2} \right) + \dot{R}_1^2 \left( \frac{3}{2} + \frac{\rho_L - \rho_S}{\rho_S} \frac{4R_2^3 R_1 - R_1^4}{2R_2^4} \right) = \frac{1}{\rho_s} \left( p_G(R_1,t) - p_0 - P(t) \right) - \frac{2\sigma_1}{R_1} - \frac{2\sigma_2}{R_2} - 4\mu_s \dot{R}_1^2 \left( \frac{V_S}{R_2^3 R_1} \right) - \frac{4\mu_L \dot{R}_1^2}{R_2}.$$  (3.19)

### 3.5.2. Viscoelastic material.

In this section it is assumed that the viscous and the elastic components add to give the overall expression for the stress tensor. This derivation follows Church(1995).

The elastic component is $\tau_{rr}^s = (\lambda_S + 2G_S) \frac{\partial \epsilon_{rr}}{\partial r} + 2\lambda_S \frac{\epsilon_{rr}}{r}$, where $\epsilon_{rr}$ is the radial strain.

An expression for $\epsilon_{rr}$ may be found for small changes in radius from the equilibrium radius $R_{1E}$, that is, for small strains. The equilibrium radius is not necessarily equal to the initial radius $R_{10}$.

The time rate of change of the strain is the velocity, and for small displacements from equilibrium the strain is $\epsilon_{rr} \approx \frac{R_2^3}{r^3} (R_1 - R_{1E})$.

Thus the integral involving the shell stress tensor becomes:

$$\tau_{rr}^s = -\frac{R_2^2}{r^3} [4G_S(R_1 - R_{1E}) + \mu_s \dot{R}_1],$$

$$\Rightarrow \int_{R_1}^{R_2} \frac{3\tau_{rr}^s}{r} \, dr = -[4G_S(R_1 - R_{1E}) + \mu_s \dot{R}_1] \left( \frac{V_S}{R_2^3 R_1} \right).$$  (3.21)
With this shell model equation (3.14) becomes:

\[
R_1 \ddot{R}_1 \left(1 + \frac{\rho_L - \rho_S}{\rho_S} \frac{R_1}{R_2}\right) + \dot{R}_1^2 \left(\frac{3}{2} + \frac{\rho_L - \rho_S}{\rho_S} \frac{4R_3^2R_1 - R_1^4}{2R_2^4}\right) = \frac{1}{\rho_S}(p_G(R_1, t) - P(t) - p_0 - \frac{2\sigma_1}{R_1} - \frac{2\sigma_2}{R_2} - 4[G_S(R_1 - R_{1E}) + \mu_SR_1] \left(\frac{V_S}{R_2^3R_1}\right) - \frac{4\mu_LR_1^2\dot{R}_1}{R_2^3}).
\]  

(3.22)

This equation may be solved for the equilibrium radius as follows. Assume that the bubble is in equilibrium at \(t = 0\). Since experimental studies have shown that the shells of certain contrast agents, for example Albunex, is permeable to gas, it is assumed that \(p_G = p_\infty\). Also at equilibrium \(R_1 = R_{10}\) etc, and all the velocities are zero.

\[-\frac{2\sigma_1}{R_{10}} - \frac{2\sigma_2}{R_{20}} - 4G_S[(R_{10} - R_{1E})] \left(\frac{R_{10}^3 - R_{20}^3}{R_{20}^3R_{10}}\right) = 0, \]

(3.23)

\[\Rightarrow R_{1E} = R_{10} + R_{10} \left(\frac{2\sigma_1}{R_1} + \frac{2\sigma_2}{R_2}\right) \frac{R_{20}^3}{V_S} \frac{1}{4G_S}. \]

(3.24)

Equation (3.22) shows the damping of the acceleration (first term) and the nonlinearity (second term) is dependent on the difference in density between the shell layer and the liquid. If \(\rho_S > \rho_L\) the acceleration and nonlinearity are both reduced and if \(\rho_S < \rho_L\) both are increased.

Church also included thermal and acoustic damping effects by the ad hoc addition of terms derived for small amplitude oscillations. The terms were derived for small changes in bubble radius and are not of the same form as the modified Herring model. Here, the viscoelastic shell model will be studied as the assumption of elastic properties of the shell seems intuitively more reasonable, for polymer and lipid shelled contrast agents, than assuming the shell layer is a viscous fluid.

3.5.3. Thin shell approximation. (Following Hoff et al. (2000)). For contrast agents the shell layer is thin compared to the radius of the bubble. For example, Albunex has a typical radius of 4 \(\mu\)m and a typical shell thickness of 15 nm. Let the shell thickness \(R_2 - R_1 = \delta\).

Church’s equation (3.22), may be simplified by substituting \(R_2 - R_1 = \delta\), expanding and retaining only linear terms in \(\delta\).

Start by writing \(R_{1E}\) and \(\delta_E\) for the equilibrium inner radius and equilibrium thickness, \(V_S\) may be approximated by:

\[V_S = (R_{1E} - \delta_E)^3 - R_{1E}^3 \approx 3R_{1E}^2\delta_E, \]

(3.25)
Substituting $R_2 - R_1 = \delta$, expanding and retaining only linear terms in $\frac{\delta}{R_1}$ for the remaining terms of the equation yields:

$$\rho_S R_1 \ddot{R}_1 \left[ \frac{\rho_L}{\rho_S} - \frac{\delta}{R_1} \left( \frac{\rho_L}{\rho_S} - 1 \right) \right] + \frac{3 \rho_L}{2} \dot{R}_1^2 =$$

$$p_G(R_1, t) - P(t) - p_0 - \frac{12 \mu_S R_1^2 \delta E \dot{R}_1}{R_1^4} - \frac{4 \mu_L \dot{R}_1}{R_1}$$

$$-12 G_S \frac{R_1^2 \delta E}{R_1^4} \left( 1 - \frac{R_1 E}{R_1} \right) - \frac{2 \sigma_1}{R_1} - \frac{2 \sigma_2}{R_1} \left( 1 + \frac{\delta}{R_1} \right).$$

(3.26)

The correction to the inertial term due to the shell $-R_1 \ddot{R}_1 \frac{\delta}{R_1} \left( \frac{\rho_L}{\rho_S} - 1 \right)$ is small compared to $R_1 \ddot{R}_1$ since $\rho_L \approx \rho_S$ and $\delta \ll R_1$ and this term is neglected.

