GPU-accelerated study of the inertial cavitation threshold in viscoelastic soft tissue using a dual-frequency driving signal

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A R T I C L E   I N F O

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A B S T R A C T

Inertial cavitation thresholds under two forms of ultrasonic excitation (the single- and dual-frequency ultrasound modes) are studied numerically. The Gilmore–Akulichev model coupled with the Zener viscoelastic model is used to model the bubble dynamics. The threshold pressures are determined with two criteria, one based on the bubble radius and the other on the bubble collapse speed. The threshold behavior is investigated for different initial bubble sizes, acoustic signal modes, frequencies, tissue viscosities, tissue elasticities, and all their combinations. Due to the large number of parameters and their many combinations (around 1.5 billion for each threshold criterion), all simulations were executed on graphics processing units to speed up the calculations. We used our own code written in the C++ and CUDA C languages. The results obtained demonstrate that using the dual-frequency signal mode can help to reduce the inertial cavitation threshold (in comparison to the single-frequency mode). The criterion based on the bubble size gives a lower threshold than the criterion using the bubble collapse speed. With an increase of the elasticity, the threshold pressure also increases, whereas changing the viscosity has a very small impact on the optimal threshold, unlike the elasticity. A detailed analysis of the optimal ultrasound frequencies for a dual-frequency driving signal found that for viscosities less than 0.02 Pa \cdot s, the first optimal frequency, in general, is much smaller than the second optimal frequency, which can reach 1 MHz. However, for high viscosities, both optimal frequencies are similar and varied in the range 0.01–0.05 MHz. Overall, this study presents a detailed analysis of inertial cavitation in soft tissue under dual-frequency signal excitation. It may be helpful for the further development of different applications of biomedical ultrasound.

1. Introduction

High-intensity focused ultrasound (HIFU) has been used in various clinical trials as a promising method of non-invasive surgery [1–4]. HIFU therapy is a non-invasive, non-ionizing method that can be applied for tumor ablation in various organs (prostate, liver, pancreas, breast, kidney, bone, and other soft tissue tumors) [5,6], for acoustic hemostasis to help to seal a bleeding site [7], and for targeted drug and gene delivery [8,9]. The two main mechanisms involved during focused ultrasound therapy are thermal and mechanical effects. Thermal effects occur when tissue absorbs the ultrasound energy. There is a consequent conversion of this energy to heat in the focal area [3,10]. Mechanical effects include acoustic streaming, radiation forces, and cavitation. Acoustic cavitation occurs due to the interaction between acoustic (ultrasonic) waves and gas nuclei in a medium [11,12], which causes bubbles to form in the medium [13]. The bubbles have different initial sizes and can subsequently expand, compress, or collapse violently [14]. Cavitation also can lead to optical effects (sonoluminescence) [15], chemical effects (sonochemistry) [16], and other thermal effects [17].

Acoustic cavitation can be classified as stable or inertial cavitation [10,17,18,14]. Stable cavitation occurs when the bubbles steadily oscillate. Inertial cavitation occurs when the ultrasound pressure reaches a critical threshold (the inertial cavitation threshold), leading to the violent collapse of a bubble, which usually occurs at a high acoustic pressure. As will be shown, inertial cavitation can have an important role in HIFU therapy.

Bubble collapse during inertial cavitation is accompanied by a huge increase in temperature inside the bubble. Therefore, inertial cavitation

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can strongly enhance the heat deposited during HIFU treatment [1,19], which can help to reduce the treatment time [20,21]. In addition, monitoring broadband noise emissions generated by collapsing bubbles may enable the non-invasive tracking of HIFU treatment [1]. Inertial cavitation can also produce shock waves and microjets, which can mechanically damage or destroy cell membranes or the surface of a blood clot. These effects due to inertial cavitation are applied in histotripsy and thrombolysis [22–25]. In contrast, stable cavitation bubbles can cause shear stress, microstreaming of the medium surrounding a bubble, and mild temperature elevation [18,3].

Understanding the inertial cavitation threshold for dual-frequency excitation was performed when both frequencies of the driving signal as well as the initial radius, tissue viscosity, and tissue elasticity were varied. In Section 3, the inertial cavitation thresholds for various dual-frequency driving signals are determined when one of the frequencies was fixed. In Section 4, a complete parametric study of the inertial cavitation threshold for dual-frequency excitation was performed when both frequencies of the driving signal as well as the initial radius, tissue viscosity, and tissue elasticity were varied.

