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Effects of boundary proximity on monodispersed microbubbles in ultrasonic fields

F. Dzaharudin [a,*], A. Ooi [b], R. Manasseh [c]

[a] Faculty of Mechanical Engineering, University Malaysia Pahang, 26600, Malaysia
[b] Department of Mechanical Engineering, University of Melbourne, 3010, Victoria, Australia
[c] Faculty of Science, Engineering and Technology, Swinburne University of Technology, Hawthorn, Victoria 3122, Australia

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ABSTRACT

Microbubbles have demonstrated the potential to redraw the boundaries of biomedical applications and revolutionize diagnostic and therapeutic applications. However, the ability to distinguish the acoustic response from a cluster of microbubbles in close proximity to the vessel endothelial cell from those that are not is a challenge that needs to be addressed. To address this, the present paper modifies the Keller-Miksis model to include the effects of a boundary. The acoustic responses are analysed via techniques from dynamical systems theory such as Poincaré plots and bifurcation diagrams. It is found that the presence of a boundary causes an intermittent route to chaos while microbubbles far from the boundary result in a period-doubling route to chaos as the single control parameter pressure amplitude is varied. The route to chaos is altered via antimonotinicity with increasing bubble-wall distance. It has also been found that the effects of coupling are significant as it alters the chaotic threshold to occur at lower driving pressure amplitudes. The results also suggest that the increase in coupling effects between microbubbles near a boundary lowers the pressure amplitude required for chaos and lowers the natural frequency of the cluster.

1. Introduction

The influence of a boundary on microbubble dynamics is a highly complex phenomenon which is important in the development of therapeutic applications such as targeted molecular imaging and therapeutic applications such as local drug/gene delivery. When driven by an ultrasonic pressure field, microbubbles expand and contract in response thus enhancing the reflectivity of perfused tissues in areas such as cardiology [1]. With further refinement, the use of microbubbles in conjunction with ultrasound has great potential and provides a unique opportunity to extend the use of microbubbles beyond diagnostic imaging to include therapeutic delivery and monitoring. Early studies by Lindner et al. [2], among many others, have reported successful use of microbubbles in targeting inflamed tissue in an animal model. While current clinical applications of ultrasound rely on the detection of free-circulating microbubbles [3], the development of state of the art of medical microbubbles rely on a departure of this behaviour where microbubbles are required to selectively remain within the targeted diseased tissue [4,5,6]. Despite significant research, the nature of the signals produced by microbubbles in proximity to the boundary are yet to be understood (see Refs. Suslov et al. [7] and Lindner [8]). The task of distinguishing the response of microbubbles in proximity to the target walls from those that are not remains a challenging one and an important step in the development of medical microbubbles in

* Corresponding author.
E-mail address: fatimahd@ump.edu.my (F. Dzaharudin).

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clinical practice [9].

The study of the dynamical behaviour of microbubbles in the medical field is built on decades of theoretical and experimental models and research of underwater acoustics pioneered by Lord Rayleigh [10] who developed the first theoretical model for the collapse of a spherical cavity. Theoretical bubble dynamics centered around hydrodynamically generated cavities until Blake [11] published a study of acoustically generated cavities. Since then, the Rayleigh model became the focus of many formulations resulting in more complete models such as the Keller-Miksis-Parlitz equations [12] which is suitable for large amplitude oscillations that often occurs in the range of pressure amplitudes applicable for medical applications. The development of microbubbles in recent years brought with it the need for accurate modelling of microbubble response to an acoustic pressure wave. Morgan et al. [13] derived a modified Keller-Herring model for microbubbles based on the study by Church [14] to include the effects of shell encapsulation. A more recent study by Dzaharudin et al. [15] incorporated the shell encapsulation for the Keller-Miksis-Parlitz equation. While many numerical studies have been done on the dynamics of microbubbles in an ultrasonic field (see Refs. [16,17,18,19,20,21]), most assume that the microbubbles oscillate in isolation, far from any neighbouring microbubbles and boundaries. In more recent years, studies have included the effects of neighbouring bubbles but did not consider the case where the bubbles are close to a wall. (see Refs. [15,17,22]). Theoretical investigations by Suslov et al. [7] and Doinikov et al. [23] considered the influence of a rigid wall but did not include neighbouring bubbles. This paper intends to fill the gap by determining the dynamical behaviour of more than one bubble near a rigid wall.