The surface tension term $\frac{2 \sigma_2}{R_1} \left( 1 + \frac{\delta}{R_1} \right) \approx \frac{2 \sigma_2}{R_1}$, since $\frac{\delta}{R_1}$ is small, and $\sigma_2$ is small, compared to $\sigma_1$. Contrast agent manufacturers attempt to minimise the surface tension on the outside of the bubble for practical reasons. Upon writing $R_1 = R$, $\sigma_1 + \sigma_2 = \sigma$, $\rho_L = \rho$, equation (3.26) becomes:

$$R \ddot{R} + \frac{3}{2} \dot{R}^2 = \frac{1}{\rho} \left( p_G(R, t) - P(t) - p_0 - \frac{12 \mu_S R^2 \delta E \dot{R}}{R^4} \right) + \frac{4 \mu_L \dot{R}}{R} - 12 G_S \frac{R^2 \delta E}{R^3} \left( 1 - \frac{R E}{R} \right) - \frac{2 \sigma}{R}.$$  

(3.27)

Note that the fundamental form of the Rayleigh-Plesset equation has been recovered, modified by the presence of the shell. For simplicity, this is also the equation that will be studied numerically. It would also be possible to include radiation damping by the ad hoc addition of the $\frac{R \dot{\rho}_L}{\rho_\infty c_\infty}$ term, and replacing $\rho$ by $\rho_\infty$. 
CHAPTER 4

Results

4.1. Linearisation

In the clinical range 2-15 MHz, the primary oscillatory response is linear with the driving frequency $\omega$. Therefore it is useful to linearise the nonlinear ODEs for $R(t)$. This will give linear ODEs of the generic form $\ddot{x} + \beta \dot{x} + \omega_0^2 x = Af(\omega t)$. Here $\omega_0$ is the resonant frequency of the undamped oscillator, $\beta$ is the constant coefficient of damping. $f(t)$ is a periodic function with frequency $\omega$. $A$ is the amplitude of the forcing term. Note that $\omega_0$ will be referred to as the resonant frequency, even in the case of a damped oscillator.

Assume that the applied pressure field $P(t)$ is low amplitude and causes the radius to vary like $R = R_0(1 + x(t))$, where $|x| \ll 1$ and retain only first order terms in $x$.

4.1.1. Rayleigh-Plesset equation. Recall the RP equation (2.24):

$$\ddot{R}R + \frac{3}{2} \dot{R}^2 = \frac{p_0 \left( \frac{R_0}{R} \right)^{3\gamma} - p_0 - P(t)}{\rho}.$$  

Substituting $R = R_0(1 + x(t))$ into the Rayleigh-Plesset equation (2.24):

$$\frac{p_0 \left( \frac{1}{1+x} \right)^{3\gamma} - p_0 - P(t)}{\rho} = R_0^2 (1 + x) \ddot{x} + \frac{3}{2} x^2.$$  \hspace{1cm} (4.1)

Neglecting second order terms in $x$. This yields:

$$\frac{p_0 \left( \frac{1}{1+x} \right)^{3\gamma} - p_0 - P(t)}{\rho} = R_0^2 \ddot{x}. \hspace{1cm} (4.2)$$

The pressure term is simplified using the binomial theorem:

$$p_0 \left( \frac{1}{1+x} \right)^{3\gamma} \approx p_0 \left( 1 - 3\gamma x \right). \hspace{1cm} (4.3)$$

Substitute (4.3) into (4.2), and dividing through by $R_0^2$ to get a familiar equation:

$$\ddot{x} + \frac{3\gamma p_0 x}{\rho R_0^2} = -\frac{P(t)}{\rho R_0^2}. \hspace{1cm} (4.4)$$

This is a driven linear oscillator equation with resonant frequency:

$$\omega_0 = \frac{1}{R_0} \sqrt{\frac{3\gamma p_0}{\rho}}. \hspace{1cm} (4.5)$$
4.1.2. **RPNNP equation.** For the RPNNP equation (2.32)
\[
R \ddot{R} + \frac{3}{2} \dot{R}^2 = \frac{1}{\rho} \left[ (p_0 + \frac{2\sigma_1}{R_0}) \left( \frac{R_0}{R} \right)^{3\gamma} - p_0 - P(t) - \frac{4\mu}{R} \dot{R} - \frac{2\sigma}{R} \right],
\]
a damped linear oscillation is obtained. As for the RP equation it is assumed that the applied pressure field \(P(t)\) is low amplitude and causes the radius to vary like \(R = R_0(1 + x(t))\), where \(|x| \ll 1\). Proceeding as for the RP equation gives:
\[
\ddot{x} + \frac{4\mu}{\rho R_0^2} \dot{x} + \omega_0^2 x = \frac{-P(t)}{\rho R_0^2}, \tag{4.6}
\]
where
\[
\omega_0^2 = \frac{1}{\rho R_0^2} \left[ 3\gamma (p_0 + \frac{2\sigma}{R_0}) - \frac{2\sigma}{R_0} \right]. \tag{4.7}
\]

4.1.3. **Modified Herring equation.** The modified Herring equation (2.65) is
\[
\ddot{R} R + \frac{3}{2} \dot{R}^2 = \frac{R_p L}{\rho c_\infty} = \frac{p_0 \left( \frac{R_0}{R} \right)^{3\gamma} - p_0 - P(t)}{\rho}.
\]
It is possible to proceed as before by substituting \(R = R_0(1 + x(t))\), where \(|x| \ll 1\). The pressure terms are found similarly to equation (4.3):
\[
p_L \approx p_0 (1 - 3\gamma x), \tag{4.8}
\]
\[
p_L' \approx -3p_0\gamma \dot{x}. \tag{4.9}
\]
Then substituting and retaining only linear terms in \(x\):
\[
\ddot{x} - \frac{3p_0\gamma}{\rho c_\infty R_0} \dot{x} + \frac{3\gamma p_0 x}{\rho R_0^2} = \frac{-P(t)}{\rho R_0^2}. \tag{4.10}
\]
Notice that the resonant frequency is the same as for the RP equation.

