

Title: Bubble dynamics in boiling histotripsy

Author names and affiliations: Ki Joo Pakh¹, Pierre Gélât², Hyungmin Kim¹ and Nader Saffari²

¹Center for Bionics, Biomedical Research Institute, Korea Institute of Science and Technology (KIST), Seoul, 02792, Republic of Korea

²Department of Mechanical Engineering, University College London, London, WC1E 7JE, UK

Corresponding author:

Nader Saffari

Department of Mechanical Engineering, University College London, Torrington Place, London, WC1E 7JE, United Kingdom

E-mail: n.saffari@ucl.ac.uk.

Tel: +44(0)2076797180

Abstract

Boiling histotripsy is a non-invasive, cavitation-based ultrasonic technique which uses a number of millisecond pulses to mechanically fractionate tissue. Though a number of studies have demonstrated the efficacy of boiling histotripsy for fractionation of solid tumours, treatment monitoring by cavitation measurement is not well studied because of the limited understanding of the dynamics of bubbles induced by boiling histotripsy. The main objectives of this work are to (a) extract qualitative and quantitative features of bubbles excited by shockwaves and (b) distinguish between the different types of cavitation activity for either a thermally or a mechanically induced lesion in the liver. A numerical bubble model based on the Gilmore equation accounting for heat and mass transfer (gas and water vapour) was developed to investigate the dynamics of a single bubble in tissue exposed to different High Intensity Focused Ultrasound fields as a function of temperature variation in the fluid. Furthermore, *ex vivo* liver experiments were performed with a passive cavitation detection system to obtain acoustic emissions. The numerical simulations showed that the asymmetry in a shockwave and water vapour transport are the key parameters which lead the bubble to undergo rectified growth at a boiling temperature of 100°C. The onset of rectified radial bubble motion manifested itself as (a) an increase in the radiated pressure and (b) the sudden appearance of higher order multiple harmonics in the corresponding spectrogram. Examining the frequency spectra produced by the thermal ablation and the boiling histotripsy exposures, it was observed that higher order multiple harmonics as well as higher levels of broadband emissions occurred during the boiling histotripsy insonation. These unique features in the emitted acoustic signals were consistent with the experimental measurements. These features can, therefore, be used to monitor (a) the different types of acoustic cavitation activity for either a thermal ablation or a mechanical fractionation process and (b) the onset of the formation of a boiling bubble at the focus in the course of HIFU exposure.

Keywords: high intensity focused ultrasound, boiling histotripsy, cavitation monitoring.

INTRODUCTION

High-Intensity Focused Ultrasound (HIFU) has been used to thermally destroy benign and malignant tumours noninvasively (ter Haar and Coussios 2007; Zhou et al. 2011; Aubry et al. 2013). The basic principle behind the use of HIFU involves focusing an ultrasound beam and delivering acoustic energy into a small region of interest within body. This leads to localised heating and protein denaturation, which causes irreversible cell death through coagulative necrosis (Dubinsky et al. 2008; Sapareto and Dewey 1984). Recent studies have shown significant interest in exploring the use of HIFU to produce a mechanically fractionated lesion without causing coagulative thermal damage. This ultrasonic technique is known as boiling histotripsy, which uses shock wave heating and millisecond boiling to fractionate soft tissue with a degree of precision (Khokhlova et al. 2011; Wang et al. 2013; Khokhlova et al. 2014; Khokhlova et al. 2015; Pahk et al. 2016a). Canney et al. (2010) showed that the production of shockwaves at the HIFU focus due to nonlinear propagation effects in tissue can raise its temperature to 100°C in a few milliseconds. A boiling vapour bubble is subsequently formed at the HIFU focus (Khokhlova et al. 2015) and then grows to millimetre size followed by the formation of cavitation clouds (Pahk et al. 2017). The dynamic behaviours of a boiling bubble and cavitation clouds can eventually lead to the formation of a “tadpole” shaped mechanically fractionated lesion, which is a characteristic of boiling histotripsy exposure (Khokhlova and Hwang 2011; Pahk et al. 2017).

Monitoring of HIFU treatment may be carried out with diagnostic ultrasound scanning. For instance, a HIFU treatment site appears as a bright hyperechoic region on B-mode ultrasound images during the course of either HIFU thermal ablation or boiling histotripsy, because HIFU-induced bubbles at the focus are highly reflective to ultrasound (Khokhlova et al. 2014). In the case of a HIFU thermal ablation process, the appearance of a boiling bubble in the HIFU focal region can be highly undesirable because increased scattering by the bubble can help promote pre-focal heating. This eventually leads to the growth of a thermally ablated lesion towards the HIFU transducer, resulting in the lesion shape distortion from a symmetric “cigar” shape to a “tadpole” shape, which is unpredictable in size and shape (Watkin et al. 1996; Bailey et al. 2003; Khokhlova et al. 2006; Coussios and Roy 2008). In contrast, the formation of a boiling bubble at the HIFU focal zone is

essentially required to initiate the mechanical tissue fractionation process for boiling histotripsy. Additional information to echogenicity is, therefore, needed to help monitor HIFU treatment under different exposure conditions (thermal ablation and boiling histotripsy) and the presence of a boiling bubble at the HIFU focus. Pahk et al. (2015) showed that acoustic emissions during HIFU thermal ablation and boiling histotripsy excitations can be distinguished in the frequency domain, both numerically and experimentally, in terms of (a) the level of broadband components and (b) the number of multiple harmonic components of the fundamental frequency. It is known that tissue temperature rapidly increases during boiling histotripsy exposure, resulting in the variation of the physical properties of the surrounding medium, and of water vapour and gas contents with time. The numerical bubble model used in Pahk et al. (2015), however, only considered the effect of the shape of an incident acoustic waveform on the dynamics of a single bubble at a constant temperature of 20°C in the fluid.

To that end, in this study, a more accurate and reliable numerical bubble model accounting for the liquid compressibility and heat and mass transfer (non-condensable gas and water vapour) is developed to investigate the dynamics of a single bubble in tissue exposed to different HIFU fields as a function of temperature variation in the fluid. Furthermore, simulated acoustic emissions resulting from bubble dynamics are compared with experimentally obtained acoustic signals using a passive cavitation detection (PCD) system.

NUMERICAL METHODS

Radial bubble motion

In this work, the Gilmore bubble model is considered as the governing equation for bubble dynamics. This bubble model uses the Kirkwood-Bethe hypothesis (Kirkwood and Bethe 1942) to take into account the compressibility of the liquid and the variation of sound velocity in the liquid as a function of the radial bubble motion. The assumptions behind this model make it suitable for studying the dynamics of a single spherical bubble subjected to high acoustic pressure amplitudes such as those encountered in lithotripter shockwave pulses where the bubble wall velocity is comparable to or even greater than the speed of sound in the liquid (Vokurka 1986; Church 1989; Phelps and Leighton 1997;

Sboros et al. 2002). The Gilmore equation is a nonlinear second order differential equation, and is given by (Gilmore 1952)

$$\ddot{R}R\left(1-\frac{\dot{R}}{C}\right)+\frac{3}{2}\left(1-\frac{\dot{R}}{3C}\right)\dot{R}^2=\left(1+\frac{\dot{R}}{C}\right)H+\frac{\dot{R}}{C}\left(1-\frac{\dot{R}}{C}\right)R\frac{dH}{dR} \quad (1.1)$$

The dot denotes time derivatives, R is the bubble radius, \dot{R} is the velocity of the bubble wall, \ddot{R} is the acceleration of the bubble wall, C is the local speed of sound and H is the liquid enthalpy difference at the pressure far from the bubble $P_\infty = P_0 + P_a$ and at the bubble wall P_w . P_0 is the ambient pressure of the surrounding liquid. P_a is the applied acoustic pressure, which was obtained by numerically solving the Khokhlov-Zabolotskaya-Kuznetsov (KZK) parabolic nonlinear wave propagation equation using the HIFU Simulator v1.2 (Soneson 2009). The enthalpy H of the liquid and the speed of sound C at the bubble wall are calculated by (Church 1989)

$$H = \frac{m}{m-1} A^{1/m} \rho_0^{-1} \left[(P_w + B)^{(m-1)/m} - (P_\infty + B)^{(m-1)/m} \right] \quad (1.2)$$

$$C = \sqrt{c_0^2 + (m-1)H} \quad (1.3)$$

where c_0 is the speed of sound in the liquid and ρ_0 is the equilibrium liquid density. A , $B = A - P_0$ and m are the empirical constants of the modified Tait equation of the state for the liquid (Chavrier et al. 2000). In equation (1.2), the pressure at the bubble wall P_w can be calculated by balancing the forces acting on the wall

$$P_w = P_i - \frac{2\sigma}{R} - \frac{4\mu\dot{R}}{R} \quad (1.4)$$

where σ and μ are the surface tension and viscosity of the liquid, respectively. The pressure inside the bubble P_i can be described either using a polytropic law of compression with the absence of any heat or mass transfer at the bubble wall (Aymé-Bellegarda 1990)

$$P_i = \left(P_0 + \frac{2\sigma}{R_0} \right) \left(\frac{R_0}{R} \right)^{3\gamma} \quad (1.5)$$

or the van der Waals equation of state in the case of the inclusion of both heat and mass transfer at the bubble wall (Yasui 1995)

$$P_i = \frac{R_{\text{gas}} T_b}{v - b_v} - \frac{a_v}{v^2} \text{ with } v = \frac{N_A \frac{4}{3} \pi R^3}{N_{\text{tot}}} \quad (1.6)$$

In equations (1.5) and (1.6), γ is the polytropic index for the gas in the bubble, R_{gas} is the universal gas constant, T_b is the temperature inside the bubble, v is the mixture molar volume in the bubble, N_A is the Avogadro's number and $N_{\text{tot}} = N_{\text{air}} + N_{\text{vap}}$ is the total number of molecules in the bubble. N_{air} and N_{vap} are the number of air and water vapour molecules, respectively. The van der Waals constants a_v and b_v for the van der Waals forces and the volume occupied by the molecules are determined by (Yasui 1995)

$$a_v = a_{\text{air}} \left(\frac{N_{\text{air}}}{N_{\text{tot}}} \right)^2 + a_{\text{vap}} \left(\frac{N_{\text{vap}}}{N_{\text{tot}}} \right)^2 + 2 \sqrt{a_{\text{air}} a_{\text{vap}}} \left(\frac{N_{\text{air}}}{N_{\text{tot}}} \right) \left(\frac{N_{\text{vap}}}{N_{\text{tot}}} \right) \quad (1.7)$$

$$b_v = b_{\text{air}} \left(\frac{N_{\text{air}}}{N_{\text{tot}}} \right)^2 + b_{\text{vap}} \left(\frac{N_{\text{vap}}}{N_{\text{tot}}} \right)^2 + 2 \left\{ \left[\frac{1}{2} (b_{\text{air}}^{1/3} + b_{\text{vap}}^{1/3}) \right] \right\}^{1/3} \left(\frac{N_{\text{air}}}{N_{\text{tot}}} \right) \left(\frac{N_{\text{vap}}}{N_{\text{tot}}} \right)$$

a_{air} and b_{air} , and a_{vap} and b_{vap} are the van der Waals constants of air and water vapour, respectively.