The modelling of microbubble oscillation is subjected to a myriad of parameters. To limit this study to a manageable set of parameters, the distance from any bubbles to any bubbles is set to a constant. Furthermore, only bubbles arranged on a plane are considered thus limiting the number of bubbles to a maximum of three bubbles where the situation for three bubbles correspond to a group of microbubbles arranged at the vertices of an equilateral triangle. Note that for $N = 4$, the bubbles are placed at the vertices of an equilateral tetrahedron which is no longer limited to a plane. Furthermore, it is not physically possible have an equi-spaced bubbles where $N > 4$. Due to all the assumptions made, the validity of a group of bubbles near a rigid boundary modelled by the mirror image would be comparable only with experiments in a microfluidic system that has been specifically designed instead of an experimental setup from a group of contrast agents *in vivo*. The results shown in this paper however, may be used to as an ideal reference for microtechnology applications and show possible trends as the number of bubbles is increased from one towards a number more typical in medical applications.

The aim of the present theoretical analysis is to investigate the effects of coupling due to neighbouring microbubbles and a boundary. In order to address this, the following will be investigated: (a) How does the presence of the boundary/rigid wall influence the dynamical behaviour? How does it compare to that from microbubbles oscillating in isolation? (b) How does varying the distance of a microbubble or a group of monodispersed microbubbles from a rigid wall affect the dynamical behaviour? (c) How does the number of microbubble near a boundary affect the dynamical behaviour? The answers to these questions are important in the development and optimisation of applications involving therapeutic microbubbles.

2. Background theory

This paper uses the Keller-Miksis-Parlitz [24,25] equation since it produces results that best agreed with those obtained from numerical solution of the full-partial differential equations of fluid dynamics [26].

$$\left(1-\frac{\dot{R}_i}{c}\right)R_i\ddot{R}_i+\frac{\dot{R}_i^{\,2}}{2}\left(3-\frac{\dot{R}_i}{c}\right)=\frac{1}{\rho}\left[1+\frac{\dot{R}_i}{c}+\frac{R_i}{c}\frac{d}{dt}\right]\left[P\left(R_i,\dot{R}_i\right)-P_0(t)\right]-P_{si} \tag{1}$$

where $i = 1,2,\ldots,N_{bub}$ is the instantaneous bubble and N_{bub} is the total number of bubbles in the cluster. The shell encapsulation term [13] is incorporated as follows,

$$P\left(R_i,\dot{R}_i\right)=\left(P_0-P_v+\frac{2\sigma}{R_{0i}}+\frac{2\chi}{R_{0i}}\right)\left(\frac{R_{0i}}{R_i}\right)^{3\kappa}-\frac{4\mu\dot{R}_i}{R_i}-\frac{2\sigma}{R_i}-\frac{2\chi}{R_i}\left(\frac{R_{0i}}{R_i}\right)^2-\frac{12\mu_{sh}\varepsilon\dot{R}_i}{R_i(R_i-\varepsilon)} \tag{2}$$

with the coupling term [27],

$$P_{si}=\sum_{j\neq i}^{N_{bub}}\frac{1}{s_{ij}}\left(R_j^2\ddot{R}_j+2R_j\dot{R}_j^2\right) \tag{3}$$

Here $R_i(t)$, R_{0i}, μ, c, ρ, σ, κ, P_0, P_v, f_{ext}, α, χ, μ_{sh} and ϵ represent the instantaneous bubble radius, equilibrium bubble radius, dynamic viscosity of the liquid, speed of sound in water, density of liquid, sum of the two interfacial tension coefficient, polytropic exponent for bubble gas, static pressure, vapor pressure, acoustic frequency, acoustic pressure amplitude, shell elasticity, shell viscosity and shell thickness respectively. The pressure in the liquid far from the bubble is given by $P_0(t) = P_0 - P_v + \alpha\, sin(\omega t)$ and the circular frequency, $\omega = 2\pi f_{ext}$. The term $2\sigma / R$ includes the sum of the gas-lipid and water-lipid interfacial tensions [13].

The typical values of the model parameters of bubbles in water at 20 °C are used with $c = 1484\ \mathrm{ms^{-1}}$, $\mu = 0.001\ \mathrm{kg\ ms^{-1}}$ and $\rho = 998\ \mathrm{kg\ m^{-3}}$. The parameters for the MP1950 shell encapsulation used in this paper is characterized by $\chi = 0.5$ N/m,