4.1.4. **Newtonian fluid shell.** Linearisation of the shell models proceeds similarly to the non-shelled models. Assume that the driving pressure is small, leading to a response in the bubble radius \(R_1(t) = R_{10}(1 + x(t))\), where \(|x| \ll 1\). Since the shell is of constant volume \(R_2(t) = R_{20}(1 + \frac{R_3^{3\gamma}}{R_{30}^3} x(t))\). The pressure is as before \(p_G = p_0 (1 - 3\gamma x)\). Hence upon substitution the resonant frequency is found to be:
\[
\omega_0 = \left( \frac{\rho_s R_{10}^2 + \rho_l - \rho_s R_{10}}{\rho_s R_{20}} \right)^{-1} \left[ 3\gamma p_0 + \frac{2\sigma_1}{R_{10}} + \frac{2\sigma_2}{R_{20}} - \frac{2\sigma_1}{R_{10}} - \frac{2\sigma_2 R_{10}^3}{R_{20}^4} \right]. \tag{4.11}
\]

4.1.5. **Viscoelastic shell.** Proceeding as for the Newtonian fluid shell:
\[
\omega_0 = \left( \frac{\rho_S}{1 + \frac{\rho_l - \rho_s R_{10}}{\rho_s R_{20}}} \right)^{-1} \left[ 3\gamma p_0 - \frac{2\sigma_1}{R_{10}} - \frac{2\sigma_2 R_{10}^3}{R_{20}^4} \right] + \frac{4V_S G_S}{R_{02}^3} \left( 1 + \left( \frac{2\sigma_1}{R_{10}} + \frac{2\sigma_2}{R_{20}} \right) \left( \frac{R_{20}^3}{4V_S G_S} \right) \left( 1 + \frac{3R_{10}^3}{R_{20}^3} \right) \right). \tag{4.12}
\]

4. Results

4.1.6. Comparison of predicted values of \( \omega_0 \). Figure (4.1) shows the resonant frequencies in a range of typical contrast agent sizes. The parameters used to calculate the resonant frequencies were for an air bubble in water. The density of water was taken as \( \rho_L = 1000 \text{ kgm}^{-3} \), the reference pressure was approximately atmospheric \( p_0 = 0.1 \text{ MPa} \). The polytropic exponent was \( \gamma = 1.4 \), which is the value for an adiabatic process in an ideal gas. The surface tension on the water-gas interface was taken as \( \sigma = 4 \text{ Pa} \).

The shell parameters were estimated for the contrast agent Albunex. The shell density was \( \rho_S = 1100 \text{ kgm}^{-3} \) the shell-gas surface tension was estimated to be \( \sigma_1 = 7 \text{ Pa} \). The liquid-shell surface tension \( \sigma_2 = 0.5 \text{ Pa} \), is considerably lower, since most contrast agents have surface coatings to reduce \( \sigma_2 \). The values were chosen such that the sum of surface tensions agreed with measurements of surface tension for a monolayer of horse serum albumin. The shell thickness \( R_2 - R_1 = 15 \text{ nm} \) was estimated from microscopy measurements. The elastic modulus \( G_s = 88.8 \text{ MPa} \). The parameters chosen were to follow Church (1995), who chose parameters to agree with experiments by de Jong and Hoff, as reported in (Church 1995).

The resonant frequency tends to infinity as the initial radius tends to zero. For the RPNNP and the shell models the value of \( \omega_0 \) rises more rapidly than for the RP and Modified Herring, since \( \omega_0 \) for a shelled model goes like the square root of the shell parameters, but is also dependent on \( R_0 \).

The surface layer of the RPNNP equation can be considered as a highly simplified shell having zero thickness. The parameters used in the calculation may be found in Table (1), along with the parameters used for simulation of the bubble oscillation. The MATLAB script to perform the calculation may be found in Appendix B.

4.2. Numerical methods

The models derived were solved numerically using the MATLAB (Version 7 (R14)) package BubbleSim (Hoff 2007) written by Lars Hoff for simulation of ultrasound contrast agents. The
4.2. Numerical methods

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>p_0</td>
<td>1.013 \times 10^9 \text{ Pa}</td>
<td>Ambient pressure</td>
</tr>
<tr>
<td>\rho</td>
<td>1000 \text{ kg/m}^3</td>
<td>Density of liquid</td>
</tr>
<tr>
<td>\gamma</td>
<td>1.4</td>
<td>Polytropic exponent</td>
</tr>
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</table>

Model specific parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>c_\infty</td>
<td>1500 \text{ m/s}</td>
<td>Speed of sound in liquid</td>
</tr>
<tr>
<td>\mu_L</td>
<td>1.0 \times 10^{-3} \text{ Pa s}</td>
<td>Viscosity in liquid</td>
</tr>
<tr>
<td>\sigma</td>
<td>4 \text{ Pa m}</td>
<td>Surface Tension</td>
</tr>
</tbody>
</table>

Shell parameters (if present)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>\delta</td>
<td>15 \text{ nm}</td>
<td>Shell thickness</td>
</tr>
<tr>
<td>G_S</td>
<td>88.8 \text{ MPa}</td>
<td>Shell elastic modulus</td>
</tr>
<tr>
<td>\mu_S</td>
<td>0.5 \text{ Pa s}</td>
<td>Shell viscosity</td>
</tr>
<tr>
<td>\sigma</td>
<td>7 \text{ Pa m}</td>
<td>Surface Tension</td>
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<table>
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</tr>
<tr>
<td>\sigma</td>
<td>7 \text{ Pa m}</td>
<td>Surface Tension</td>
</tr>
</tbody>
</table>

Table 1. Table of parameters used for the numerical calculations.

parameters for the liquid, gas and shell, if present, are shown in Table 1. All the solutions assume an adiabatic process for a microbubble, containing air, and the external liquid is water.

