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Effects of varying ultrasound parameters on the oscillation of a microbubble near a boundary

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Abstract. Microbubbles are currently used as ultrasound contrast agents. However, microbubbles have the potential to be used in diagnostic imaging and therapeutic applications. Most numerical work on simulating microbubble oscillation involves modelling microbubbles in infinite medium whereas clinical trials and experiments involve microbubbles near a boundary such as an endothelium and blood vessels. This study will extend previous research by investigating the effects of varying the ultrasound parameters on a microbubble near a boundary. The microbubble oscillation was found to become increasingly irregular as the driving pressure amplitude is increased. The maximum amplitude of oscillation was found to decrease with increasing ultrasound frequency.

Keywords. Dynamics; nonlinear systems; vibrations; ultrasound; oscillations; microbubble; boundary.

1. Introduction

Microbubbles are used as a contrast agent in medical diagnostics for ultrasound imaging [1]. Microbubbles have a great level of echogenicity, which is the ability to reflect ultrasound waves. Thus, microbubble contrast agents improves the ultrasound backscatter, or reflection of the ultrasound waves, to generate a unique sonogram with improved contrast due to the high echogenicity difference.

Recent studies have shown that microbubbles have the potential to be used in diagnostic imaging and therapeutic applications [2, 3]. Here, microbubble ultrasound contrast agents flow within constrained bloodstream such as arteries, veins, and capillaries [4]. These clinical trials and experiments involve microbubbles passing through blood vessels by using micro-sized tubes to emulate the vessels [5-8]. These experiments employ optical trapping system that has allowed manipulation of single and numerous bubble [9-12].

Theoretical studies of microbubble oscillation involve numerical solution of the governing equation. The equation was first formulated by Lord Rayleigh model in 1917 [13]. The mathematical model was then developed by Rayleigh, Plesset, Moltingk, Neppiras, and Poristky (RPPNNP) equation [14], Herring [15] and Keller-Miksis-Parlitz [16]. These mathematical models assume that the bubble is in infinite medium in which there are no boundaries. The boundary has been shown to have influence on the microbubble oscillation [11]. Since the interaction between ultrasound and microbubble oscillation are nonlinear in nature, any changes in parameters and conditions will subsequently change their dynamics behaviour.

It is thus important to understand how the boundary effects the vibration of the microbubbles in order



to effectively manipulate and control microbubble oscillation to achieve it's full potential in therapeutic and theranostic applications

In this research, the Takahira[17] coupling term will be incorporated in the Keller-Miksis-Parlitz equation [16] suitable for large amplitude oscillation. The result of a single microbubble near a boundary will be investigated by varying acoustic pressure and driving frequency.

2. Modelling & methodology

2.1. Mathematical model for a free microbubble

A Keller-Miksis-Parlitz [16] equation, which governs the nonlinear motion of a free gas bubble will is given by,

$$\left[1 - \left(\frac{\dot{R}}{c} \right) \right] R \ddot{R} + \frac{3}{2} \left[\frac{\dot{R}}{3c} \right] \dot{R}^2 = \frac{1}{\rho} \left[\left(\frac{\dot{R}}{c} \right) + \left(\frac{R}{c} \frac{d}{dt} \right) \right] \left[P(R, \dot{R}) - P_{\infty}(t) \right], \tag{1}$$

where,

$$P(R, \dot{R}) = \left(P_0 - P_v + \frac{2\sigma}{R_0} \right) \left(\frac{R_0}{R} \right)^{3\kappa} - \frac{4\mu\dot{R}}{R} - \frac{2\sigma}{R} - P_0 + P_v - P_s, \tag{2}$$

The symbol R is the instantaneous bubble radius, R_0 is the equilibrium bubble radius, μ is the liquid dynamic viscosity, ρ is the density of the liquid, κ is the polytropic exponent for the bubble gas, c is the speed of sound in air and σ is the surface tension of the bubble wall. For all simulations in this study, $R_0 = 10\mu\text{m}$, $\mu = 0.001 \text{ kg/m s}$, $\kappa = 1.33$, $c = 1484 \text{ m/s}$, $\sigma = 0.0725 \text{ N/m}$, $P_v = 2.33 \text{ kPa}$ and $P_0 = 100 \text{ kPa}$ for bubble in water at 20°C [18]. Here, $P_s = \alpha \sin(2\pi f_{ext} t)$ represents the pressure in the liquid, where α is the acoustic pressure amplitude and f_{ext} is the acoustic frequency.