The constant values are: $a_{\text{air}} = 1.402 \times 10^{-1}$, $a_{\text{vap}} = 5.536 \times 10^{-1}$ [J m³ mol⁻²], $b_{\text{air}} = 3.753 \times 10^{-5}$, $b_{\text{vap}} = 3.049 \times 10^{-5}$ [m³ mol⁻¹]. Lastly, the time-varying pressure p_{rad} radiated by the radial bubble motion in the form of an outward travelling spherical wave in the liquid is calculated by (Akulichev 1971, Church 1989)

$$p_{\text{rad}} = A \left[\frac{2}{m+1} + \frac{m-1}{m+1} \left(1 + \frac{m+1}{r_d c_0^2} G \right)^{1/2} \right]^{2m/(m-1)} - B \quad (1.8)$$

where $G = R(H + \dot{R}^2/2)$ is an invariant of the bubble motion evaluated at the bubble wall and $r_d (\geq R)$ is the distance away from the centre of a bubble. This invariant G propagates outward from the bubble along a path or a characteristic curve in such a way where it remains unchanged (Church 1989).

Furthermore, equation (1.8) does not take into account the nonlinear distortion of the radiated pressure resulting from the radial bubble motion as it propagates away from the bubble (Cleveland et al. 1999).

Mass transport

Church (1989) suggested that non-condensable gas diffusion plays an important role in the radial bubble motion driven by a shockwave. The effects of gas flux caused by the relatively longer duration of negative pressure cycle in a shockwave, for example, can increase the time of the bubble growth phase, reduce the violence of the primary collapse and prolong the afterbounces. In addition to incondensable gas diffusion, the importance of the presence of water vapour inside a bubble has been confirmed both numerically and experimentally (Kamath et al. 1993; Yasui 1997; Colussi and Hoffmann 1999; Storey and Szeri 2000). During the bubble expansion phase, water vapour transports into the bubble. Once the bubble collapses, the vapour in the bubble cannot completely diffuse out because the time scale of the collapse becomes much faster than the time scale of the diffusion of vapour out of the bubble. Water vapour is, therefore, trapped inside the bubble. This results in an increased heat capacity due to the additional number of water vapour particles limiting both the maximum temperature and pressure in the bubble (Brenner et al. 2002). In boiling histotripsy, the effect of water vapour on radial bubble motion is significant because the surrounding temperature reaches a boiling temperature of 100°C (Kreider et al. 2011). To include the effects of mass transport in the present numerical model, rates of change of water vapour (H₂O) and non-condensable gas (air) with respect to time are modelled separately at the bubble wall.

Water vapour transport: evaporation and condensation

To model the evaporation and condensation of vapour (i.e. the phase change between liquid and gas), the Hertz-Knudsen equation derived from the classical kinetic theory of gasses is employed, which estimates the change of molar rate of water vapour \dot{n}_{vap} [mol s⁻¹] at the bubble interface (Holzfuss 2005)

$$\dot{n}_{\text{vap}} = \dot{n}_{\text{vap}}^{\text{evap}} - \dot{n}_{\text{vap}}^{\text{cond}} = \frac{4\pi R^2}{M_{\text{vap}}} \frac{\alpha_m \bar{c}(T_s)}{4} [\rho_{\text{vap}}^{\text{sat}} - \rho_{\text{vap}}(R, t)] \quad (2.1)$$

$$\text{with } \bar{c}(T_s) = \sqrt{\frac{8R_{\text{gas}}T_s}{\pi M_{\text{vap}}}}$$

This simple Hertz-Knudsen model, which has been used in various bubble models driven by ultrasound (Holzfuss 2005, 2010; Hauke et al. 2007; Kreider et al. 2011), assumes the liquid-vapour interface is planar and takes the temperature distributions in the bubble and liquid as fixed (Holzfuss 2008). This model is generally applicable as an estimate of phase change below the critical temperature of the liquid (Kreider 2008). Because of the assumption of planar interface used in the Hertz-Knudsen model, effects associated with the curvature of the liquid-vapour interface such as bulk motion of water vapour relative to the interface were neglected in the simulation performed in the present study. An evaporation-condensation model accounting for a curved interface such as the approach used in Demsky and Ma (2004) could possibly be adopted to simulate the water vapour transport across the bubble wall (i.e., curvilinear interface). However, this is beyond the scope of the present work. In equation (2.1), $\dot{n}_{\text{vap}}^{\text{evap}}$ and $\dot{n}_{\text{vap}}^{\text{cond}}$ are the molar rates of evaporation and condensation of water vapour and M_{vap} is the molar mass of vapour. α_m is the accommodation coefficient for evaporation or condensation (i.e. the diffusive behaviour of water vapour) and \bar{c} is the average velocity of molecules. Because it is known that the surface temperature T_s of the bubble exceeds the surrounding liquid temperature T_0 for only a very short time during collapse (Kamath *et al* 1993), the bubble surface temperature is taken as $T_s = T_0$. The saturated density of water vapour $\rho_{\text{vap}}^{\text{sat}}$ is estimated by (Wagner and Pruß 2002)

$$\rho_{\text{vap}}^{\text{sat}} = 322 \exp\left(b_1 \mathcal{G}^{2/6} + b_2 \mathcal{G}^{4/6} + b_3 \mathcal{G}^{8/6} + b_4 \mathcal{G}^{18/6} + b_5 \mathcal{G}^{37/6} + b_6 \mathcal{G}^{71/6}\right) \quad (2.2)$$

with $\mathcal{G} = 1 - T_0/647.096$

where the constants are: $b_1 = -2.0315024$, $b_2 = -2.6830294$, $b_3 = -5.38626492$, $b_4 = -17.2991605$, $b_5 = -44.7586581$ and $b_6 = -63.9201063$. The time-varying density of water vapour ρ_{vap} depends on the bubble dynamics and is calculated using the following equation (Yasui 1995)

$$\rho_{\text{vap}} = \frac{M_{\text{vap}} \left(\frac{N_{\text{vap}}}{N_{\text{tot}}} \right)}{v} \quad (2.3)$$

Non-condensable gas transport

The instantaneous rate of change of non-condensable gas \dot{n}_g [mol s⁻¹] is estimated using Fick's law with the boundary layer approximation developed by Toegel et al. (2000) and Toegel and Lohse (2003) and validated in Stricker et al. (2011)

$$\dot{n}_{g,i} = 4\pi R^2 D_i \frac{c_{\infty,i} - c_{s,i}}{L_{g,i}} \quad (2.4)$$

$$L_{g,i} = \min\left(\sqrt{\frac{RD_i}{|\dot{R}|}}, \frac{R}{\pi}\right) \quad (2.5)$$

The subscript i denotes different gas species (Nitrogen N₂, Oxygen O₂, Argon Ar), L_g is the instantaneous characteristic diffusion length and $c_s = p_i (n_g/n_{\text{tot}}) K_H^{-1}$ is the instantaneous concentration of molecules per unit volume [mol m⁻³] at the bubble wall. $c_\infty = p_0 K_H^{-1}$ is the concentration of dissolved gas far from the bubble, and is used as the initial concentration everywhere in the liquid. Henry's constant K_H [Pa m³ mol⁻¹] for different gas species i as a function of temperature can be obtained by (Battino et al. 1984)

$$K_{H,i}(T_0) = \left[\frac{\rho_0}{P_0 M_i} \exp\left(A_h + \frac{B_h}{\tau_h} + C_h \ln \tau_h \right) \right]^{-1}, \quad \tau_h = \frac{T_0(\text{K})}{100} \quad (2.6)$$

where M_i is the molar mass for gas species i . The alphabetical constants for N₂, O₂ and Ar are given in Table 1. The diffusivity of gas in liquids D_i [m² s⁻¹] in equation (2.4) is generally correlated with the viscosity of the liquid, which can be calculated empirically by (Othmer and Thakar 1953)

$$D_i = \frac{1.4 \times 10^{-8}}{[1000\mu_L(T_0)]^{1.1} V_{m,i}^{0.6}} \quad (2.7)$$

where $V_{m,i}$ [mL g⁻¹ mol⁻¹] is the diffusion volume of gas.