2. Mathematical model

2.1. Bubble dynamics model

Various mathematical models are used to describe bubble dynamics. The Rayleigh–Plesset model [36,37] has been widely used for its simplicity. However, it was derived under the assumption that the liquid is an incompressible fluid, which leads to an unphysical infinite speed of sound. Another limitation of this model is that it is valid only for low Mach numbers \(R/c \ll 1\). Multiple modifications have been proposed and, nowadays, the Keller–Miksis equation [35] is one of the most frequently used models. It can be applied for a wide range of Mach numbers \(R/c \lesssim 1\). Nevertheless, at high acoustic pressures of the focused, incident ultrasound, the Mach number can exceed this limit. The Gilmore–Akulichev model [33] is applicable for larger Mach numbers up to \(R/c < 2.2\) and was used for the current study.

Most of the earlier studies on cavitation were on Newtonian liquids. For soft tissues, which are viscoelastic fluids, it is important to consider both the viscosity and the elasticity. Usually, the Maxwell, Kelvin–Voigt, or Zener models are used to model the viscoelastic properties [38]. The Zener model (1) is the most general of these three models:

\[
\lambda \dot{r}_r + r_r = 2G r_r + 2\mu \dot{r}_r, 
\]

(1)

since it considers all the main tissue properties: stress \(r_r\) in the \(r\) direction (where \(r\) is the distance from the bubble center), strain \(\gamma\), viscosity \(\mu\), elasticity \(G\), and relaxation time \(\lambda\). The Kelvin–Voigt and Maxwell models are encompassed within the Zener model, since if \(\lambda = 0\) in (1), the Kelvin–Voigt model is obtained and if \(G = 0\), the Maxwell model is obtained.

In the current paper, the Gilmore–Akulichev–Zener model (GAZ) is used to simulate bubble dynamics in a viscoelastic medium. This model is described in detail in the previous paper published by the authors [34]. It can be represented by the following equations:

\[
RR \left(1 - \frac{\dot{R}}{C} \right) + \frac{3}{2} \ddot{r}_r \left(1 - \frac{\dot{R}}{C} \right) = \left(1 + \frac{\dot{R}}{C} \right) \left( - \frac{\tau_{ri} |q|}{\rho} + \frac{3q}{\rho} \right) + \frac{R}{C} \left(1 - \frac{\dot{R}}{C} \right) - \frac{\tau_{ri} |q|}{\rho} + \frac{3q}{\rho}, 
\]

(2)

\[
H = \frac{1}{\rho} \frac{\mu}{n} \frac{n}{R} \left( p_0 + p_1(t) + B \right) \left( \frac{p_i - (2\sigma/R) + \tau_{ri} |q| + B}{p_0 + p_1(t) + B} \right)^{n-1/2} - 1, 
\]

(3)

\[
C = c_w \left( \frac{p_i - (2\sigma/R) + \tau_{ri} |q| + B}{p_0 + p_1(t) + B} \right)^{n-1/2}, 
\]

(4)

\[
p_i = \left( p_0 + 2\sigma \frac{R_i}{R} \right) \left( \frac{R_0}{R} \right)^{3y}, 
\]

(5)

\[
q + \dot{q} + \lambda \frac{\dot{R}}{R} \tau_{ri} |q| = \frac{1}{3} \left( -4G \left( 1 - \frac{R_i}{R} \right) - 4 \mu \frac{\dot{R}}{R} \right), 
\]

(6)

\[
\tau_{ri} |q| + \lambda \dot{r}_r |q| = -4G \left( 1 - \frac{R_i}{R} \right) - 4 \mu \frac{\dot{R}}{R}, 
\]

(7)

where \(R\) is the bubble radius, the time derivative is denoted by the dot \(\dot{R}\).
Fig. 1. Bubble dynamics for single- and dual-frequency excitations. The red bold line represents the bubble oscillations for the single-frequency signal $f = 1$ MHz. There are two combinations of the dual-frequency signal: $f_1 = 1$ MHz and $f_2 = 0.5$ MHz (green dashed line) and $f_1 = 1$ MHz and $f_2 = 2$ MHz (blue dotted line). Simulation parameters: $R_0 = 1 \mu$m and $A = 1$ MPa. The tissue parameters are listed in Table 2.

c_w is the speed of sound, $\rho$ is the environmental density, $p_0$ is the static background pressure, $p_A$ is the time-varying sound field, $p_i$ is the internal pressure of the bubble, $\sigma$ is the surface tension, $R_0$ is the initial bubble radius, $\gamma$ is the polytropic index (we assume adiabatic behavior here), $H$ is the enthalpy at the bubble wall, $C$ is the speed of sound at the bubble wall, and $B$ and $n$ are constants characterizing the surrounding medium.