BubbleSim uses the inbuilt MATLAB stiff ODE solver ode15s, based on numerical differentiation formulas. BubbleSim was verified by writing code to solve the RP equation. BubbleSim was also modified to include surface tension and the viscoelastic shell model. The code is shown in Appendix B. BubbleSim originally included liquid viscosity and a different shell model, called the exponential model. The viscosity was set to 0 for the solution of models not including viscous damping. The values in Table 1 represent literature values for typical contrast agents, rather than a full exploration of parameter space. MATLAB allows the relative tolerance of the numerical scheme to be set. This was taken as $1 \times 10^{-6}$. The timestep was taken as $1 \times 10^{-8}$ s. These parameters gave stable numerical solutions in the region of interest for microbubble contrast agents, however for very low amplitude driving pressures, close to the resonant frequency of the bubble, this parameter choice was found to be inappropriate.

The driving pressure function was an enveloped sinusoid, with centre frequency, the angular frequency of the sinusoid, $\omega$. The Hann window, equation (4.14) of width $x$, was chosen as it is a typical medical ultrasound pulse. The total integration time was set by the length of driving
pressure pulse, which was specified by the frequency $\omega$ and the number of cycles in the pulse. The integration time was 4 times the pulse length. A Hanning pulse (a pulse with a Hann window) is shown in Figure 4.2.

$$w(x) = \frac{1}{2}(1 + \cos(x))$$  \hspace{1cm} (4.14)

BubbleSim calculates the scattered pulse at 1 m, such as would be observed at the ultrasound receiver. The scattered pulse is resulting echo from the microbubble. This is calculated from the bubble oscillation. See (Hoff 2001) for further information.

The power spectra is the amplitude of the discrete Fourier transform of the driving pulse and the scattered pulse. The spectrum shows the amplitude of the various frequency responses of the bubble radius. Hence, the linear response and the higher and possibly subharmonics may be observed. More information can be gained by studying the spectra, rather than simply the radial response.

4.3. The Rayleigh-Plesset equation

4.3.1. Linear regime. The Rayleigh-Plesset equation reduces to a linear equation (4.4) for small changes in the radius. The numerical solutions of the linearised equation and the full nonlinear RP equation were compared for small driving pressures. Figures (4.3) and (4.4) show the results for the case where $\omega$ was close to and much larger than the resonant frequency of the bubble $\omega_0$, respectively. In the case of the RP equation for small driving pressure amplitudes far below the resonant frequency the numerical solutions predicted no radial oscillation.

The plots show that the solution of the linearised RP equation agrees fairly well with the nonlinear RP results for small driving amplitudes for the duration of the driving pulse. The higher harmonic responses in the nonlinear case are small relative to the linear response.

After the driving pulse amplitude decreases towards zero, the bubble will continue to oscillate freely with a lower amplitude. The linearised RP equation tends to underestimate the bubble
4.3. The Rayleigh-Plesset Equation

**Figure 4.3.** Left: the simulated radial response of a 4 µm radius RP air microbubble in water to a Hanning pulse with centre frequency 5 MHz, 5 cycles in length, 0.1 MPa amplitude. The solution to the linearised equation (black) agrees well with the full RP equation (red). Right: the power spectra of the pulse (blue), the behaviour is dominantly the linear response, as shown by the linearised solution (black) and the full RP solution (red).

**Figure 4.4.** Left: the simulated radial response of a 4 µm radius RP air microbubble in water to a Hanning pulse with centre frequency 8 MHz, 5 cycles in length, 0.1 MPa amplitude. The solution to the linear equation (black) agrees well with the full RP equation (red) over the period of the driving pulse, however it tends to underestimate the amplitude the following free oscillation. Right: the power spectra of the pulse (blue), the linear solution (black and the full RP solution (red) show the dominant linear response. Notice the generation of the third harmonic, relatively small compared to the linear response.

radius and over estimate the oscillation frequency of the freely oscillating bubble, after the driving pressure stops. This shows that the linear equation may not be valid even for the low driving pressure of 0.1 MPa.
4.3.2. Higher harmonics. The following set of simulations shown in Figures (4.5), (4.6) and (4.7) show the generation of higher harmonic oscillations for a RP bubble. The power spectra shows a dominant response at the driving frequency $\omega$ and, for increased amplitudes, peaks are seen at $2\omega$ and $3\omega$. The third harmonic is small compared to the linear response and only appears at very high driving pressures. The generation of higher harmonics may be used to form specialist images. As will be seen later, the presence of a shell drastically changes the higher harmonic responses.

**Figure 4.5.** Simulated response of a RP air bubble 4 $\mu$m radius in water to low amplitude driving pressure. Hanning pulse amplitude: pulse amplitude: 0.1 MPa (top left), the scattered pulse (top right), the radial response (bottom left) and the power spectra showing the linear response (bottom right).
4.3. THE RAYLEIGH-PLESSET EQUATION

Figure 4.6. Simulated response of a RP air bubble 4 µm radius in water, to increased amplitude driving pressure. Hanning pulse amplitude: 0.5 MPa (top left), the scattered pulse (top right), the radial response (bottom left) and the power spectra showing the second harmonic response (bottom right).

Figure 4.7. Simulated response of a RP air bubble 4 µm radius in water, to high amplitude driving pressure. Hanning pulse amplitude: 2 MPa (top left), the scattered pulse (top right), the radial response (bottom left) and the power spectra showing the third harmonic response (bottom right).
4.3.3. **Large bubble oscillations.** The radial response of an RP bubble driven at high amplitudes with frequencies below resonance will exhibit rapid growth and collapse. The timescale over which a bubble responds is of the order of $\omega_0^{-1}$. If the bubble is small, the resonant frequency is large and the response timescale is low. If the driving frequency is low, then the bubble has time to grow very large in the low driving pressure cycle leading to rapid collapse during the high driving pressure cycle. The bubble may undergo destructive collapse, where the predicted radius becomes zero.

Solutions of this form are of particular interest when studying a cavitation bubble, however, similar behaviour can occur in contrast agents. The high amplitude oscillations leading to destructive collapse is called ‘transient’ cavitation, shown in Figure (4.8(a)). It is possible for the large oscillations to persist indefinitely. This is called ‘stable cavitation’ shown in Figure (4.8(b)).

![Figure 4.8](image)

**Figure 4.8.** Left: simulated response of a RP bubble 2 $\mu$m radius in water exhibiting transient cavitation the driving pressure is a Hanning pulse 2.25 MHz centre frequency 1.5 MPa amplitude. Right: simulation of a RP bubble 2 $\mu$m radius in water undergoing stable cavitation. The driving pressure is a Hanning pulse 2.25 MHz centre frequency 1 MPa amplitude.