Heat transfer and bubble temperature

Heat transfer at the bubble wall

Similarly to equations (2.4) and (2.5), the rate of heat transferred to the bubble \dot{Q} and the thermal boundary layer thickness L_{th} can be approximated by (Toegel and Lohse 2003)

$$\dot{Q} = 4\pi R^2 \lambda_{mix} \frac{T_0 - T_b}{L_{th}} \quad (2.8)$$

$$L_{th} = \min \left(\sqrt{\frac{RK_{mix}}{|\dot{R}|}}, \frac{R}{\pi} \right) \quad (2.9)$$

The thermal conductivity of an air-vapour mixture λ_{mix} [$\text{W m}^{-1}\text{K}^{-1}$] depends on temperature and density of the gas and vapour. The temperature dependence of the thermal conductivities of air λ'_{air} and of water vapour λ'_{vap} are assumed to be linear and calculated as follows (Yasui 1995):

$$\lambda'_{air} = \alpha_{air} T_b + \beta_{air} \quad (2.10)$$

$$\lambda'_{vap} = \alpha_{vap} T_b + \beta_{vap}$$

where $\alpha_{air} = 5.39 \times 10^{-5}$ [$\text{W m}^{-1}\text{K}^{-2}$], $\beta_{air} = 0.0108$ [$\text{W m}^{-1}\text{K}^{-1}$] for air and $\alpha_{vap} = 9.98 \times 10^{-5}$ [$\text{W m}^{-1}\text{K}^{-2}$],

$\beta_{vap} = -0.0119$ [$\text{W m}^{-1}\text{K}^{-1}$] for water vapour. The temperature dependence of the thermal conductivity

of the mixture (air and vapour) λ'_{mix} is then expressed as (Poling et al. 2004)

$$\lambda'_{mix} = \left(\frac{n_{vap}}{n_{tot}} \sqrt{\lambda'_{vap}} + \frac{n_{air}}{n_{tot}} \sqrt{\lambda'_{air}} \right)^2 \quad (2.11)$$

The density dependence of the thermal conductivity of the mixture λ_{mix} is calculated by (Hirschfelder et al. 1964)

$$\lambda_{mix} = \frac{b_v}{v} \left(\frac{1}{y_a} + 1.2 + 0.755y_a \right) \lambda'_{mix} \quad (2.12)$$

$$y_a = \frac{b_v}{v} + 0.6250 \left(\frac{b_v}{v} \right)^2 + 0.2896 \left(\frac{b_v}{v} \right)^3 + 0.1150 \left(\frac{b_v}{v} \right)^4 \quad (2.13)$$

The thermal diffusivity K_{mix} [$\text{m}^2 \text{s}^{-1}$] of the air-vapour mixture in equation (2.9) can be expressed as (Toegel and Lohse 2003)

$$K_{\text{mix}} = \frac{\lambda_{\text{mix}}}{c_p} \quad (2.14)$$

$$c_p = \sum_1^4 \frac{f_i + 2}{2} K_B \frac{N_i}{V} \quad (2.15)$$

where c_p is the specific heat capacity per unit volume at constant pressure [$\text{J m}^{-3} \text{K}^{-1}$], N_i/V is the molecular concentration [m^{-3}] at the bubble wall, $V = 4\pi R^3/3$ is the bubble volume, and f_i is the number of translational and rotational degrees of freedom of gas species i . K_B is the Boltzmann constant.

Temperature change of the bubble

The first law of thermodynamics is employed for calculating the internal energy change inside the bubble (Toegel et al. 2000; Samiei et al. 2011; Chakma and Moholkar 2013)

$$\dot{E} = \sum_{i=1}^4 (h_i - u_i) \dot{N}_i + \dot{Q} - \dot{W} \quad (2.16)$$

$$h_i = \frac{f_i + 2}{2} K_B T_0 \quad (2.17)$$

$$u_i = \left[\frac{f_i}{2} + \sum_1^n \frac{\theta_n/T_b}{\exp(\theta_n/T_b) - 1} \right] K_B T_b \quad (2.18)$$

where \dot{E} is the rate of total energy change, $(h_i - u_i) \dot{N}_i$ is the energy loss due to mass diffusion,

$\dot{W} = P_i \dot{V}$ is the work done by the bubble expansion and $\dot{V} = 4\pi R^2 \dot{R}$ is the rate of bubble volume

change. h_i is the molecular enthalpy and u_i is the internal energy. θ_n represents the characteristic vibrational temperatures in kelvin. n is the number of the characteristic vibrational temperatures.

Because of the assumption of the constant temperature distribution at the bubble wall which equals to T_0 (Toegel et al.2000), the latent heat of evaporation and condensation, which would likely limit both the maximum temperature and pressure in the bubble, is neglected and does not contribute to the energy balance in equation (2.16). The values f_i , θ_n and n for air (N_2 , O_2 , Ar) and water vapour H_2O are given in Table 2.

By combining equations (2.8)–(2.18), the rate of temperature change inside the bubble \dot{T}_b [K s⁻¹] can be obtained algebraically

$$\dot{T}_b = \frac{\dot{E}}{C_{v,\text{mix}}} = \frac{\sum_{i=1}^4 (h_i - u_i) \dot{N}_i}{C_{v,\text{mix}}} + \frac{\dot{Q}}{C_{v,\text{mix}}} - \frac{\dot{W}}{C_{v,\text{mix}}} \quad (2.19)$$

In equation (2.19), $C_{v,\text{mix}}$ is the heat capacity of the gas mixture (air and vapour) at constant volume [J K⁻¹] and is given by (Toegel et al. 2000; Samiei et al. 2011; Chakma and Moholkar 2013)

$$C_{v,\text{mix}} = K_B \sum_{i=1}^4 \left(\frac{f_i}{2} + \sum_{n=1}^n \left(\frac{(\theta_n/T_b)^2 \exp(\theta_n/T_b)}{(\exp(\theta_n/T_b) - 1)^2} \right) \right) N_i \quad (2.20)$$

The physical constants for the gas dynamics used in the model are displayed in Table 3.

Model assumptions, initial boundary conditions and nondimensionalisation

Assumptions

The underlying assumptions of the present model are that:

- the single spherical bubble is initially at rest;
- the bubble remains spherical during its oscillations, there is no bubble fragmentation process after the bubble collapses;
- the internal pressure and temperature inside the bubble are spatially uniform, there is no bubble coalescence process;
- the initial bubble radius is much smaller than the wavelength of an acoustic excitation;
- the bubble is initially filled with air (78% N₂, 21% O₂, 1% Ar) (Lemmon et al. 2000) and water vapour (H₂O);
- the gas in the bubble follows the ideal gas law and
- there is no gravity acting on the bubble.

Initial boundary conditions

The initial boundary conditions (at $t = 0$) were taken as

$$R = R_0; \quad \dot{R} = 0; \quad n_{\text{vap}} = \frac{P_v(T_0)}{K_B T_0} \frac{4\pi}{3} R_0^3; \quad n_{\text{N}_2} = 0.78 \frac{P_0}{K_B T_0} \frac{4\pi}{3} R_0^3; \quad (2.21)$$

$$n_{\text{O}_2} = 0.21 \frac{P_0}{K_B T_0} \frac{4\pi}{3} R_0^3; \quad n_{\text{Ar}} = 0.01 \frac{P_0}{K_B T_0} \frac{4\pi}{3} R_0^3; \quad T_b = T_0$$

where P_v is the water vapour pressure at a given ambient temperature, and is given by (Webb et al. 2011)

$$P_v = 610 \exp \left[\left(\frac{T_0(\text{K})}{273.16} - 1 \right) \left(22.486 \frac{273.16}{T_0(\text{K})} + 0.3182 \frac{T_0(\text{K})}{273.16} - 2.9558 \right) \right] \quad (2.22)$$

Nondimensionalisation

The physical parameters used in the present numerical model are nondimensionalised according to the following schemes:

- In the absence of any heat or mass transfer (see equation 1.5)

$$\text{Length (L)} = R_0; \quad \text{Time (T)} = (2\pi f_0)^{-1}; \quad \text{Mass (M)} = P_0 L T^2 \quad (2.23)$$

- In the presence of heat and mass transfer (see equation 1.6)

$$\text{Length (L)} = R_0; \quad \text{Temperature } (\theta) = T_0; \quad \text{Time (T)} = (2\pi f_0)^{-1}; \quad (2.24)$$

$$\text{Mole (MOL)} = n_{0,\text{total}}; \quad \text{Mass (M)} = R_{\text{gas}} \theta \text{MOL T}^2 \text{L}^{-2}$$

The sets of five coupled ordinary differential equations, ODEs, (1.1), (2.1), (2.4), (2.8) and (2.19) were numerically integrated with ode15s in MATLAB[®] (MathWorks Inc., R2013a) due to equation stiffness.

Temperature-dependent physical properties of liver

In the present bubble model, the surrounding liquid is modelled as a fluid whose properties are representative of those of human liver (Pahk et al. 2015). The liver properties (density, speed of sound, viscosity and surface tension) as a function of temperature (independent of acoustic pressure fields) are assumed to follow similar trends to those of water, as it is acknowledged that information

regarding this is not readily available (Choi et al. 2011). The temperature dependences of the physical properties of water were initially calculated using the empirical equations (2.25)–(2.28)

$$\rho_{0,\text{water}} = 1000 \left[1 - \frac{(T_c - 4)^2}{119000 + 1365T_c - 4T_c^2} \right] \text{ with } T_c = T_0 (\text{°C}) \quad (2.25)$$

$$c_{0,\text{water}} = 1402.4 + 5.0384\tau - 5.8117 \times 10^{-2} \tau^2 + 3.3464 \times 10^{-4} \tau^3 - 1.4826 \times 10^{-6} \tau^4 + 3.1659 \times 10^{-9} \tau^5, \text{ with } \tau = T_0 (\text{K}) - 273.16 \quad (2.26)$$

$$\mu_{0,\text{water}} = \frac{1.779\mu(T_0 = 20\text{°C})}{1 + 0.03367T_c + 2.2099 \times 10^{-4} T_c^2} \quad (2.27)$$

$$\sigma_{0,\text{water}} = 0.2358 \vartheta^{1.256} (1 - 0.625 \vartheta) \text{ with } \vartheta = 1 - T_0(\text{K})/647.1 \quad (2.28)$$

Equations (2.25)–(2.28) respectively give the variation of water density ρ_0 (Kravchenko 1966), speed of sound c_0 (Bilaniuk and Wong 1993), dynamic viscosity μ_0 (Joseph 1964) and surface tension σ_0 (Webb *et al* 2011) with temperature. To estimate the liver properties, the calculated water properties at a given ambient temperature were multiplied by the ratio of the liver and water properties measured at $T_0 = 20\text{°C}$

$$\text{Ratio} = \text{Liver } (T_0 = 20\text{°C}) / \text{Water } (T_0 = 20\text{°C}) \quad (2.29)$$

$$\text{Liver } (T_0) = \text{Water}_{\text{calculated}}(T_0) \times \text{Ratio}$$

Table 4 shows the properties of water and of liver at $T_0 = 20\text{°C}$. The temperature dependent parameters of water and of liver over a range of 20°C to 100°C are shown in Figure 1.