2.2. Acoustic model

The effects of nonlinear wave propagation in a viscoelastic medium can be described by the following generalized Westervelt equation [7,39]:

$$\nabla^2 p_A - \frac{1}{c_0^2} \frac{\partial^2 p_A}{\partial t^2} + \delta \frac{\partial p_A}{\partial t} + \frac{\beta}{\rho c_0^2} \frac{\partial^2 p_A}{\partial x^2} + \sum_i P_i = 0, \quad (8)$$

with

$$\left( 1 + \tau \frac{\partial}{\partial t} \right) P_i = \frac{2}{c_0^2} \frac{\partial^2 p_A}{\partial x^2}, \quad (9)$$

where $p_A$ is the pressure of the sound field, $\delta$ is the sound diffusion originating from viscosity and heat conduction, $\beta$ is the coefficient of nonlinearity, $\tau$ is the relaxation time, and $c_i$ is a small increment of the speed of sound of the signal for the relaxation process $P_i$.

For simplicity and clarity, in the current study, only the effects of linear wave propagation are considered, as in previous studies on the inertial cavitation threshold. Therefore, the following acoustic equation is used:

$$\nabla^2 p_A - \frac{1}{c_0^2} \frac{\partial^2 p_A}{\partial t^2} + \delta \frac{\partial p_A}{\partial t} = 0. \quad (10)$$

The effects of nonlinear propagation can be included in the model by using the nonlinear Westervelt model, (8) and (9), as was shown in the present authors’ previous papers [39,40].

In the present study, two types of ultrasonic excitation are considered: the classical single-frequency mode in the form $p_A(t) = A \sin(2\pi f t)$ and the dual-frequency mode in the following form:

$$p_A(t) = \frac{A}{\sqrt{2}} \left[ \sin(2\pi f_1 t) + \sin(2\pi f_2 t) \right], \quad (11)$$

where $A$ is the acoustic pressure amplitude, and $f, f_1$, and $f_2$ are the driving acoustic frequencies. An additional coefficient $1/\sqrt{2}$ in Eq. (11) is necessary to ensure the output power is the same as that delivered by the single-frequency signal [27–29].

Fig. 1 shows the difference between the behavior of the bubbles when using single- or dual-frequency signals. For the single-frequency signal, $f = 1$ MHz, which is commonly used for studying focused ultrasound and acoustic cavitation. For the dual-frequency signal, two frequency combinations were used. In both, the first frequency was $f_1 = 1$ MHz (for better visual comparison with the single-frequency signal). The second frequency was either half ($f_2 = 0.5$ MHz) or twice ($f_2 = 2$ MHz).

Fig. 2. Comparison of the impact of single- and dual-frequency acoustic signals on the inertial cavitation threshold. Two different threshold criteria were used: a) $R > 2R_0$ and b) $R \leq -c$. The tissue parameters are listed in Table 2.
In the dual-frequency signal mode (logarithmic scale).

Ranges of the parameter values for simulations when one frequency is fixed

Table 3

| Parameter | Definition | Parameter | Definition |
|-----------|------------|-----------|------------|
| $\varepsilon$ | Speed of sound in the air | $n, B$ | Constants in GAZ model |
| $\varepsilon_0$ | Speed of sound in the tissue | $R_0$ | Initial bubble radius |
| $p_0$ | Static background pressure | $A$ | Acoustic pressure amplitude |
| $\rho$ | Tissue density | $f$ | Acoustic frequency (single-frequency mode) |
| $\sigma$ | Surface tension | $f_1$ | First acoustic frequency (dual-frequency mode) |
| $\gamma$ | Polytropic index | $f_2$ | Second acoustic frequency (dual-frequency mode) |
| $\mu$ | Tissue viscosity | $\dot{\gamma}$ | Tissue relaxation time (dual-frequency mode) |

Constant parameter values of viscoelastic media.

For all simulations | For liver tissue | For varied $\mu$ and $G$
|-------------------|----------------|-----------------|
| $p_0$ | 0.0103 MPa | $\varepsilon_0$ | 1549 m/s | $\varepsilon_0$ | 1540 m/s |
| $\sigma$ | 0.056 kg/s² | $\rho$ | 1100 kg/m³ | $\rho$ | 1060 kg/m³ |
| $B$ | $(\varepsilon_0/\mu)_0 - p_0$ | $\dot{\gamma}$ | $3 \times 10^{-4}$ s | $\dot{\gamma}$ | $10^{-5}$ s |
| $f$ | 1.4 | $\mu$ | 0.009 Pa s |
| $n$ | 7 | $G$ | 0.04 MPa |

Ranges of the parameter values for simulations when one frequency is fixed ($f_1 = 1$ MHz) in the dual-frequency signal mode (linear scale).

Parameter | Min | Max | Steps
|-----------|-----|-----|-----|
| $A$ (MPa) | 0.01 | 10 | 1000 |
| $f_1$ (MHz) | 0.01 | 5 | 500 |
| $R_0$ (μm) | 0.1 | 10 | 100 |
| $G$ (MPa) | [0.01; 0.11] | | |
| $\mu$ (Pa s) | [0.001; 0.01; 0.05; 0.1] |

Ranges of the parameter values for simulations when both frequencies are varied in the dual-frequency signal mode (logarithmic scale).