4.4. **The RPNNP equation**

BubbleSim was modified to include surface tension effects as described by the RPNNP equation (2.32). The modified surface pressure function may be found in Appendix B.

For the RPNNP equation, the linear regime results are similar to the RP equation. The linear results are shown in Figure (4.9). During the pulse, the radial oscillation predicted by the RPNNP equation and the linearised equation agree well. After the pulse, the bubble oscillates freely. In this region, the solutions are similar in amplitude, but the linear equation greatly underestimates the oscillation frequency, again suggesting that the linear equation is insufficient to predict the radial response for these parameters. The linear response and the RPNNP equations both predict almost identical power spectra and in that sense, the linear equation is a good approximation.
Higher harmonic generation for the RPNNP equation is similar to the RP equation. The results of a simulation of the RPNNP equation predicting higher harmonic generation are shown in Figure (4.10). Compare these results with the results found for the RP equation (for the same driving pulse) shown in Figure (4.7). The amplitude of the radial response is considerably damped for the RPNNP equation, however, the power spectra predicts the same higher harmonic generation, all with similar intensities.

**Figure 4.9.** Simulated response of a RPNNP air microbubble in water to a low amplitude driving pressure. Hanning pulse with centre frequency 5 MHz, 5 cycles in length, 0.1 MPa amplitude. The linearised (black) solution is also shown. The power spectra includes the spectrum of the pulse (blue), the linearised solution (black) and the full RPNNP solution (red) showing a dominant linear response.
Figure 4.10. Simulated response of a RPNP air microbubble in water to a high amplitude driving pressure. Hanning pulse with centre frequency 5 MHz, 5 cycles in length, 2 MPa amplitude. The linear (black) solution is also shown. The power spectra includes the spectrum of the pulse (blue), the linearised solution (black) and the full RPNP solution (red) showing the higher harmonics.
4.5. Comparison of radiation damping models

The radiation damping models are the modified Herring equation (2.65), the Herring-Trilling equation (2.64) and Keller-Miksis equation (2.81). The modified Herring model is often the most convenient model to study numerically for reasons outlined in 2.7.2.

For the linear regime with small driving pressures, the wall velocity is small and a comparison of the numerical solutions of the Rayleigh-Plesset equation (2.24) and the Herring-Trilling equation (2.64) shows no significant difference in radial response. Overlaid plots of the radial response are shown in Figure (4.11). The maximum difference between the solution curves is $1.49 \times 10^{-8}$ m.

![Figure 4.11](image)

**Figure 4.11.** Comparison of the simulated response of the RP model and the Herring-Trilling model for a 4 µm air microbubble in water, for a low amplitude driving frequency. Hanning pulse, centre frequency 5 MHz, 5 cycles in length, 0.1 MPa amplitude. This plot shows the difference between the models is negligible in the linear regime.

To compare the effects of viscous damping and radiation damping the RP, RPNNP and the Modified Herring equations (equations (2.24), (2.32) and (2.65)) were simulated for a bubble undergoing stable cavitation. Since the viscous damping is proportional to $\dot{R}$ the cavitation regime would be the most affected by viscous damping. A plot of the radial response is shown in Figure (4.12). Both radiation and viscous damping reduce the amplitude and increase the frequency of the oscillations compared to the undamped RP case. It is observed that the effect of viscous damping is more significant than the radiation damping in this regime.
4. RESULTS

Figure 4.12. Comparison simulated results of damping models for a 4 µm air microbubble in water. Hanning pulse with centre frequency 3 MHz, 2.5 cycles in length, 0.3 MPa amplitude. Viscous damping reduces the amplitude and increases the frequency of the oscillations compare RPNNP to the RP results. Similar comparison of the modified Herring model and the RP shows the effect of viscous damping.

4.6. Church’s equation

The effect of an encapsulating shell was investigated by solving Church’s equation assuming a thin shell, that is equation (3.27). BubbleSim was modified to include this equation, see Appendix B. Results are presented for parameters, as given in Table 1, estimated for the commercial contrast agents Albunex, with an albumin shell, and Nycomed, which has a polymer shell.

The resonant frequency, as predicted by linearised Church’s equation (4.13), of an Albunex bubble of radius 4 µm is approximately 35 MHz, far above the clinical range. For a Nycomed bubble of radius 5 µm, the resonant frequency is approximately 21 MHz.

The results of simulations of Church’s equation assuming a thin shell, equation (3.27), for a low driving pressure are shown in Figure 4.13(a), for Albunex, and Figure 4.14(a) for Nycomed. The linear and nonlinear results agree well for the radial response in both cases. The power spectra in both cases are similar to the low driving pressure results for the RPNNP equation, shown in Figure 4.9, which are also similar to the results for the RP equation.

Reducing the frequency and increasing the amplitude of the driving pressure for a shelled microbubble gives a response considerably different to the response of an unshelled gas bubble to the same driving pressure. The unshelled gas bubble will undergo cavitation, rapidly growing and collapsing as shown for the RP equation in Figures 4.8(a) and 4.8(b). For a shelled
microbubble, the shell suppresses this behaviour. The growth is much smaller in amplitude and collapse is not violent.

Results of simulations for Albunex and Nycomed, for a high driving amplitude, are shown in Figures (4.13(b)) and (4.14(b)), respectively. As can be seen, the bubble does not undergo a response similar to stable cavitation. For both contrast agents the maximum radial growth is approximately 1 \( \mu \text{m} \). The response for both models is, however, highly nonlinear with many higher harmonics present. For the Nycomed contrast agent Figure (4.14(b)), the \( \frac{1}{2} \) subharmonic is also observable. The \( \frac{1}{2} \) subharmonic is superimposed with the tail of the driving pulse.
(a) Centre frequency 8 MHz, 0.1 MPa amplitude. Comparing the linear response (black) with the nonlinear equation (red).

(b) Centre frequency 3 MHz, 0.3 MPa amplitude. Showing the generation of sub and higher harmonics.

Figure 4.13. Simulation results for a Albunex contrast agent in water (parameters shown in Table 1). Hanning pulse, 5 cycles in length, the spectra of the pulse is shown in blue.
(a) Centre frequency 5 MHz, 0.1 MPa amplitude. Comparing the linear response (black) with the nonlinear equation (red).