A piecewise constant approximation for the dynamics of a bubble

It is known that tissue temperature rapidly increases during the course of boiling histotripsy (Canney et al. 2010; Khokhlova et al. 2011). This eventually results in the variation of:

- the physical properties of the surrounding medium;
- the saturated water vapour density and Henry's constants for different gas species.

One simple approach to take into account the effects of the temperature-dependent parameters on the bubble dynamics is to apply a piecewise constant approximation. The change of tissue temperature with time at the HIFU focus was initially obtained by numerically solving the bioheat transfer (BHT)

equation (Pennes 1948) using the HIFU Simulator v1.2. The saturated water vapour density, Henry's constants for incondensable gases and the physical properties of liver were then calculated using equations (2.2), (2.6) and (2.25)–(2.29) for each simulated temperature step $T_{0,n}$. Additionally, the initial bubble boundary conditions (BCs) (i.e. bubble radius R_0 , bubble wall velocity \dot{R}_0 , temperature inside the bubble T_{b0} and molecular contents $N_{\text{vap},0}$, $N_{\text{O}_2,0}$, $N_{\text{N}_2,0}$, $N_{\text{Ar},0}$) at $T_{0,n}$ were updated from the previous numerical results simulated at $T_{0,n-1}$. Figure 2 shows an example of the piecewise constant approach used in this study. With the help of this approach, the dynamics of a single bubble in the liver can be investigated as a function of temperature variation from 20°C to 100°C. The effects of the temperature-dependent parameters on acoustic and temperature fields, which would affect the accuracy of numerical results, in particular the onset time of a boiling bubble at the HIFU focus, were neglected in the KZK and the BHT simulations, because a number of boiling histotripsy studies (Canney et al. 2010; Khokhlova et al. 2011; Pakh et al. 2017) have shown that the time to initiate boiling simulated with constant acoustic and thermal properties of a tissue phantom is in good agreement with the experimental observations.

Numerical quantification of stable and inertial cavitation energies

When analysing cavitation activity for a given HIFU exposure condition in this study, the Akulichev equation (1.8) is employed to calculate the time-varying radiated acoustic pressure resulting from radial bubble motion in the form of an outward travelling spherical wave. This simulated radiated pressure is then converted to the frequency domain for characterising and quantifying cavitation activity, using a fast Fourier transform (FFT). The quantification process used in this study is similar to the methods described by Chen et al. (2003), Tu et al. (2006a, 2006b), Farny et al. (2009) and Zhou and Gao (2013). In an FFT plot, specific narrow frequency windows with a fixed bandwidth of 0.1 MHz, whose central frequencies are the mean values of each harmonic component of the fundamental frequency, are chosen to investigate broadband emissions resulting from inertial cavitation (IC). Meanwhile, multiple harmonics, excluding the fundamental frequency, are used to indicate stable cavitation (SC). Cavitation activity is quantified by integrating the areas under the specified frequency windows and these are cumulated to obtain the amount or energy of SC and IC. A width of 0.1 MHz

was chosen in order to have sufficient number of data points within the specified frequency windows for the integration. As there is no absolute basis by which to quantify the “amount” of cavitation that has occurred (Chen et al. 2003), these values provide relative measures of cavitation under a given HIFU insonation condition.

Further details of the numerical model and its implementation are available in Pakk (2016b).

Model validation

For validation purposes, the present bubble model was compared with other published numerical and experimental observations. Two cases including a single-bubble sonoluminescence (SBSL) (Storey and Szeri 2000) and a lithotripsy bubble (Matula et al. 2002) were considered. These situations were chosen because (a) numerical models for SBSL in the literature address essential features of both heat and mass transfer and (b) boiling lithotripsy uses high acoustic peak pressures which are comparable with those in the shockwaves used in lithotripsy. For SBSL comparison, $R(t)$ and $N_{\text{vap}}(t)$ were calculated with the same parameters $f_0 = 26.5$ kHz, $R_0 = 4.5$ μm and $P_a = 120$ kPa as used by Storey and Szeri (2000), who implemented one of the most complete models in the literature for violent spherical collapses (Kreider 2008). Simulation results for the variation of the bubble radius and molecular content inside the bubble with respect to time are plotted in Figure 3. The present bubble model predicts essentially similar radial bubble motions and vapour trapping effects to within an order of magnitude. When comparing the maximum and the minimum bubble sizes attained and the amount of water vapour trapped during the primary collapse over one acoustic cycle, the present model shows $R_{\text{max}} = 30.3$ μm , $R_{\text{min}} = 0.79$ μm and 14.7% of the vapour content while Storey and Szeri (2000) predicted 31.3 μm , 0.70 μm and 14%, respectively.

In lithotripsy bubbles, as noted by Church (1989), the negative pressure component of a lithotripter shockwave causes a bubble to expand over 100 times its initial size and the gas diffusion increases the duration of afterbounces following primary collapse. In addition, Matula et al. (2002) showed that the majority of the bubble contents throughout the growth phase consists of water vapour, and that the

afterbounces were dominated by vapour transport, not non-condensable gas diffusion. These features can also be observed from the present model as shown in Figure 4.

EXPERIMENTAL METHODS

HIFU experimental setup

A schematic diagram of the *ex vivo* experimental set up used in this study is illustrated in Figure 5. The experiments were performed in a water bath filled with degassed and de-ionised water at a temperature of 20°C. A 1.1 MHz HIFU source with a 20 mm central aperture (nominal active diameter of 64 mm, nominal focal length of 62.6 mm, nominal lateral full width half maximum FWHM of 1.33 mm, nominal axial FWHM of 13.5 mm, nominal electrical to acoustic power conversion efficiency of 85%, Sonic Concepts H102, Bothell, WA, USA) was used. The characteristics of the HIFU transducer used were measured in degassed and deionised water and provided by the manufacturer, Sonic Concepts (Bothell, WA, USA). The HIFU device was positioned at one end in the water bath and an acoustic absorber (Precision Acoustics Ltd AptFlex F28, Dorchester, UK) was placed at the opposite side to minimise acoustic reflections from the wall. The same electronics used in our previous studies (Pahk et al. 2015, 2016a) were used to drive the HIFU transducer: a function generator (Agilent 33220A, Santa Clara, CA, USA), an RF power amplifier (ENI 1040L, Rochester, NY, USA) with a fixed gain of 55 dB and waveform generation software (Agilent Waveform Builder, Santa Clara, CA, USA). To measure the level of the electrical power supplied to the HIFU source, a power meter (Sonic Concepts 22A, Bothell, WA, USA) was connected between the power amplifier and the transducer.

HIFU exposure condition

The HIFU pulsing protocols used in the experiments are shown in Table 5. Acoustic peak positive and negative pressures (P_+ and P_-) at the HIFU focus *in situ* and time t_b to reach a boiling temperature of 100°C were numerically obtained from the HIFU simulator v1.2. The physical properties of the *ex vivo* liver used in the simulations are listed in Table 6. The same HIFU exposure conditions used in

our previous study (Pahk et al. 2015), where well-defined mechanically fractionated or thermally ablated lesion was created in *ex vivo* liver, were employed in the present study, as provided in Table 5.

Liver sample preparation and HIFU focus positioning

A cuboid tissue sample of dimensions $3 \times 6 \times 2$ cm was obtained from an *ex vivo* chicken liver purchased from a local grocery store on the same day as the experiments and kept at room temperature of 20°C. The liver sample was then clamped by a custom-built tissue holder of dimensions $4.5 \times 7.5 \times 5$ cm. The holder coupled with the sample was connected to a customised manual three-axis positioner. The distance from the centre of the HIFU transducer surface to the liver surface was set to 57.6 mm. Hence, the HIFU focus was 5 mm below the surface of the liver sample. *Ex vivo* livers used in the experiments were not degassed prior to HIFU exposure although it is well known that gases released by autolysis can increase the probability of acoustic cavitation events (McLaughlan 2008; ter Haar 2015).

Experimental quantification of cavitation energy

A 10 MHz focused PCD with a diameter of 20 mm and a geometric focal length of 64 mm (Sonic Concepts Y107, Bothell, WA, USA) was used to monitor acoustic emissions produced at the HIFU focus. The PCD transducer was inserted into the central hole of the 1.1 MHz HIFU transducer and aligned confocally with the HIFU focus. Acoustic emissions emitted from either a thermally or a mechanically induced lesion were recorded via a digital oscilloscope (LeCroy HDO 6054, Berkshire, UK) at a sampling rate of 125 MHz over a period of 10 ms.