Parameter | Min | Max | Steps
|-----------|-----|-----|-----|
| $A$ (MPa) | 0.01 | 10 | 100 |
| $f_1$ (MHz) | 0.01 | 10 | 55 |
| $f_2$ (MHz) | 0.01 | 10 | 55 |
| $R_0$ (μm) | 0.1 | 10 | 21 |
| $G$ (MPa) | 0.001 | 1 | 15 |
| $\mu$ (Pa s) | 0.001 | 0.2 | 15 |

MHz) the first frequency $f_1$. From Fig. 1, it is clear that the dual-frequency signal can either decrease or increase the maximum bubble radius in comparison with the single-frequency excitation. For instance, the combination of $f_1 = 1$ MHz with a lower frequency of $f_2 = 0.5$ MHz increases the maximum size of the bubble, whereas the combination with a high frequency of $f_2 = 2$ MHz leads to a decrease in the bubble size. Thus, different combinations of frequencies have different effects on the behavior of the bubble and, therefore, on the threshold of inertial cavitation.

2.3. Inertial cavitation threshold criteria

Inertial cavitation is characterized by rapid expansion of a bubble and the following violent collapse. Inertial cavitation generally occurs at high acoustic pressures. However, using a dual-frequency signal can reduce the required pressure amplitude.

There are different definitions of the criterion for inertial cavitation to occur [27,31,32,41]. One of the most popular and commonly used definitions of the inertial cavitation threshold is when the bubble has expanded to twice the size of the initial bubble: $R \geq 2R_0$ [42]. The inertial cavitation threshold can also be based on the bubble-wall velocity, especially the collapse velocity: $R \leq c$, where $c$ is the speed of sound in air ($c = 340$ m/s) [32]. In the work of Apfel and Holland [43], the threshold was based on the bubble’s internal temperature: $T > 5000$ K. In this study, we used two threshold criteria, one based on the radius and the other on the speed of bubble collapse.

Fig. 2 presents the predicted inertial cavitation thresholds for single- and dual-frequency excitations for the two different inertial cavitation criteria. For the dual-frequency mode with $f_1 = 1$ MHz and $f_2 = f_1/2 = 0.5$ MHz, the cavitation threshold can be lower compared to the single-frequency excitation with $f = 1$ MHz. Moreover, when $f_2 = 2f_1 = 2$ MHz, the dual-frequency excitation does not reduce the threshold but increases it in comparison to the single-frequency excitation.

In Fig. 2, note that the cavitation criterion based on the bubble collapse speed (Fig. 2b), in general, leads to higher thresholds for the pressure amplitude than the radius criterion (Fig. 2a). The following sections show that the two criteria based on the radius and collapse velocity can be considered as lower and upper limits of the inertial cavitation threshold, as noted in Ref. [32].

2.4. Simulation parameters

This section describes in detail the ranges of the main parameters used in the simulations (see Table 1).

2.4.1. Dual-frequency driving signal when one frequency was fixed

The threshold was first analyzed by applying a dual-frequency driving signal when the first frequency $f_1$ was fixed at 1 MHz. The second frequency $f_2$ was varied from 0.01 to 5 MHz (see Section 3). As was mentioned in the previous section, the frequency of 1 MHz was chosen since it is the frequency most often used during focused ultrasound therapy and in acoustic cavitation studies. For the dual-frequency signal mode, the optimal threshold pressures and optimal frequency combinations were found for two cases of the viscoelastic medium: (1) when the medium properties were fixed to the values for liver tissue (see Section 3.1) and (2) when the viscosity and elasticity of the tissue have several different values (see Section 3.2). The tissue and simulation parameters for both these cases are listed in Tables 2 and 3, respectively. All values of the material parameters are taken to correspond to soft tissues [44].

The effect of the phase shift $\theta$ is not considered in the current investigation. Previous studies demonstrated that for single spherical bubbles in water, the effect of the phase shift on the threshold can be neglected [26]. Moreover, in Ref. [27], the authors showed that the inertial cavitation threshold in tissue has the lowest pressure when the two frequencies are in phase ($\theta = 0$ or $2\pi$).

2.4.2. Dual-frequency driving signal when both frequencies are varied

Next, a large parametric study of the inertial cavitation thresholds was carried out. Both frequencies of the dual-frequency signal were changed, and the tissue viscosity and elasticity were simultaneously varied (see Section 4).

To make the analysis more comprehensive, the frequency range was extended, going from 0.01 to 10 MHz. The phase shift between the two frequencies of the excitation was zero. The values of the viscoelastic parameters (Table 4) were based on the physical properties of soft tissues [44] and on the previous studies of bubble dynamics in a viscoelastic medium [34,30].