2.2. Mathematical model for a microbubble near a boundary

To include the influence of a boundary, as shown in figure 1, we follow the derivation by Dzaharudin et al. [19] where the image bubble technique is used to emulate the boundary.

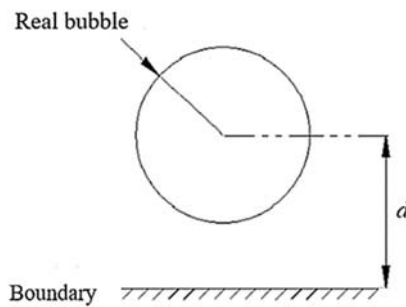


Figure 1. Schematic of a bubble near a boundary.

The governing equation of a microbubble near a solid wall boundary [19] is given by;

$$\ddot{R} \left[\left(1 - \frac{\dot{R}}{c} \right) R + \frac{4\mu}{\rho c} + \frac{1}{2d} R^2 \right] =$$

$$\left[\begin{aligned} & \left(1 + (1 - 3\kappa) \frac{\dot{R}}{c} \right) \left(\frac{P_O - P_V}{\rho} + \frac{2\sigma}{\rho R_O} \right) \left(\frac{R_O}{R} \right)^{3\kappa} \\ & - \left(1 - \frac{\dot{R}}{c} \right) \frac{P_O - P_V + \alpha \sin 2\pi f_e t}{\rho} - \frac{2\sigma}{\rho R} - \frac{4\mu \dot{R}}{\rho R} \\ & - \frac{2\pi f_e R \alpha}{\rho c} \cos 2\pi f_e t - \frac{\dot{R}^2}{2} \left(3 - \frac{\dot{R}}{c} \right) - \frac{1}{d} R \dot{R}^2 \end{aligned} \right] \quad (3)$$

where d is the distance between the wall and the bubble centre (see figure 1).

The numerical solution of equation (3) for an interbubble-wall distance $d/R_0=15$ is shown in figure 2(a) for a microbubble of size $R_0 = 2 \mu\text{m}$ subjected to an ultrasound parameter of 40kPa and 1MHz. Table 1 show the list of the ODE solvers in MATLAB.

Table 1. List of ODE Solvers in MATLAB [20].

Solver	Problem Type	Description
ode45	Non- stiff	Based on the explicit Runge-Kutta formulas.
ode23	Non- stiff	Based on the Bogacki-Shampine pair
ode113	Non- stiff	Based on an explicit implementation of Adams-Bashforth-Moulton predictor corrector methods
ode15s	Stiff	Implicit methods based on backward differences which belong to a family of the numerical difference formula consisting of a quasi-constant step size implementation.

2.3. Ordinary Differential Equation (ODE) solver

The Ordinary Differential Equation (ODE) in equation (3) is solved numerically using MATLAB®. There are several types of ODE solvers in MATLAB®.

The numerical methods used in MATLAB® are called ode45, ode23, ode113 and ode15s. The description of the numerical methods is described in table 1.

Stiff equations are differential equations which may cause certain numerical methods to be unstable unless the step size is extremely small. Microbubble oscillations have been found to belong to this class of stiff equations [21]. Stiff equations are typically solved using implicit methods such as the backward difference formula.

2.4. Validation

In this section, the results of our code are compared with those in published literature to ensure the validity of the code.