The PCD output signals (voltage vs time) were transferred to a computer for analysing cavitation activity using the quantification method described in the numerical method section. A 10 ms-long recorded raw PCD data window was initially divided into 50 segments, so that each of these represented a 0.2 ms-long acoustic emission with the calculated temperature rise of $\Delta 3.6^\circ\text{C}/0.2$ ms approximately. This PCD data was then converted to the frequency domain using an FFT. In an FFT plot, the areas under multiple harmonic components of the fundamental frequency (of the form nf_0 ,

where n is a positive integer) and specified frequency windows (of the form $(2n+1)f_0/2$) with a fixed bandwidth of 0.1 MHz were numerically integrated. These were then cumulated to obtain SC and IC cavitation energies. Because of the limited bandwidth of the PCD transducer (10 kHz to 20 MHz) and the reflections of the driving frequency (1.1 MHz), frequencies in the range of the 2nd harmonic (2.2 MHz) to the 18th harmonic (19.8 MHz) were considered in the calculations. As an acoustic cavitation energy was calculated over each 0.2 ms time segment, it was possible to investigate the temporal variation of both IC and SC energies. With the use of 0.2 ms time interval, 200 data points within a fixed bandwidth of 0.1 MHz were available for the integration. MATLAB[®] (MathWorks Inc., R2013a) was used for the signal processing associated with this task.

During the *ex vivo* experiments, 13 PCD data sets in total ($n_s = 9$ for the boiling histotripsy and $n_s = 4$ for the thermal ablation exposures) were collected. Quantified IC and SC energies were presented as the means \pm standard deviations (SD).

NUMERICAL RESULTS

Dynamics of a single bubble in the liver at a constant temperature

Effects of the shapes of acoustic waveforms on an oscillating bubble in the absence of any heat or mass transfer

The effect of different shapes of acoustic pressure waveforms on the dynamics of a single bubble, was investigated in the absence of any heat or mass transfer. Three acoustic pressure waveforms were considered, which were obtained by varying the shock parameter σ_{sh} (the degree of nonlinear distortion of the wave):

- purely sinusoidal (WF1, $\sigma_{sh} = 0$);
- slightly distorted with harmonic components up to the third harmonic (WF2, $\sigma_{sh} = 4.5$) and
- nonlinear shocked (WF3, $\sigma_{sh} = 10.8$).

Simulated slightly distorted nonlinear waves ($P_{act} = 51$ W, $P_+ = 13.4$ MPa, $P_- = -7.5$ MPa, hereafter referred to as the thermal ablation case) and nonlinear-shocked waves ($P_{act} = 298$ W, $P_+ = 82$ MPa, P_-

= -15 MPa, hereafter referred to the boiling histotripsy case) are shown in Figure 6. The shock parameter σ_{sh} was obtained using (Hamilton and Blackstock 2008)

$$\sigma_{sh} = \frac{\beta \varepsilon k_w d_{rc}}{\sqrt{1 - G_f^{-2}}} \ln \left[\left(G_f + \sqrt{G_f^2 - 1} \right) \left(R_c + \sqrt{R_c^2 + 1} \right) \right] \text{ with } R_c = -\left(1 - z_i / d_{rc} \right) \left(G_f^2 - 1 \right)^{1/2} \quad (3)$$

where ε is the ratio of the particle velocity amplitude at the sound source to the small-signal sound speed c_0 , k_w is the acoustic wave number, d_{rc} is the radius of curvature of the source, $G_f = 35.89$ (Sonic Concepts H102, Bothell, WA, USA) is the focal gain and z_i is the distance from the sound source. At first, the bubble dynamics in the liver exposed to both sinusoidal (WF1, $P_+ = -15$ MPa, $\sigma_{sh} = 0$) and nonlinear-shocked (WF3, boiling histotripsy, $P_+ = 82$ MPa, $P_- = -15$ MPa, $\sigma_{sh} = 10.8$) waveforms were compared at a temperature of 20°C. Because the acoustic cavitation threshold is dependent upon the peak negative pressure at a given driving frequency (Kreider et al. 2011), the peak negative pressure amplitude of the sinusoidal wave was set to equal that of the shockwave (i.e., P_- of -15 MPa). In the bubble dynamics simulation, the initial bubble radius was chosen as $R_0 = 15$ μm , as this simply demonstrated the effect of the different shapes of the acoustic pressure waveforms after only a few acoustic cycles in the absence of any heat or mass transfer. The physical parameters of the liver at 20°C used in the bubble model are displayed in Table 7.

Figure 7 shows the responses of a single spherical gas bubble driven by the sinusoidal (WF1) and the nonlinear-shocked (WF3) waves. For the sinusoidal excitation case (see Figure 7(a)), the bubble continues to grow and collapse with time; whereas the nonlinear-shocked waveform leads the bubble to respond more to the negative pressure cycle and its radial motion is biased towards increase over each acoustic cycle (indicated by an arrow in Figure 7(a)). This bubble behaviour is known as rectified bubble growth and is thought to be due to the asymmetry between compressive and tensile portions of shocked waveforms (Kreider et al. 2011).

In contrast with the explosive bubble growth caused by the nonlinear-shocked waves (WF3, $\sigma_{sh} = 10.8$), no rectified radial motion is observed under the slightly distorted nonlinear waveforms (WF2, $\sigma_{sh} = 4.5$) as shown in Figure 7(b). Nevertheless, the bubble growth is enhanced (maximum bubble radius $R_{max} = 65$ μm) compared with that of the sinusoidal excitation ($R_{max} = 63$ μm) since it has a slightly longer duration of negative pressure cycle than that of the sine wave.

Additional calculations were performed by varying the shock parameters σ_{sh} from 5 to 9. This was to investigate the effects of nonlinear distortion of the waveform on the bubble growth. Acoustic waveforms used in the simulations are plotted in Figure 8. Figure 8(b) shows the dynamics of a single gas bubble as a function of the shock parameter $\sigma_{sh} = 5, 7$ and 9. As σ_{sh} increases, the maximum bubble radius R_{max} becomes larger. However, rectified bubble growth only appears when $\sigma_{sh} = 9$. This is summarised in Table 8.

Effects of heat and mass transfer on an oscillating bubble

Khokhlova et al. (2011) demonstrated that purely mechanical damage of soft tissue is only observed when both boiling and shockwaves are present at the HIFU focus. Figure 9 shows the responses of a 1 μm gas-vapour bubble in the liver excited by the nonlinear-shocked waves (WF3, $P_+ = 82$ MPa, $P_- = -15$ MPa, $\sigma_{sh} = 10.8$) at a boiling temperature of 100°C. Temperature-dependent physical properties of liver at 100°C (i.e. density, speed of sound, viscosity and surface tension) were used in the simulations and are given in Table 9.

Examining the molecular contents of H_2O and of the gas in the bubble (see Figure 9(b)), it is noticed that the number of gas molecules gradually increases over each acoustic cycle by rectified gas diffusion (Crum 1984); however H_2O behaves differently. The number of H_2O molecules in the bubble gradually decreases starting from 30 μs , causing it to start shrinking. This amount is then biased towards increase by rectified heat transfer (Hao and Prosperetti 1999, 2002) at 40 μs , leading to the explosive bubble growth with an average growth rate of $U = 7$ m s⁻¹ (see Figure 9(a)). In addition, water vapour comprises the majority of the bubble contents during the growth phase (99.99% molar basis, see Figure 9(b)). Rectified bubble growth can also be observed without gas diffusion (i.e. accounting for vapour transfer only), as shown in Figures 9(c) and (d).

When neglecting the water vapour transport in the bubble model (i.e. accounting for gas diffusion only), rectified bubble growth does not occur (see Figures 9(e) and (f)). However, the maximum bubble radius R_{max} is 1.2 times larger than that which would occur with shockwaves only ($R_{max} = 58$ μm , the blue line in Figure 9(a)). The effects of vapour transport on the radial bubble motion at 100°C are summarised in Table 10.

Rectified bubble growth is caused by the combination of the asymmetry in shockwaves and by water vapour (H_2O) that transports into the bubble at $100^\circ C$. Removing the impact of the asymmetry in the acoustic waveform shape on the bubble growth, a sinusoidal excitation (WF1) at $P_- = -15$ MPa can lead to rectified bubble growth with $U = 2.2$ m s^{-1} by vapour transport when ambient temperature exceeds $100^\circ C$, as shown in Figure 10.

Dynamics of boiling histotripsy bubbles and acoustic emissions in liver tissue as a function of temperature variation in the surrounding medium

Radial bubble motion

The piecewise constant approximation method was implemented in this study to explore the bubble dynamics as a function of temperature variation in the fluid. In the bubble simulations, the surrounding temperature T_0 was varied from $20^\circ C$ to $100^\circ C$ with $\Delta T_0 = 10^\circ C/200$ acoustic cycles. The responses of a 1 μm gas-vapour bubble in the liver exposed to both the slightly distorted nonlinear (WF2, thermal ablation, $P_+ = 13.4$ MPa, $P_- = -7.5$ MPa) and the nonlinear-shocked waves (WF3, boiling histotripsy, $P_+ = 82$ MPa, $P_- = -15$ MPa) are shown in Figure 11. For both HIFU excitations, the time of the bubble growth phase increases as the surrounding temperature increases. When the temperature reaches a boiling temperature of $100^\circ C$, rectified bubble growth occurs at 1.45 ms under the nonlinear-shocked waves (WF3) with an average bubble growth rate of $U = 3.4$ m s^{-1} (see Figure 11(a)). This rectified radial motion can also be attained via exposure to the slightly distorted nonlinear waveform (WF2) with $U = 2.3$ m s^{-1} , once the surrounding temperature exceeds $100^\circ C$ (see Figure 11(b)).

Pahk et al. (2017) experimentally observed that a boiling vapour bubble always appears within a localised heated region and the extent of this oscillating bubble is confined to this region in a tissue phantom during the course of boiling histotripsy. Additional simulations were therefore performed with the reduction of the surrounding temperature from $100^\circ C$ to $70^\circ C$ under the nonlinear-shocked wave excitation case (WF3) to investigate whether a boiling vapour bubble continuously undergoes rectified growth when the size of the bubble becomes larger than that of a localised heated region ($100^\circ C$) at the HIFU focus (i.e. the surrounding temperature becomes lower than $100^\circ C$). It is

observed in Figure 12 that the average bubble growth rate decreases to 2.9 m s^{-1} (90°C), 1.3 m s^{-1} (80°C) and -1.1 m s^{-1} (70°C).