(b) Centre frequency 3 MHz, 0.3 MPa amplitude. Showing the generation of sub and higher harmonics.

Figure 4.14. Simulation results for a Nycomed contrast agent in water (parameters shown in Table I). Hanning pulse, 5 cycles in length, the spectra of the pulse is shown in blue.
Chapter 5

Discussion

5.1. Limitations of models

The fundamental assumptions of the models, such as spherically symmetric and stationary bubbles are unrealistic for contrast agents in the body. Smaller blood vessels are often of comparable size to the microbubble and the presence of boundaries will break the spherical symmetry. The fluid flow around the bubble may be of the order of $10^{-100}$ centimetres per second for microbubbles in the major arteries. Blood is also much more viscous with a slightly higher sound speed than water. The general behaviour of the contrast agents, as illustrated in the numerical solutions, will persist but will be more highly damped. Blood is also a non-Newtonian fluid. The red blood cells are of comparable size to the contrast agent, hence there will be collisions between the cells and the contrast agents.

The persistence of the bubble is also an idealisation. The gas within the bubble will diffuse across the boundary and the bubble will collapse. Bubble collapse will also violate the assumption of spherical symmetry. Stability of the bubble was a major problem with commercial ultrasound contrast agents. To be useful in practice, the contrast agent must persist so that it can travel from the injection site to the site of interest.

Thermal effects have been idealised by the polytropic gas assumption. The study of cavitation bubbles shows that the thermodynamic behaviour of the bubble is crucial to understanding collapse. Thermal damping of oscillations due to heat flow across the boundary is included in many cavitation models. It is possible to include thermal damping effects in the study of ultrasound contrast agents. The inclusion of such effects is not as important for understanding contrast agent behaviour, as the oscillatory behaviour of the bubble wall is smaller in magnitude, compared to cavitation bubbles.

Continuum mechanical modelling of the shell may be unrealistic. For thin shelled contrast agents such as Albunex the shells are of the order of 15 nm thick. The shell is only a few molecules thick and the continuum approximation may be incorrect. For Nycomed, with a shell thickness of approximately 250 nm, the approximation may be more reasonable. Experimental studies tend to validate the continuum modelling of the shell. The resonant frequency $\omega_0$ of contrast agents may be measured and found to be of the same form as predicted by the continuum models. The estimates of the elasticity and viscosity parameters $G_S$ and $\mu_S$ are from experiments measuring $\omega_0$. The estimates of $G_S$ and $\mu_S$ cannot be derived from first principles. It is possible to experimentally discover models for the shell, based on curve fitting to the resonant frequency measurements. This is the origin of Hoff’s model for Albunex (Hoff 2001).
5.2. Developments and other applications

Translation of the bubble may be included in models. Work by Doinkov & Dayton (2006) generalised Church’s equation by deriving a system of coupled equations describing the radial and translational dynamics of a microbubble with an encapsulated shell, using the Lagrangian formalism. Their model also derived a radiation damping term, which Church added in an ad hoc manner.

A new application of microbubble contrast agents is targeted drug delivery. The drug may be included in the contrast agent shell. The location of the microbubbles can be tracked by ultrasound imaging, and when the contrast agents reach the target object the bubble can be ruptured, releasing the drug. Specific ligands can be attached to the contrast agent shell. The ligand will preferentially attach to target object, enhancing drug delivery (Blomley et al. 2001).

It is possible to use the second harmonics from the bubble response to form ultrasound images. The image is formed by using pulse inversion. See Hoff (2001) for further information. This technique has been applied to study the tissue perfusion of brain tumours, allowing identification of tumours, but also allowing the diagnosis of particular types of tumour. (Harrer et al. 2003)

5.3. Comparison of models

The models derived all have the same persistent form as the fundamental Rayleigh-Plesset equation. The additions to the model, such as radiation damping, addition of viscosity and shell layers can be shown only to change the pressure term in the fundamental RP equation.

This thesis has reviewed and derived most of the important bubble models, starting with the RP equation. This was extended by to the RPNNP equation modifying the pressure at the bubble wall so that the model included viscous and surface tension terms. Similarly, radiation damping models were considered, and it was shown that these effectively changed the conditions at the boundary. The Herring-Trilling and Keller-Miksis models were considered in this thesis. Importantly for contrast agents, the modified Herring model, which is the RP equation with a single correction term added, was derived for small bubble wall velocities from the Herring-Trilling model. The radiation damping models considered here are unsatisfactory for high velocity oscillations, since the acoustic assumption will break down. For models that include an encapsulating shell, which is thin compared to the bubble radius, once again the model will reduce to the RP equation with corrections to the pressure term. This allows flexibility in the numerical simulation of the contrast agent behaviour, since the ODEs all have the same form.

At low driving pressures, all the models may be reduced to a linear oscillator equation, with a well defined resonant frequency. Numerical simulations have shown that the linearised equation for the radial response of the bubble is largely in agreement the full nonlinear models. The linear response is of great physical importance as it is the most easily observed physical quantity. Hence the linear response of the microbubble may be used experimentally to estimate the parameters of contrast agents.
The presence of a shell dramatically changes the response to an acoustic driving pressure pulse. To successfully model the behaviour of modern contrast agents the shell layer must be considered. The differences in the acoustic response between and a bubble without a shell and a bubble with a shell were shown in Section 4.6. In general the behaviour of contrast agents is also greatly affected by the shell properties. The highly nonlinear stable cavitation bubble oscillations are reduced by the shell. The presence of the shell will make the bubble more viscous, hence, more of the energy from the pulse will be absorbed and converted to heat, rather than being scattered or radiated by the bubble. Several models exist for the shell layer, such as the viscoelastic model studied here. It is possible to use different rheological models, and no one model is considered to be completely encompassing of all the contrast agents.
References


Hoff L 2007 ‘Ultrasound contrast bubble simulation’. 

http://home.online.no/~fam.hoff/Bubblesim/Bubblesim.htm.