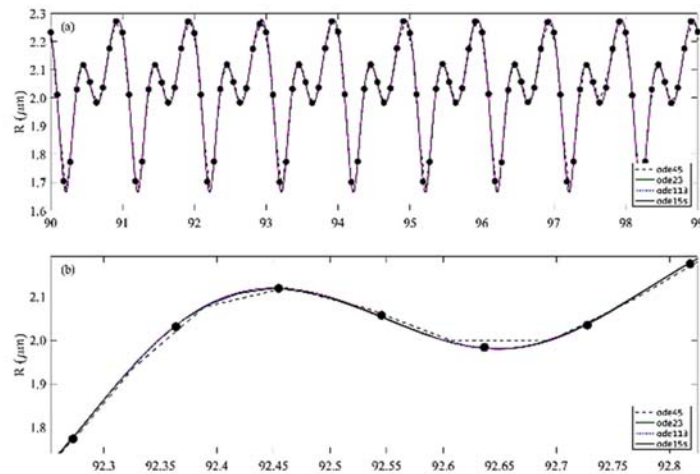


Figure 2. The normalised radial response R for a microbubble with $R_0 = 2.0 \mu\text{m}$ positioned $d/R_0 = 15$ away from a solid wall subjected to an ultrasonic frequency of 1 MHz and driving pressure of 40 kPa using different ODE solver which are ode45 (dash black), ode23 (green), ode113 (dot blue) and ode15s (purple) compared to the obtained from code (line) with figure 5(a) from Li et al. [22] (black dots) (b) is the zoom in of figure 2(a).

Figure 2(a) shows the plots produced by the solvers, listed in table 1, in solving the ODE in equation (3). These plots are compared to the black dots obtained from published literature [22]. Here a single bubble with initial radius $R_0 = 2.0 \mu\text{m}$ located $d/R_0 = 15$ from the wall was subjected to an ultrasound pressure amplitude of 40 kPa. The plot shows good agreement between the result of coding and with published results. The oscillation produced by all the solvers overlap with the black dots obtained from figure 5(a) in Li et al. [22]. A zoom in of figure 2(a) is shown in figure 2(b). Here, the solution produced by the ode15s solver shows a smoother curve which best overlaps published results (black dots).

Thus, for this study, we will use the ode15s solver to numerically solve the governing equation in equation (3). The bubble is solved for the initial conditions $R(0) = R_0$ and $dR/dt(0) = 0$ where the bubble is in a motionless state. To ensure that the validity of the model, it will be ensured that the bubble will remain spherical throughout the dynamical oscillation.

3. Results and discussions

In this section we shall study the dynamics of microbubble oscillation by varying the ultrasound parameters. Here, we will be consider a microbubble of size $R_0 = 10 \mu\text{m}$ positioned $d/R_0 = 15$ away from a solid wall subjected to the values of acoustic pressure 200 kPa and 400 kPa and the driving frequency 0.5 MHz and 1 MHz, in range of commonly experimentally used [23].