Simultaneously varying both frequencies greatly increases the number of calculations. Therefore, to cover the largest possible range of parameter values and to ensure the computations were performed in a reasonable time, a logarithmic scale was used (Table 4).
2.5. Numerical method

The explicit fifth-order Runge–Kutta–Dormand–Prince numerical method [45] was used with step size control to solve the GAZ Eqs. (2)–(7). The absolute and relative errors were 10^-9 [45,34]. As was mentioned in Section 2.2, the same output power was applied for both the single- and dual-frequency excitations. For all simulations, the initial conditions have the following values: \( R(0) = R_0 \), \( \dot{R}(0) = 0 \), \( \tau(0) = 0 \), \( q(0) = 0 \) (values of \( R_0 \) are defined in Tables 3,4).

In this work, for each frequency combination, the optimal threshold and the optimal frequencies were determined with the following procedure. The GAZ model (2)–(7) was simulated for five periods using different acoustic pressures. The period was selected for the smallest of the two frequencies for each combination of the dual-frequency signal. Starting from the minimum, the pressure amplitude was increased until the threshold criterion was not fulfilled or the maximum pressure was not reached. After the threshold amplitudes had been obtained for all frequency combinations and for all initial radii, the minimum threshold pressure were determined for each initial radius \( R_0 \). The frequencies that give these minimum thresholds are called in this paper minimum threshold frequencies. However, the minimum threshold frequencies may be different for each \( R_0 \). After this step, we determined the optimal frequency combinations simultaneously for all considered initial radii.

![Fig. 3. Inertial cavitation thresholds for the dual-frequency driving signal when one frequency has a fixed value of 1 MHz (liver tissue). The thresholds for different frequency combinations and the optimal thresholds are presented in a) and b). The minimum threshold second frequencies are presented in c) and d). On the left (a and c), the results are presented for the radius criterion \( R \geq 2R_0 \), whereas on the right (b and d), the results are presented for the bubble collapse speed criterion \( \dot{R} \leq c \). The simulation parameters are listed in Tables 2 and 3.](image)

![Fig. 4. Bubble dynamics for different viscosities \( \mu \) and elasticities \( G \). a) \( \mu = 0.001 \text{ Pa}\cdot\text{s} \) and b) \( \mu = 0.1 \text{ Pa}\cdot\text{s} \). The elasticity \( G \) was varied from 0.001 to 1 MPa. Simulation parameters: \( R_0 = 1 \mu\text{m}, A = 1 \text{ MPa}, \text{ and } f = 1 \text{ MHz} \). The tissue parameters are listed in Table 2.](image)
Fig. 5. Impact of the viscosity $\mu$ and elasticity $G$ on the inertial cavitation threshold (radius criterion $R \geq 2R_0$). a) $G = 0.01$ MPa. $\mu$ was varied from 0.01 to 0.1 Pa⋅s. b) $\mu = 0.01$ Pa⋅s. $G$ was varied from 0.01 to 1 MPa. Simulation parameters: $A = 1$ MPa and $f = 1$ MHz. The tissue parameters are listed in Table 2.

Fig. 6. Predicted inertial cavitation threshold for different viscosities $\mu$ (low) and elasticities $G$. The two threshold criteria were used: the radius criterion $R \geq 2R_0$ (a and c) and the collapse velocity criterion $\dot{R} \leq c$ (b and d). Dashed lines represent the threshold for the single-frequency mode ($f = 1$ MHz). Solid lines represent the threshold for the dual-frequency mode when one frequency is fixed ($f_1 = 1$ MHz). Three elasticity values are considered: $G = 1$ MPa (red line), $G = 0.1$ MPa (blue line), $G = 0.01$ MPa (green line). The simulation parameters are listed in Tables 2 and 3.
To determine the optimal frequencies, the threshold amplitudes for all considered \( R_0 \) were compared with the minimum threshold pressures using the Euclidean norm. The frequency combination that gave threshold pressures with the smallest error from the minimum threshold pressures is defined as the optimal combination in the current study. The threshold pressure for the optimal frequency combination is called the optimal threshold pressure, correspondingly. For most of the investigated parameter combinations, the difference between the optimal and minimum threshold pressures is negligible (or even absent). More details are reported in Appendix A.

The described above numerical method was implemented in a program written in the C++ and CUDA C programming languages. Due to the large number of parameter values investigated (around 1.5 billion for each criterion), to determine the inertial cavitation threshold, the CUDA C language was used to run the computations in parallel on GPUs (four K80 Nvidia Tesla and four Nvidia Titan V graphics cards). The total calculation time was about 5 weeks.

3. Inertial cavitation thresholds for the dual-frequency driving signal when one frequency was fixed

In this section, we investigate the inertial cavitation thresholds and the optimal values of the second frequency \( f_2 \) for the different threshold criteria. For clarity, the section is divided into two parts. In the first part (Section 3.1), the tissue properties are fixed and correspond to liver tissue. Then, different viscoelastic properties are investigated (Section 3.2).