APPENDIX A

Analytical solution of a special case of the Rayleigh-Plesset equation

Analytic solutions of (2.24) may be found for \( P(t) = -AH(t) \) where \( H \) is the Heaviside step function and \( A \) is a constant. For convenience assume \( \gamma = 1 \). Equation (2.24) may be written:

\[
\frac{A - p_0}{\rho} + p_0 \frac{R_0^3}{R \rho} = \ddot{R}R + \frac{3}{2} \dot{R}^2. \tag{A.1}
\]

Multiply both sides by \( 2 \dot{R}R^2 \):

\[
2 \frac{A - p_0}{\rho} \dot{R}R^2 = 2 \ddot{R}RR^3 + 3 \dot{R}^3 R^2.\tag{A.2}
\]

Notice that \( 2 \ddot{R}RR^3 + 3 \dot{R}^3 R^2 = \frac{d}{dt}(R^3 \dot{R}^2) \), then forming time derivatives on both sides:

\[
\frac{d}{dt} \left( \frac{2(A - p_0)R^3}{3\rho} \right) + \frac{d}{dt} \left( 2p_\infty \frac{R_0^3 \ln(R)}{\rho} \right) = \frac{d}{dt}(R^3 \dot{R}^2).\tag{A.3}
\]

Note that the second term on the right hand side would be different if \( \gamma \neq 1 \). Integrating with respect to \( t \) gives

\[
\frac{2(A - p_0)R^3}{3\rho} + 2p_\infty \frac{R_0^3 \ln(R)}{\rho} = R^3 \dot{R}^2 + C, \tag{A.4}
\]

where \( C \) is the constant of integration. The initial condition of a motionless bubble \( \dot{R} = 0 \) and \( R(0) = R_0 \) gives:

\[
C = \frac{2(A - p_0)R_0^3}{3\rho} + 2p_\infty \frac{R_0^3 \ln(R_0)}{\rho}, \tag{A.5}
\]

hence:

\[
\frac{2(A - p_0)(R^3 - R_0^3)}{3\rho} + 2p_\infty \frac{R_0^3 \ln(R/R_0)}{\rho} = R^3 \dot{R}^2, \tag{A.6}
\]

and

\[
\frac{dR}{dt} = \left( \frac{2(A - p_0)(R^3 - R_0^3)}{3\rho} + 2p_\infty \frac{R_0^3 \ln(R/R_0)}{\rho} \right)^{\frac{1}{2}}. \tag{A.7}
\]

This is separable, and leads to

\[
t = \int_{0}^{R/R_0} \left( \frac{2(A - p_0)(\chi^3 - 1)}{3\rho \chi^3} + 2p_0 \frac{\ln(\chi)}{\chi^3 \rho} \right)^{-\frac{1}{2}} d\chi. \tag{A.8}
\]
The solution for $\gamma \neq 1$ proceeds in the same manner and the solution obtained is:

$$t = \int_{0}^{R/R_0} \left( \frac{2(A - p_0)(\chi^3 - 1)}{3\rho\chi^3} + \frac{2p_0(\chi^{3\gamma} - \chi^3)}{3(1 - \gamma)\rho} \right)^{-\frac{1}{2}} d\chi.$$  \hspace{1cm} (A.9)

This solution may yield asymptotic results for the bubble wall velocity, $R_0 \ll R$, such as a maximum velocity, the approximate time of growth of the bubble radius. Also the rate of collapse $R \ll R_0$ may be estimated, this also yields a minimum size of the bubble radius. See Brennen (1995).
Appendix B

MATLAB code

1. Resonant frequency

```matlab
% Code to generate figure 4.1.

% Res freqs.
R0 = [2:1e-3:10];
p0 = 101300; % Reference pressure, Pa
R0 = R0 * 1e-6; % Define vector of R0s
D = 15e-9; % Shell thickness
R01 = R0; % Inner radius
R02 = R0 + D; % Outer radius
sigma = 7;
sigma1 = 4; % Pa
sigma2 = 0.5; % Pa
rho = 1000; % Fluid density, kg/m3
rhoS = 1100; % Shell density, kg/m3
gamma = 1.4; % Polytropic exponent
Gs = 88.8e6; % Pa
Vs = R02.^3 - R01.^3;
alpha = (1 + ((rho - rhoS) / rhoS) * (R01 ./ R02));
Z = (2 * sigma1 ./ R01 + 2 * sigma2 ./ R02) .* (R02.^3 ./ Vs) ./ (4 * Gs);

w0rp = R0.^(-1) .* sqrt(3 * gamma * p0 / rho); % Rp resfreq.
w0rp = w0rp ./ 1e6;
w0rpnnp = R0.^(-1) .* sqrt((3 * gamma * (p0 + 2 * sigma ./ R0) - 2 * sigma ./ R0) / rho); % Rp nnp
w0rpnnp = w0rpnnp ./ 1e6;

% Church:
w0sh2 = (rhoS * R01.^2 .* alpha).^(-1) .* (3 * gamma * p0 - 2 * sigma1 ./ R01 - ...
2 * sigma2 .* R01.^3 ./ (R02.^4) + 4 * Vs * Gs ./ (R02.^3) .* (1 + Z .* (1 + 3 * R01.^3 ./ R02.^3)));
w0sh = sqrt(w0sh2);
w0sh = w0sh ./ 1e6;

% Newtonian shell
w0n2 = (rhoS * alpha .* R01.^2).^(-1) .* (3 * p0 + 2 * sigma1 ./ R01 ...
+ 2 * sigma1 ./ R02 + gamma - 2 * sigma1 ./ R01 - 2 * sigma2 .* R01.^3 ./ (R02.^4));
w0n = sqrt(w0n2);
w0n = w0n ./ 1e6;

lstr1 = ['NF Shell ', num2str(D*1e9), ', nm'];
lstr2 = ['VE Shell ', num2str(D*1e9), ', nm'];

plot(R0, w0rp, 'r', R0, w0rpnnp, 'g', R0, w0n, 'b', R0, w0sh, 'k');
h = legend('RP Mod. Herring', 'RPNNP', lstr1, lstr2);
set(h, 'Interpreter', 'none')
xlabel('Initial bubble radius, m')
ylabel('Resonant frequency, MHz')
title('Resonant frequency')
```

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2. Modified surface pressure function