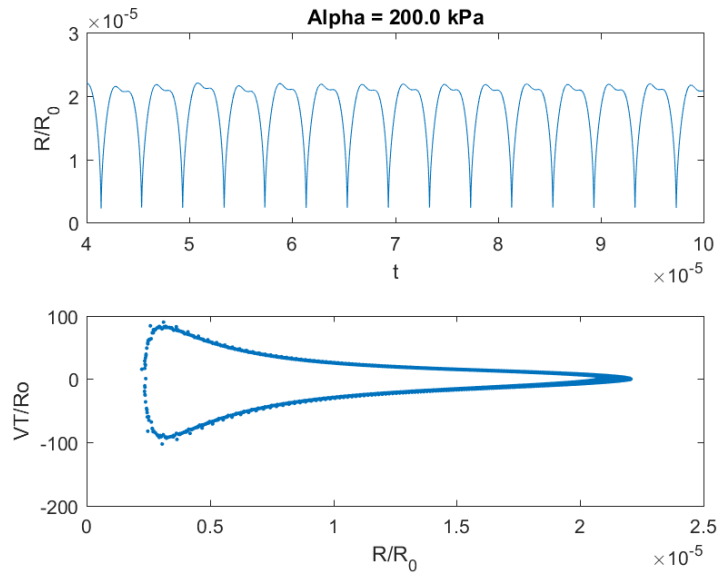


Figure 3. The top row is the time series of microbubble with size $R_0 = 10 \mu\text{m}$ positioned $d/R_0 = 15$ away from a solid wall subjected to an ultrasonic frequency of 0.5 MHz and driving pressure of 200 kPa Whereas the bottom rows are the phase diagrams represented by the normalized velocity vs. the normalized radius.

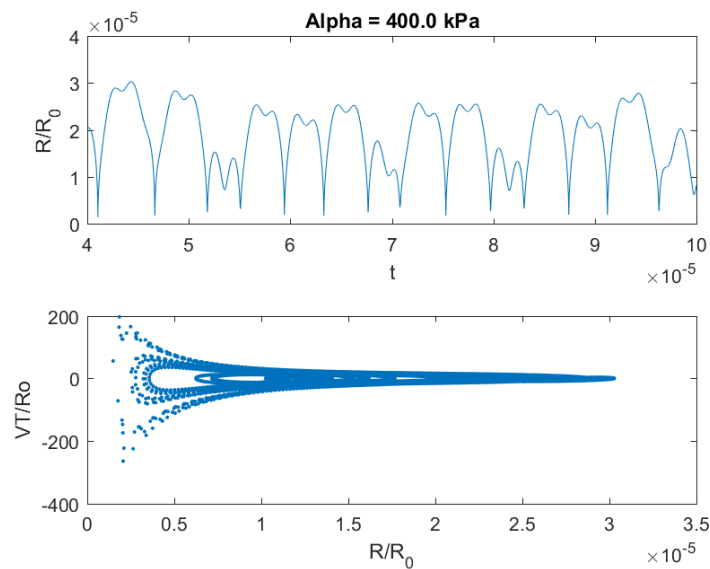


Figure 4. The top row is the time series of microbubble with size $R_0 = 10 \mu\text{m}$ positioned $d/R_0 = 15$ away from a solid wall subjected to an ultrasonic frequency of 0.5 MHz and driving pressure of 400 kPa Whereas the bottom rows are the phase diagrams represented by the normalized velocity vs. the normalized radius.

Figure 3 and figure 4 shows the microbubble oscillation for the ultrasound driving frequency of 0.5 MHz for pressure amplitude of 200 kPa and 400 kPa respectively. The top rows in the figure represent

the time series produced by solving the mathematical model in equation (3). Whereas the bottom rows show the trajectory for the phase diagrams represented by the normalized velocity vs. the normalized radius.

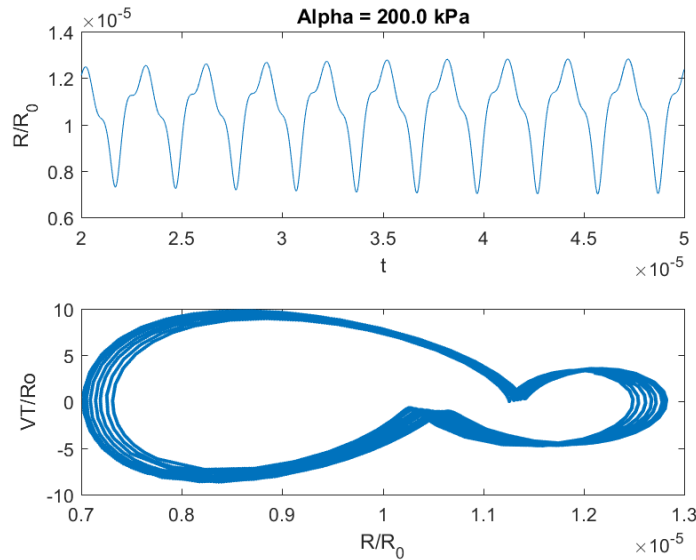


Figure 5. The top row is the time series of microbubble with size $R_0 = 10 \mu\text{m}$ positioned $d/R_0 = 15$ away from a solid wall subjected to an ultrasonic frequency of 1 MHz and driving pressure of 200 kPa Whereas the bottom rows are the phase diagrams represented by the normalized velocity vs. the normalized radius.