### 3.1. Inertial cavitation threshold for liver tissue

As described in Section 2.3, a dual-frequency excitation can reduce or increase the threshold pressure compared to a single-frequency signal depending on the second frequency \( f_2 \). Fig. 3 shows the effect of the second frequency \( f_2 \) on the threshold pressure for the two inertial cavitation criteria. \( f_2 \) was varied in the range from 0.01 to 5 MHz (Table 3) whereas the first frequency was fixed at \( f_1 = 1 \) MHz. The results for these combinations were analyzed and the frequencies that give the optimal inertial cavitation threshold simultaneously for all the initial values considered for the bubble radius were found (Fig. 3). Note that the minimum threshold amplitude for each initial radius (blue dashed line in Fig. 3a–b) has a different minimum threshold frequency \( f_2 \) for each \( R_0 \) (Fig. 3c–d). However, during HIFU therapy, bubbles of various sizes can appear in the tissues. Therefore, only one optimal second frequency \( f_2 \) was found simultaneously for all the initial radius values. This optimal second frequency \( f_2 = 0.39 \) MHz for the bubble radius criterion (Fig. 3a and \( f_2 = 0.02 \) MHz for the bubble collapse speed criterion (Fig. 3b). These frequencies give the optimal threshold pressure (magenta line in Fig. 3a–b) simultaneously for all the initial radii \( R_0 \). The optimal threshold pressure is close to the minimum threshold pressure. For a more detailed description of how to calculate the optimal threshold and optimal frequency, see Section 2.5.

First, the results in Fig. 3 demonstrate that the radius criterion, in general, gives smaller thresholds than the criterion using the speed of bubble collapse. Second, for the optimal \( f_2 \), it is possible to achieve a very low threshold pressure that practically does not depend on the...
Fig. 8. Optimal threshold pressure (MPa) when the radius criterion $R \geq 2R_0$ was used for different values of the viscoelastic parameters and for different initial bubble radii: a) $R_0 = 0.1 \, \mu\text{m}$, b) $R_0 = 0.5 \, \mu\text{m}$, c) $R_0 = 1 \, \mu\text{m}$, d) $R_0 = 2.5 \, \mu\text{m}$, e) $R_0 = 5 \, \mu\text{m}$, and f) $R_0 = 10 \, \mu\text{m}$. The simulation parameters are listed in Tables 2 and 4.

Fig. 9. Optimal frequency combinations (MHz) when the radius criterion $R \geq 2R_0$ was used for different values of the viscoelastic parameters: a) first frequencies and b) second frequencies.
initial bubble radius \( R_0 \). For a single-frequency excitation, the threshold depends significantly on the initial bubble radius. In Fig. 3c and 4d, the minimum threshold second frequencies \( f_2 \) are presented as a function of the initial bubble radius for the two inertial cavitation criteria. For the bubble collapse speed criterion, the minimum threshold frequency \( f_2 \) is almost the same for all initial bubble radii (around 0.02 MHz, Fig. 3d); whereas for the radius criterion, there is a wide range of minimum threshold frequencies \( f_2 \) for each initial radius (from 0.01 to 1 MHz, Fig. 3e).

In the following sections, we are going to investigate only optimal threshold frequencies, since there are no preexisting bubbles with the known radius in the tissue (we don't consider contrast agents or stabilized bubbles in the current study). In addition, using the predicted optimal frequencies, it is possible to reach the minimum threshold pressures (or relatively close to) simultaneously for almost all values of \( R_0 \) (see Appendix A).

3.2. Inertial cavitation threshold for different viscoelastic media

Figs. 4 and 5 illustrate the influence of different values of the viscosity \( \mu \) and elasticity \( G \) on the bubble dynamics and, accordingly, on the inertial cavitation threshold. Both viscosity and elasticity can damp bubble oscillations (Fig. 4), which lead to an increase of the threshold pressure (Fig. 5).

Figs. 6 and 7 show the predicted optimal threshold pressures and optimal second frequencies for different viscoelastic media. The simulation parameters are those in Tables 2 and 3. Both threshold criteria were used (radius \( R \geq 2R_0 \) and bubble collapse speed \( \dot{R} \leq c \)).

Fig. 6 shows the inertial cavitation thresholds for low viscosities (\( \mu = 0.001 \) and 0.01 Pa-s). The threshold amplitude, as in previous results, is larger for the criterion using the bubble collapse speed (Fig. 6b and d). As in Fig. 5, the threshold increases with an increase of the viscosity or elasticity, regardless of the choice of the criterion for the inertial cavitation threshold. The largest threshold pressures are observed for low values of the initial radius (around \( R_0 = 0.1 \) \( \mu \)). However, note that for a very high elasticity (\( G = 1 \) MPa), the threshold pressure is much larger in comparison to thresholds for a lower elasticity (\( G = 0.1 \) or 0.01 MPa). In addition, thresholds for the single-frequency driving signal \( f = 1 \) MHz are much larger than for the optimal dual-frequency excitation (especially, for a large initial bubble).