Acoustic emissions

Radiated acoustic pressures resulting from the bubble radial motions plotted in Figure 11 were calculated using equation (1.8) to investigate the changes in the emitted acoustic signal as a function of changes in the incident acoustic field. The simulated time-varying radiated pressures were converted to the frequency domain using an FFT. SC and IC energies were quantified using the method described in the numerical method section. Figure 13 shows the simulated radiated acoustic pressures and the corresponding spectrograms (frequency vs time) during boiling histotripsy (WF3, nonlinear-shocked waves) and thermal ablation (WF2, slightly distorted nonlinear waves) exposures. For the boiling histotripsy insonation, there are noticeable differences in the acoustic emissions before and after $t = 1.45 \text{ ms}$. In the radiated pressure vs time plot (see Figure 13(a)), the pressure amplitude is fairly uniform; it, however, increases significantly at $t = 1.45 \text{ ms}$. The corresponding spectrogram also indicates these changes (see Figure 13(b)). Multiple harmonic components from 1.1 MHz to 8.8 MHz (first to eighth harmonic) can be observed before $t = 1.45 \text{ ms}$ followed by the significant occurrence of higher harmonics up to 19.8 MHz (18^{th} harmonic) at $t = 1.45 \text{ ms}$. The presence of these multiple harmonics in the spectrogram is due to strongly nonlinear radial bubble oscillations and is the indication of stable cavitation (Pahk et al. 2015). The time of occurrence of a local maximum in the radiated pressure vs time curve, as well as in the spectrogram, matches the onset of the rectified bubble growth plotted in Figure 11(a).

Prior to the inception of rectified radial motion at $t = 1.45 \text{ ms}$, higher order multiple harmonic components with larger amplitudes gradually appear in the spectrogram whilst the magnitude of the levels of broadband emissions reduces with time (see Figure 13(b)). The broadband component is the result of the short-duration pressure spikes caused by violent bubble collapses (Leighton 1994). The corresponding quantified SC and IC energies plotted in Figure 14 also indicate the inverse relationship between SC and IC with time. In contrast to the acoustic emissions which occur during the boiling histotripsy exposure, a lower peak-to-peak radiated pressure amplitude and lower multiple

harmonics with lower levels of broadband emissions are observed under the thermal ablation exposure (see Figures 13(a), (c) and 15). Indeed, the amount of quantified cavitation energy (both SC and IC) is less than that produced by the boiling histotripsy insonation (see Figure 14).

EXPERIMENTAL RESULTS *EX VIVO*

Acoustic emissions recorded over a period of 10 ms under boiling histotripsy and thermal ablation exposures are shown in Figure 16. Variations of the peak-to-peak PCD voltage output present the amplitudes of acoustic cavitation during HIFU exposure (Everbach et al. 1997; Zhou and Gao 2013). Higher order multiple harmonic components of the fundamental frequency ($f_0 = 1.1$ MHz) up to the 17th harmonic (18.7 MHz) with larger amplitudes, as well as higher levels of broadband emissions, can be seen under the boiling histotripsy insonation relative to those during thermal ablation exposure (see Figures 16(b) and (d)). These frequency domain features are in agreement with the numerically obtained spectrograms in Figures 17(e) and (f).

As shown in Figure 13, a significant appearance of higher order multiple harmonics in the frequency domain is an indicator of the presence of a boiling bubble at the HIFU focus during the course of HIFU exposure. In the case of the boiling histotripsy excitation, the manifestation of a boiling bubble occurs at $t = 4.72$ ms (see Figure 16(b)), whereas this is not observed under the thermal ablation exposure (see Figure 16(d)). This is due to the fact that the absorption of the acoustic waves used in the thermal ablation exposure condition does not increase tissue temperature to a boiling temperature of 100°C within 10 ms. The corresponding computed time at which boiling occurs was predicted to be 2.2 s (see Table 5). Nevertheless, the recorded acoustic emissions suggest that acoustic cavitation may be occurring (see Figure 16(d)), but that this is not due to the formation of a boiling bubble.

During the experiments, the indication of the appearance of a boiling bubble in the *ex vivo* liver occurred at 4.56 ± 1.15 ms (mean \pm SD with $n_s = 9$), which was similar to the heat transfer simulation ($t_b = 4.45$ ms, see Table 5) with a difference of 2.5% between the PCD measurement and the calculation.

Figure 17 shows calculated IC and SC energies over 4 ms prior to the onset of a boiling bubble. Acoustic emissions emitted from an inertial cavitation cluster, which are likely to occur after the production of a boiling bubble at the HIFU focus in the course of boiling histotripsy (Pahk et al. 2017), were not accounted for in the analyses. Under both HIFU exposure conditions, the SC energy increases (Figure 17(a)) while the IC energy reduces (Figure 17 (b)) with time. It is also noticed that cavitation energy (both SC and IC) under the boiling histotripsy insonation is greater relative to that under the thermal ablation exposure (see Figures 17(a) and (b)). Whilst the *ex vivo* liver samples used were not degassed prior to the HIFU exposure which likely affected the probability of cavitation events, these experimental observations are in agreement with the numerical simulations displayed in Figures 17(c) and (d). Experimental results obtained with degassed *ex vivo* livers would provide a better agreement with the numerical results.

DISCUSSION

Effects of the shapes of acoustic waveforms

In this study, the dynamics of a single bubble in the liver exposed to different HIFU waveforms were investigated. Three different acoustic pressure waveforms were considered to excite bubble motions: (a) sinusoidal WF1, slightly distorted nonlinear WF2 and (c) nonlinear-shocked WF3 waves. With the absence of any heat or mass transfer, the bubble continued to grow and collapse with time when excited by the sinusoidal waves (WF1, $P_+ = -15$ MPa), whereas the nonlinear-shocked waves (WF3, boiling histotripsy, $P_+ = 82$ MPa, $P_- = -15$ MPa) caused the bubble to undergo rectified growth after 10 acoustic cycles (see Figure 7(a)). Because these calculations did not take heat and mass transport at the bubble wall into account, this qualitative difference in the radial motions must be attributable to the shape of the acoustic excitation waveforms. As the peak positive pressure phase has a shorter duration than the negative pressure part in the shockwaves (i.e. $0.27 \mu\text{s}$ vs $0.62 \mu\text{s}$, see Figure 6(a)), the bubble has a relatively longer time to undergo expansion rather than collapsing, leading to rectified bubble growth. As the bubble gets larger over each acoustic cycle, its resonance frequency decreases, and thereby the bubble responds increasingly to the negative pressure part of the waveform

(Kreider et al. 2011). This radial behaviour is clearly visible in Figure 7(a), where the bubble growth rate accelerates as the bubble grows.

Effects of heat and mass transfer

Rectified heat and mass diffusion can occur at a bubble wall in the presence of acoustic pressure fields (Crum 1984; Hao and Prosperetti 1999, 2002). When the bubble is compressed during the positive half cycle, the internal pressure P_i as well as the bubble temperature T_b increases and some vapour condenses. Heat is, therefore, conducted away from the bubble into the surrounding medium.

Conversely, the opposite holds true during the bubble expansion phase: a decrease in P_i and T_b , and evaporation takes place. There is, however, a net flux of heat into the bubble (i.e. rectified heat diffusion) because the bubble wall becomes thicker during the bubble compression phase than that during the expansion process. Furthermore, the bubble surface area available for the phase change between liquid and gas is larger during the expansion phase; thereby, more volatile species in the surrounding medium evaporate into the bubble (Hao and Prosperetti 1999, 2002). Rectified incondensable gas diffusion, in addition to a net flux of heat, can also appear where the bubble can grow further. The gas in the bubble diffuses out into the surrounding medium during the positive half cycle, and vice versa. As the bubble grows during the negative half cycle, the diffusion boundary layer and the surface area become thinner and larger, respectively, causing a net flux of gas into the bubble (Crum 1984). The presence of a shocked wavefront in an acoustic waveform can enhance both nonlinear heat transfer and incondensable gas diffusion due to the asymmetry in the waveform. Since this asymmetry increases the time of the bubble expansion process, more volatile species and gas molecules in the surrounding medium will evaporate and diffuse into the bubble, resulting in an enhanced bubble growth. When accounting for both the heat and mass transport in the bubble model, it was seen that excitation by WF1 (sinusoidal excitation, $P. = -15$ MPa) led to rectified bubble growth at 105°C with the average growth rate of $U = 2.2$ m s⁻¹. The maximum bubble radius and the total number of molecules (water vapour and gas) in the bubble at the end of the growth phase were 188 μm and 6.302×10^{14} , respectively (see Figures 10(a) and (b)). On the other hand, an explosive rectified bubble growth occurred at 100°C in the case of excitation by WF3 (nonlinear-shocked

excitation, $P_+ = 82$ MPa, $P_- = -15$ MPa) (see Figure 9(a)). Relative to excitation by WF1 (sinusoidal excitation), the average growth rate was 3.2 times faster, R_{\max} was twice as large and the molecular contents was 5.3 times greater (see Figure 9(b)). These results are summarised in Table 11.

The increase of water vapour and gas molecules in the bubble due to the presence of asymmetry in the acoustic excitation waveform was examined. It was observed that the amount of water vapour was enhanced by a factor of 5.3 whereas that of gas was only increased by a factor of 1.3 (see Table 11). This is most probably due to the fact that temperature significantly affects the number of available water vapour and gas molecules in the surrounding medium. For example, at a boiling temperature of 100°C, the molecular concentration of water vapour in the liver is 27 times higher than that of the gas, as shown in Figure 18. Therefore, relatively greater amounts of water vapour in the surrounding medium diffuse into the bubble during the bubble expansion process over a given time. Equation (2.2) and the concentration of dissolved gas c_∞ used in equation (2.4) were respectively employed to calculate the molecular concentrations for water vapour and gas.