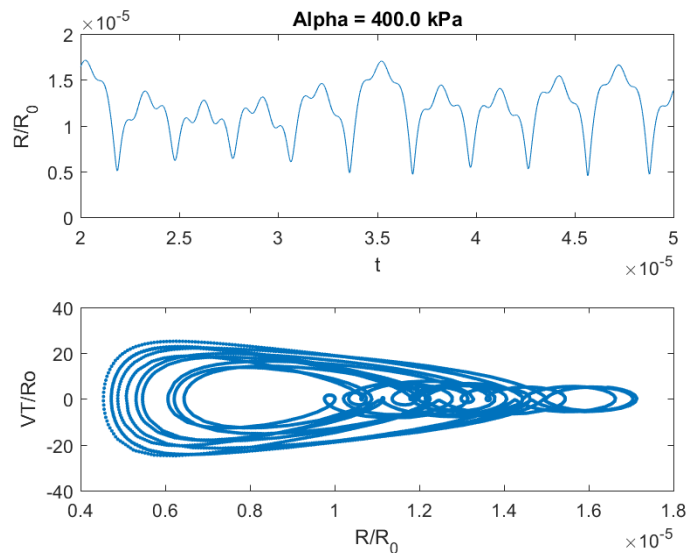


Figure 6. The top row is the time series of microbubble with size $R_0 = 10 \mu\text{m}$ positioned $d/R_0 = 15$ away from a solid wall subjected to an ultrasonic frequency of 1 MHz and driving pressure of 400 kPa Whereas the bottom rows are the phase diagrams represented by the normalized velocity vs. the normalized radius.

From figure 3 we can see that the oscillation is regular as the oscillation repeats itself. However, when the pressure amplitude of the ultrasound is increased, it no longer becomes regular as shown in figure 4, characterised by different oscillation patterns that does not repeat itself. The regular oscillation in figure 3 produces a single line orbit in the phase diagram. The irregular pattern in figure 4 reveals a trajectory with no intertwining, but does not overlap itself at small amplitude oscillations

A similar pattern is observed in Figs. 5 and 6 as the ultrasound frequency is increased to 1 MHz. A comparison between the top rows show that the regular oscillation becomes irregular as the pressure amplitude is increased. The trajectory of the paths of the phase diagram reveals an increase in bubble trajectory crossings and intertwines at higher ultrasound pressure amplitude 400 kPa. It is also apparent that the maximum radius is decreased as the frequency is increased.

Here, it can be concluded that the increase in pressure amplitude, α , will result in increasingly irregular oscillation reflected in the oscillation pattern and the intertwines of trajectories in the phase diagrams of a microbubble near a boundary. The increase in ultrasound frequency however, suggests a decrease in the maximum radius of oscillation. This highlights the significance of a slight change in ultrasound parameters to the overall microbubble behaviour.

4. Conclusions

Microbubbles have the potential to be used in various applications for diagnostic imaging and therapeutic purposes. In this paper, we studied the influence of varying ultrasound parameters on bubble oscillation for a bubble near a boundary. The boundary is an important consideration since the microbubbles travel near endothelium and blood vessels in real clinical applications. Most mathematical models governing microbubble oscillation do not consider the influence of a wall and assumes infinite medium. This study investigated the effects of varying the ultrasound parameters on a microbubble near a boundary. The microbubble oscillation was found to become increasingly irregular as the driving pressure amplitude is increased. The maximum amplitude of oscillation was found to decrease with increasing ultrasound frequency.

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