The optimal second frequency \( f_2 \) is smaller than the first fixed frequency \( f_1 = 1 \) MHz. However, for the bubble collapse speed criterion and for high elasticity \( G = 1 \) MPa, the optimal \( f_2 \) is the same as the fixed \( f_1 \) and equal to 1 MHz (Fig. 6b and d).

Fig. 7 shows the inertial cavitation thresholds for high viscosities (\( \mu = 0.05 \) or 0.1 Pa-s). The optimal threshold pressures are larger for high viscosities than for low viscosities. Moreover, the difference between the results for single- and dual-frequency driving signals are larger with increasing viscosity or elasticity. Like the previous results, the threshold pressures in Fig. 7 also demonstrate that the threshold amplitudes for the radius criterion (Fig. 7a and c) are much smaller than for the bubble collapse speed criterion (Fig. 7b and d).

All the optimal second frequencies \( f_2 \) for high viscosities (Fig. 7) are less than \( f_1 \) for all the elasticities considered. Note that the optimal \( f_2 \) values in Fig. 7 are also different for different threshold criteria. However, these \( f_2 \) values are very close to each other. In average, for high viscosities (\( \mu = 0.05 \) or 0.1 Pa-s), the optimal \( f_2 \) as around 0.01–0.02 MHz.

4. Inertial cavitation thresholds for the dual-frequency driving signal when both frequencies were varied

In the previous section, the inertial cavitation threshold was investigated when one frequency was varied and the other frequency was fixed. In this section, the full parametric study is described. We demonstrate how the inertial cavitation threshold depends on the viscoelastic parameters when both frequencies are varied during the dual-frequency acoustic excitation.

When analyzing the optimal threshold pressures for the radius criterion (Fig. 8), the largest thresholds are obtained for the smallest initial bubbles (\( R_0 = 0.1 \) \( \mu \)). Overall, the thresholds in Fig. 8 are smaller than the thresholds for the dual-frequency signal with one fixed frequency (Figs. 6 and 7). Thus, by varying both frequencies in the dual-frequency driving signal, it is possible to optimize the thresholds even further.

Since both the viscosity and the elasticity damp the bubble oscillations, we expected that an increase of either the viscosity or the elasticity would lead to an increase in the threshold pressure. This behavior was observed in the previous section when only one frequency in the dual-frequency excitation was varied (Figs. 5–7). When both frequencies are varied, an increase of the elasticity \( G \) causes an increase of the threshold pressure from 0.1 to 1 MPa (Fig. 8). The dependence of the threshold pressure on the viscosity is more complex in this case. For elasticities \( G \leq 10^5 \) Pa, an increase of the viscosity causes an increase of the threshold pressure. For high elasticities \( G > 10^5 \) Pa, the threshold pressure is almost independent of the viscosity. Therefore, vertical stripes can be seen in the contour graphs.
The optimal frequency combinations as a function of the viscosity and elasticity (for the threshold pressures in Fig. 8) are presented in Fig. 9. The optimal frequencies can be divided into two regions depending on the viscosity. In the first region, for viscosities $\mu \leq 10^{-2}$ Pa s, the optimal frequencies $f_1$ and $f_2$ are very different from each other. The first optimal frequency $f_1$ (Fig. 9a) varies from 0.01 to 1 MHz, whereas the second optimal frequency $f_2$ (Fig. 9b) varies from 0.1 to 1 MHz in this region. In the second region, for $\mu > 10^{-2}$ Pa s, both frequencies are low (around 0.01 MHz) and have similar values.

This behavior of the optimal frequencies can be explained by the resonance frequency. By definition, the linear resonance frequency of bubble oscillations is the frequency at which the bubble first-harmonic response (linear amplitude-frequency response) has a local maximum [46]. The resonance frequency in the tissue is given by [46,47]:

$$f_{res} = \frac{1}{2\pi R_0 \sqrt{\rho}} \sqrt{3\gamma(p_v - p_0) + (3\gamma - 1)\frac{2\sigma}{R_0} - \frac{8\mu^2}{\rho R_0^2} + 4G},$$

(12)

where $p_v = 0.06$ MPa is the vapor pressure in the tissue. The resonance frequency is inversely proportional to the bubble radius. It can be also seen that an increase of the elasticity or a decrease of the viscosity leads to an increase of the resonance frequency, which can be observed in Fig. 9 and in the previous sections (and also further in Fig. 10). The highest resonance frequencies are for small values of $\mu$ and large values of $G$. However, it is important to note that the above equation is applicable only to single-frequency excitations.