Effects of temperature variation in the fluid

The piecewise constant method was adopted in the bubble model to investigate the bubble dynamics resulting from the nonlinear-shocked waves (WF3) at elevated temperatures from 20°C to 100°C. It was observed that the radial bubble growth persisted for a longer period as the surrounding temperature increased with time (see Figure 11(a)). This is because of the combination of the vapour trapping effect and the increased vapour pressure in the bubble (Matula et al. 2002; ter Haar and Coussios 2007). This combination reduces the inertial bubble collapses and leads to the bubble oscillating more stably. As a result, higher order multiple harmonic components gradually appear (leading to a greater SC energy) whilst the levels of broadband emissions reduce (leading to a lesser IC energy) as a function of time. This can be visualised in the spectrogram displayed in Figure 13(b), as well as in the quantified cavitation energies plotted in Figure 14.

Additional calculations for the radial bubble motions were performed under the nonlinear-shocked wave excitation case (WF3), this time reducing the surrounding temperature from 100°C to

70°C (see Figure 12). Interestingly, the average bubble growth rate gradually decreases with time (i.e. $U_{100^\circ\text{C}} = 3.4 \text{ m s}^{-1}$, $U_{90^\circ\text{C}} = 2.9 \text{ m s}^{-1}$, $U_{80^\circ\text{C}} = 1.3 \text{ m s}^{-1}$) and drops to $U = -1.1 \text{ m s}^{-1}$ at 70°C. These numerical observations suggest that the extent of an exploding bubble growth at the HIFU focus during boiling histotripsy is likely to be limited to the HIFU focal volume owing to the significant differences in tissue temperatures inside and outside of the focal region.

Acoustic emissions resulting from the formation of a boiling bubble

Canney et al. (2010) experimentally observed that there was a significant increase in amplitude in the PCD voltage output and a sudden occurrence of higher order multiple harmonic components of the fundamental frequency in the spectrogram when a millimetre-sized boiling bubble formed at the HIFU focus in a tissue phantom. The authors speculated that these significant changes were likely to be due to the reflection of the incident nonlinear-shocked waves from the boiling bubbles filled with gas and vapour because of the large acoustic impedance mismatch at their surface. Whilst the present bubble model does not take into account the shock scattering effect for simulating the acoustic emissions, the numerical results presented in this study showed similar features to those described by Canney et al. (2010). The data shown in Figures 11(a) and 13(a) and (b) demonstrates that the explosive rectified bubble growth at 100°C manifests itself as a significant increase of the amplitude in the radiated pressure vs time curve (see Figure 13(a)). Simultaneously, stronger and higher order multiple harmonics appear in the spectrogram (see Figures 13(b) and 16(b)). These observations together with the experimental results from Canney et al. (2010) suggest that the acoustic emissions resulting from the formation and the dynamic behaviour of a boiling bubble at the HIFU focus can be monitored, because the bubble acts as a strong scatterer and oscillates with a highly nonlinear radial behaviour.

Monitoring HIFU thermal ablation and boiling histotripsy

The numerical and the experimental results presented in this study demonstrate that emitted acoustic signals during thermal ablation and boiling histotripsy exposures can be distinguished in the frequency domain. From the experiments, the acoustic emissions which occurred during the boiling

histotripsy exposure consisted of higher order multiple harmonics with higher levels of broadband components in the spectrogram relative to those during thermal ablation insonation (see Figure 16). These features were consistent with the numerical results plotted in Figures 13, 15 and 17(e) and (f). The significant differences in acoustic emissions are primarily due to the acoustic waveform and the peak pressure amplitudes at the HIFU focus. For example, the shockwave ($P_+ = 82$ MPa, $P_- = -15.1$ MPa at the HIFU focus) resulting from the boiling histotripsy excitation consists of higher order multiple harmonics in the frequency domain (see Figure 6). This yields a high degree of nonlinearity in the bubble oscillations and violent bubble collapses with larger amplitude short-duration pressure spikes (Pahk et al. 2015). In contrast, the slightly distorted nonlinear wave excitation resulting from the thermal ablation exposure condition ($P_+ = 13.4$ MPa, $P_- = -7.5$ MPa at the HIFU focus) contains a fewer number of multiple harmonics with lower acoustic peak pressures, resulting in a lower degree of nonlinearity in the radial bubble motions and less violent bubble collapses. These phenomena eventually lead to the significant differences in (a) the radiated pressures resulting from the bubble dynamics and (b) the acoustic pressure fields scattered by a bubble.

CONCLUSIONS

The dynamics of bubbles in liver tissue exposed to different HIFU fields (thermal ablation and boiling histotripsy exposure cases) have been investigated both numerically and experimentally. The numerical results presented in this study showed that the asymmetry in a shockwave together with water vapour transport are the key parameters that lead the bubble to undergo rectified growth at a boiling temperature of 100°C. The extent of this growing bubble process is, however, likely to be limited to the HIFU focal zone due to the large temperature gradient across the edge of the HIFU focus. The onset of rectified bubble growth manifested itself as (a) a significant increase in the radiated pressure vs time curve and (b) the sudden appearance of higher order multiple harmonics with larger amplitudes in the corresponding spectrogram. Examining the frequency spectra produced by the thermal ablation (slightly distorted nonlinear waveforms) and the boiling histotripsy (nonlinear-shocked waves) exposures, it was clearly noticed that higher order multiple harmonics as well as higher levels of broadband emissions occurred during the boiling histotripsy insonation. These

unique features in the emitted acoustic signals were consistent with the PCD *ex vivo* experimental measurements. These features can, therefore, be used to monitor (a) the different types of cavitation activity for either a thermally or a mechanically induced lesion and (b) the onset of a boiling bubble at the HIFU focus in the course of HIFU exposure. The numerical approach described in this work can be used for predicting cavitation activity under a given HIFU exposure condition.

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Figure Legends

Figure 1. Calculated properties of water (solid line) and of liver (dashed line) as a function of temperature from 20°C to 100°C. (a) density, (b) speed of sound, (c) viscosity and (d) surface tension. The blue circles indicate experimental measurements of properties of water as a function of temperature variation. These values were obtained from Haar et al. (1984) for density, Del Grosso and Mader (1972) for speed of sound, Korson et al. (1969) for viscosity and Vargaftik et al. (1983) for surface tension.

Figure 2. An example of the piecewise constant approach used in the study. R_0 , \dot{R}_0 , $N_{i,0}$ at t_0 are obtained from equation (2.21). Saturated water vapour density, Henry's constants for incondensable gases and the physical properties of liver are calculated using equations (2.2), (2.6) and (2.25)–(2.29), respectively.

Figure 3. Dynamics of a single argon-vapour bubble in water excited by a sinusoidal wave over one acoustic cycle with parameters $f_0 = 26.5$ kHz, $R_0 = 4.5$ μm , $P_a = 120$ kPa and $T_0 = 298\text{K}$ as used by Storey and Szeri (2000). (a) Radius vs time curve. (b) Molecular contents vs time curve. The accommodation coefficient α_m was 0.1.

Figure 4. Dynamics of a single air-vapour bubble in water excited by a lithotripter shockwave. (a) Radius vs time curve for an air-vapour bubble. (b) Molecular contents (H_2O and air) vs time curve. The present calculations included the same parameters used by Matula et al. (2002) i.e. a 4.5 μm air-vapour bubble in water at 298K. The peak positive and negative acoustic pressures used in the lithotripter shockwave were $P_+ = 33$ MPa and $P_- = -11$ MPa, respectively.

Figure 5. A schematic diagram of the *ex vivo* experimental setup used.

Figure 6. (a) Sinusoidal (WF1, black solid line, $P_+ = 7.5$ MPa), slightly distorted nonlinear (WF2, blue solid line, thermal ablation, $P_+ = 13.4$ MPa, $P_- = -7.5$ MPa) and nonlinear-shocked (WF3, red solid line, boiling histotripsy, $P_+ = 82$ MPa, $P_- = -15$ MPa) waveforms at the HIFU focus with a driving frequency of 1.1 MHz. (b) Corresponding frequency spectra over 100 acoustic cycles. f_0 is the fundamental frequency. The HIFU simulator v1.2 (Soneson 2009) was used to compute the acoustic waveforms.

Figure 7. Radius vs time curves at $T_0 = 20^\circ\text{C}$ in the absence of any heat or mass transfer at the bubble wall (a) resulting from the sinusoidal waves (WF1, black solid line, $P_- = -15$ MPa) and the nonlinear-shocked waveforms (WF3, red solid line, boiling histotripsy, $P_+ = 82$ MPa, $P_- = -15$ MPa at the focus). (b) with the sinusoidal waves (WF1, black solid line, $P_- = -7.5$ MPa) and the slightly distorted nonlinear waves (WF2, blue solid line, thermal ablation, $P_+ = 13.4$ MPa, $P_- = -7.5$ MPa at the focus). The initial radii were $15\ \mu\text{m}$ in the simulations.

Figure 8. (a) Simulated acoustic waveforms with $\sigma_{\text{sh}} = 5, 7, 9$. (b) Radius vs time curves with $\sigma_{\text{sh}} = 5, 7$ and 9 over 100 acoustic cycles. The initial bubble radii were $15\ \mu\text{m}$ in the simulations.

Figure 9. Dynamics of a $1\ \mu\text{m}$ gas-vapour bubble in the liver at 100°C with the nonlinear-shocked waveforms (WF3, $P_+ = 82$ MPa, $P_- = -15.1$ MPa) over 100 acoustic cycles. (a) Radius vs time curves with (red solid line) and without (blue solid line) heat and mass transfer. (b) Corresponding molecular contents of water vapour and gas of (a). (c) Radius vs time curve without gas diffusion. (d) Corresponding molecular contents of (c). (e) Radius vs time curve without water vapour transport. (f) Corresponding molecular contents of (e).

Figure 10. (a) Radius vs time curves with the sinusoidal waves (WF1, $P_- = -15$ MPa) at temperatures of 95°C (blue solid line) and 105°C (red solid line) over 100 acoustic cycles. (b) Corresponding molecular contents of (a) at 105°C . The initial bubble radii were $1\ \mu\text{m}$.