The surface pressure calculation was modified to include the surface tension effects (the variable \( \text{sig} \)).

```matlab
function [qL, q1, q2] = BS_SurfacePressureM(x, dx, gs, ns, nL, kappa, sig);

% function [qL, q1, q2] = BS_SurfacePressure(x, dx, gs, ns, nL, kappa);
%
% Pressure at the bubble surface
%
% x : Radial strain
% dx = dx/dt
% gs : Normalized shell shear modulus
% ns : Normalized shell shear viscosity
% nL : Normalized liquid viscosity
% kappa: Polytropic exponent
%
% qL : Pressure at bubble surface
% q1 = dqL/dx
% q2 = dqL/ddx
%
% Calculate pressure at bubble surface
% Boundary condition for ODE giving bubble motion
%
% Lars Hoff, NTNU, Dept. of Telecommunications
% Trondheim, Norway
%
%--- Gas pressure ---
qs = (1+2*sig)*(1+x).^(-3*kappa);
dqs= -3*kappa*(1+2*sig)*(1+x).^(-3*kappa-1);

%--- Shell pressure ---
%--- Thin Shell Model ---
%--- MODIFICATION ---
qs = -12*(gs*x+ns*dx)./(1+x).^4;
dqs1= -12*(gs*(1./(1+x).^4 -4*x./(1+x).^5)-4*ns*dx./(1+x).^5);
dqs2= -12*ns./(1+x).^4;

%--- Pressure at bubble wall ---
qL = -4*nL*dx./(1+x) - 2*sig./(1+x) + qs + qg;
q1 = 4*nL*dx./(1+x).^2 +dqs1 +dqg;
q2 = -4*nL* 1./(1+x) +dqs2;
return
```

In functions that did not require \( \text{sig} \), the value that was passed to the function was 0. Similarly for functions that did not require the viscosity \( nL \).

The shell model was changed from Hoff’s exponential model to Church’s model with the thin shell approximation.

The surface tension \( \text{sig} \) is specified in `BS_PhysicalConstants.m`

```matlab
%---------------------
particle.sig=7; %[Pam]

It is non dimensionalised in `BS_SimulateOscillation.m`

normalized.sig=sig*(a0*p0);
...(code removed)
sig= normalized.sig;
```
BubbleSim was validated by comparing the output with the radial response calculated from the following program.

```
% ode solver for the rayleigh bubbles
% ----------------------------------------
function bubbles(filename)
%clear globals and figures

clear global
clear flg
clf

global A w w_0 p_ref rho R0 g t0 env %set globals
flg=0; %set linearised plot flag
%----------------------------------------
%PHYSICAL CONSTANTS
%----------------------------------------
p_ref = 1e5; %reference pressure Pa
rho = 1e3; %density of fluid kg/m3
g = 1; %polytropic exponent Unitless
s = 0; %surface tension N/m

%----------------------------------------
%READ PARAMETERS FROM DATAFILE
%----------------------------------------

x=importdata(filename,"'","0");   %freq. Hz
A=x.data(2); % Pa pulse amplitude
env=x.data(3); %envelope, currently 'rectangular' or 'hanning'
R0=x.data(4); % m initial bubble radius
R1=x.data(5); % m initial bubble wall velocity
R2=x.data(6); % initial time
t2=x.data(7); %final time
n=x.data(8); %timesteps
t0=x.data(9); %cutoff
t1=x.data(10); %plotting parameters
t2=x.data(11); %plotting parameters
t3=x.data(12); %plotting parameters
solver=x.data(13); %ode solver
eqn=x.data(14); %equation to solve

%----------------------------------------
%this lot is the time range and timestep
%----------------------------------------
tstep =(t2-t1)/n;
Tspan = [t1:tstep:t2];
%----------------------------------------
%CALCULATIONS START HERE
%----------------------------------------

w_0 = (1/R0)*sqrt(3*g*p_ref/rho); %reasonant freq.
options=odeset('RelTol',1e-5);
switch (eqn)
    case 1
        func = 'linearrhs_1';
```

```
A = (A / (R0 * rho));
IC = [0, 0]; % ics fixed
flg = 1; % to transform perturbation into radius.
case 2
    func = 'rayleighrhs_2';
    IC = [R0, R1];
case 3
    func = 'modrayleighrhs_3';
case 4
    % insert more
end

switch (solver)
    case 45 % calls ode45 solver with the function func
        [T, R] = ode45(func, tspan, IC, options);
    case 15 % calls ode15s solver with the function func
        [T, R] = ode15s(func, tspan, IC, options);
end

if flg == 1
    R(:, 1) = R0 + R(:, 1);
end

% -------------------------------------
% Save whole workspace as *.mat the filename is date and time
% -------------------------------------
outfile = datestr(now, 'yyyyMMddTHHMMSS'); % generate date and time string with only numbers and letters in string
save(outfile); % save the workspace

% -------------------------------------
% Prints.
% -------------------------------------

if pltspar(1) == 1
    figure(1)
    plot(T, R(:, 1), 'g')
    title('Bubble Radius')
    xlabel('Time s')
    ylabel('Bubble radius m')
end

if pltspar(2) == 1
    figure(2)
    plot(tspan, pulse(tspan))
    title('Driving pressure')
    xlabel('Time s')
    ylabel('Pressure Pa')
end

if pltspar(3) == 1
    figure(3)
    plot(T, R(:, 2), 'r')
    title('Bubble wall velocity')
    xlabel('Time s')
    ylabel('Bubble wall velocity m/s')
end
function f = linearrhs_1(t,y)
global w_0 w p t0 rho R0

f = [y(2); pulse(t) - w_0^2*y(1)];
return

function f = rayleighrhs_2(t,y)
global p_ref rho A t0 g w env R0 %accept globals

f = [y(2); (pulse(t) - p_ref + p_ref*(R0./y(1))^(3*g))/(rho*y(1))... - (1.5*y(2)^2/(y(1)))];
return;

function z = pulse(t)
global A w t0 sigma env %accept globals.

switch (env)
    case 0
        z = A*sin(w*t); %no window
    case 1
        z = A*(heaviside(t0)-heaviside(t-t0)).*sin(w*t); %box shaped window
    case 2
        z = A*(1-cos(2*pi*t/t0).*sin(w*t))/2; %hann window
    case 3
        z = A*(sin(pi*t/t0)).*sin(w*t); %cosine window
end

return