Figure 11. Dynamics of a $1\ \mu\text{m}$ gas-vapour bubble as a function of temperature variation from 20°C to 100°C with $\Delta T_0 = 10^\circ\text{C}/200$ acoustic cycles. Radius vs time curves with (a) the nonlinear-shocked waves (WF3, boiling histotripsy, $P_+ = 82$ MPa, $P_- = -15$ MPa) and (b) the slightly distorted nonlinear waveforms (WF2, thermal ablation, $P_+ = 13.4$ MPa, $P_- = -7.5$ MPa). The liver properties (density, speed of sound, viscosity and surface tension) that change with temperature were calculated using equations (2.25)–(2.29).

Figure 12. Radius vs time curve under the nonlinear-shocked waves (WF3, $P_+ = 82$ MPa, $P_- = -15$ MPa) at temperatures of 100°C , 90°C , 80°C and 70°C .

Figure 13. Simulated radiated pressures and spectrograms with the thermal ablation (WF2, slightly distorted nonlinear waveforms, $P_+ = 13.4$ MPa, $P_- = -7.5$ MPa) and the boiling histotripsy (WF3, nonlinear-shocked waves, $P_+ = 82$ MPa, $P_- = -15$ MPa) exposures. (a) Radiated acoustic pressures

during boiling histotripsy (WF3, red solid line) and thermal ablation (WF2, blue solid line) insonations. (b) and (c) are the corresponding spectrograms for the boiling histotripsy and the thermal ablation exposures, respectively. A sampling frequency of 22 GHz was used in the simulations.

Figure 14. Corresponding amounts of (a) SC and (b) IC during boiling histotripsy (red solid line, $P_+ = 82$ MPa, $P_- = -15$ MPa) and thermal ablation (blue solid line, $P_+ = 13.4$ MPa, $P_- = -7.5$ MPa) exposures.

Figure 15. Corresponding simulated frequency spectra of the radiated pressures plotted in Figure 13(a) during boiling histotripsy (red solid line, $P_+ = 82$ MPa, $P_- = -15$ MPa) and thermal ablation (blue solid line, $P_+ = 13.4$ MPa, $P_- = -7.5$ MPa) exposures.

Figure 16. Recorded acoustic emissions resulting from cavitation activity at the HIFU focus during the boiling histotripsy and the thermal ablation exposures. (a) and (c) are the raw PCD voltage vs time plots obtained under the boiling histotripsy and the thermal ablation exposure conditions, respectively. (b) and (d) are the corresponding spectrograms. The time at 0 ms corresponds to the start of HIFU insonation.

Figure 17. (a) and (b) are the experimentally obtained SC and IC energies under the boiling histotripsy (mean \pm SD with $n_s = 9$) and the thermal ablation (mean \pm SD, $n_s = 4$) exposures, respectively. (c) and (d) are the simulated SC and IC energies. (e) and (f) are the predicted spectrograms under the boiling histotripsy and the thermal ablation excitations, respectively.

Figure 18. Saturated density of water vapour H_2O and gas (Nitrogen N_2 + Oxygen O_2 + Argon Ar) in the liver with temperature. Equation (2.2) and the concentration of dissolved gas c_∞ used in equation (2.4) were respectively employed to calculate the molecular concentrations for water vapour and gas.

Tables

Table 1. The alphabetical constants in Henry's law and the diffusion volumes for N₂, O₂ and Ar.

Gases	A_h	B_h	C_h	V_m (Poling et al. 2004)
N ₂ (Battino 1982)	-67.4	86.3	24.8	18.5
O ₂ (Battino 1981)	-66.7	87.5	24.5	16.3
Ar (Clever 1980)	-57.7	74.8	20.1	16.2

Table 2. The number of translational and rotational degrees of freedom f_i , the characteristic vibrational temperatures θ_n and the number of the characteristic vibrational temperatures n for N₂, O₂, Ar and H₂O (Toegel and Lohse 2003).

Gases	f_i	θ_n	n
N ₂	5	3350	1
O ₂	5	2273	1
Ar	3	-	-
H ₂ O	6	2295, 5255, 5400	3

Table 3. Physical constants for the gas dynamics used in the bubble model (Wagner and Pruß 2002; Poling et al. 2004).

Symbol	Definition	Value	Units
R_{gas}	Universal gas constant	8.314472	J mol ⁻¹ K ⁻¹
K_B	Boltzmann constant	$1.3806503 \times 10^{-23}$	J K ⁻¹
N_A	Avogadro's constant	$6.02214179 \times 10^{23}$	mol ⁻¹
M_{air}	Molar mass of air	28.97×10^{-3}	kg mol ⁻¹
M_{vap}	Molar mass of water vapour	18.015268×10^{-3}	kg mol ⁻¹
M_{N_2}	Molar mass of nitrogen	28×10^{-3}	kg mol ⁻¹
M_{O_2}	Molar mass of oxygen	31.9988×10^{-3}	kg mol ⁻¹
M_{Ar}	Molar mass of argon	39.95×10^{-3}	kg mol ⁻¹

Table 4. Physical properties of water and of liver at 20°C. These values were obtained from Duck (1990), Choi et al. (2011) and Church et al. (2012).

Symbol	Definition	Values measured at 20°C		
		Water	Liver	Ratio
ρ_0	density [kg m^{-3}]	998.2	1060	1.06
c_0	speed of sound [m s^{-1}]	1482	1575	1.06
μ_0	viscosity [$\text{kg m}^{-1} \text{s}^{-1}$]	1.0019×10^{-3}	9×10^{-3}	8.98
σ_0	surface tension [N m^{-1}]	0.073	0.056	0.77

Table 5. HIFU exposure settings used in the *ex vivo* experiments. A continuous 5s HIFU insonation was used for the thermal ablation process whereas the duty cycle, pulse length, pulse repetition frequency and the number of HIFU pulses for the boiling histotripsy were 1%, 10 ms, 1 Hz and 50, respectively.

Acoustic power P_{act} (W)	Exposure type	P_+ (MPa) <i>in situ</i>	P_- (MPa) <i>in situ</i>	Time to boil	Duty cycle	Pulse length	Pulse repetition frequency	Number of pulses
51	Thermal ablation	13.4	-7.5	2.2 s	100%	5 s		
298	Boiling histotripsy	82.1	-15.1	4.45 ms	1%	10 ms	1 Hz	50

Table 6. Properties of *ex vivo* liver used in the simulations.

Liver (Choi et al. 2013)	
Parameter	Values
Small-signal speed of sound	1575 m s ⁻¹
Mass density	1060 kg m ⁻³
Absorption at 1 MHz	52 dB m ⁻¹
Exponent of absorption vs frequency curve	1.1
Coefficient of nonlinearity	4.4
Specific heat capacity	3628 J kg ⁻¹ K ⁻¹
Thermal conductivity	0.572 W m ⁻¹ K ⁻¹
Perfusion rate	0 kg m ⁻³ s ⁻¹
Ambient temperature	20 °C

Table 7. Parameters used in the Gilmore bubble model at $T_0 = 20^\circ\text{C}$. The density, speed of sound, viscosity and the surface tension were calculated using equations (2.25)–(2.29). The material dependent constants m and A for the liver were obtained from Pakh et al. (2015).

Symbol	Definition	Liver at 20°C
ρ_0	density	1058 kg m ⁻³
c_0	speed of sound	1575 m s ⁻¹
μ_0	viscosity	0.0087 kg m ⁻¹ s ⁻¹
σ_0	surface tension	0.056 N m ⁻¹
γ	polytrophic exponent of a diatomic gas	1.4
p_0	ambient pressure	1.01325×10^5 Pa
T_0	ambient temperature	20 °C
m	empirical material dependent constant	5.527
A	empirical material dependent constant	614.6 MPa
B	empirical material dependent constant	$A - p_0$ MPa

Table 8. The effects of the degree of nonlinear distortion of the waveform on the bubble growth.

Shock parameter	P_+	P_-	R_{\max}	Does rectified bubble growth
σ_{sh}	(MPa)	(MPa)	(μm)	appear?
5	16.4	-8.7	69.9	No
6	22.2	-9.9	73.0	No
7	29.7	-11.1	75.4	No
8	39.9	-12.1	77.9	No
9	55.4	-13.4	124.1	<i>Yes</i>

Table 9. Physical properties of liver at $T_0 = 100^\circ\text{C}$ used in the bubble model. These values were calculated using equations (2.25)–(2.29). The material dependent constants m , A and B are shown in Table 7.

Symbol	Definition	Liver at 100°C
ρ_0	Density	1015 kg m ⁻³
c_0	speed of sound	1640 m s ⁻¹
μ_0	Viscosity	2.3×10^{-3} kg m ⁻¹ s ⁻¹
σ_0	surface tension	0.0453 N m ⁻¹

Table 10. The effects of water vapour on the bubble dynamics at a boiling temperature of 100°C.

Bubble simulation conditions at 100°C	Does rectified bubble	R_{\max} (μm)
	growth appear?	
Shockwaves (SWs) only	No	58
SWs + heat + gas transfer	No	69
SWs + heat + vapour transfer	<i>Yes</i>	362
SWs + heat + gas + vapour transfer	<i>Yes</i>	370

Table 11. The maximum bubble radius, average bubble growth rate and the number of molecular contents attained by the sinusoidal (WF1, $P_- = -15$ MPa) and the nonlinear-shocked excitations (WF3, $P_+ = 82$ MPa, $P_- = -15$ MPa) over 100 acoustic cycles.

Waveform types	Maximum bubble radius (μm)	Average growth rate (m s^{-1})	Number of molecules in the bubble	
			Water vapour	Gas
Sine waves ($\sigma_{\text{sh}} = 0$)	188	2.2	6.301×10^{14}	1.286×10^{11}
Shock waves ($\sigma_{\text{sh}} = 10.8$)	370	7	3.318×10^{15}	1.633×10^{11}