The simulated results for the optimal threshold pressure for the bubble collapse speed criterion (Fig. 11) are consistent with those for the radius criterion (Fig. 8). The highest thresholds are achieved for the smallest initial bubble radius as well. The dependence of the threshold amplitude on the elasticity and viscosity is also the same for both criteria. An increase in the elasticity leads to an increase of the threshold, whereas an increase in the viscosity affects the threshold only for some elasticity values ($G < 10^5$ Pa). The main difference between the two threshold criteria is that the threshold pressures are larger for the bubble collapse speed criterion (Fig. 11) than for the radius criterion (Fig. 8).

The optimal frequency combinations for the bubble collapse speed criterion are shown in Fig. 10. Here both predicted optimal frequencies vary over the same range, from 0.01 to 1 MHz. Like the results for the
radius criterion (Fig. 9), these optimal frequencies can be divided in two groups: (1) the optimal frequencies that are different from each other (for $\mu \leq 10^{-2}$ Pa·s) and (2) both frequencies are similar and low (for $\mu > 10^{-2}$ Pa·s). However, in the first group, $f_1$ and $f_2$ are not as different from each other as they are for the radius criterion (Fig. 9).

In the current section, we demonstrated the dependency of the optimal frequency combinations on the viscosity and elasticity values. The optimal frequencies were defined over a whole wide range of the bubble size (see Section 2.5). The predicted optimal frequency combinations provide in most cases the minimum threshold pressure and have a minor (or even don’t have) dependency on the initial bubble size (see Appendix A).

5. Discussion

In this research, a large parametric investigation of the inertial cavitation threshold was performed. The impact of the dual-frequency signal, frequency combinations, initial bubble sizes, and viscoelastic tissue parameters was studied. The GAZ model was used to simulate bubble oscillations and collapses. The threshold pressure was determined by two criteria, based on either the radius ($R \geq 2R_0$) or the speed of bubble collapse ($R \leq 340$ m/s). In this work, we found frequencies and thresholds that are optimal for the entire range of initial bubble radii considered.

The results obtained for the optimal inertial cavitation threshold under a dual-frequency driving signal demonstrate that by using the optimal combination of frequencies it is possible to significantly reduce the threshold pressure relative to a single-frequency signal at 1 MHz. Moreover, when both frequencies in the dual-frequency signal were varied simultaneously, optimal combinations of frequencies were found, which allowed us to further reduce the threshold pressure. For the optimal dual-frequency excitation, the thresholds were almost independent of the initial size of the bubble, whereas for the single-frequency signal, the threshold depended significantly on the initial bubble radius. This result is in agreement with a previous study [48] on the stabilization of chaotic bubble oscillations with a dual-frequency driving signal.

The viscosity and elasticity of tissue have a complex effect on the optimal threshold under dual-frequency ultrasonic excitations when both frequencies are varied. The impact of the elasticity is as follows. With an increase of the elasticity, the threshold also increased. However, the viscosity does not have such a strong effect on the threshold. For low viscosities, an increase of the viscosity results in a small increase of the

![Fig. A.1. Difference between the optimal and minimum threshold pressures (MPa) for different values of the viscoelastic parameters and for different initial bubble radii when the radius cavitation criterion $R \geq 2R_0$ was used: a) $R_0 = 0.1$ μm, b) $R_0 = 0.5$ μm, c) $R_0 = 1$ μm, d) $R_0 = 2.5$ μm, e) $R_0 = 5$ μm, and f) $R_0 = 10$ μm. The white color in the plots represents zero difference.](image-url)
threshold amplitude. For high elasticities, an increase of the viscosity does not affect the threshold amplitude. Therefore, it can be concluded that for optimal frequencies in dual-frequency excitation, the influence of elasticity prevails over that of the viscosity.

For the dual-frequency excitation with low viscosities, the analysis found that the predicted optimal frequencies were different from each other. However, for high viscosities, the predicted optimal frequencies had similar, low values. Thus, it can be concluded that to achieve lower threshold pressures for high viscosities, it may be better to use a single-frequency excitation.

In this study, two different criteria for inertial cavitation were used. The obtained optimal thresholds and corresponding optimal frequencies demonstrate that the results depend on the inertial cavitation criteria. The choice of threshold criterion can impact the behavior of the threshold pressures, since each criterion relies on different aspects of the bubble dynamics. The criterion based on the bubble collapse speed resulted in higher thresholds than the criterion based on the bubble radius. In addition, different values of the optimal frequencies can be obtained for different thresholds.

The present study showed how the optimal threshold pressures depend on viscoelastic parameters. In addition, the predicted optimal frequency combinations can provide the minimum threshold pressure simultaneously almost for all bubble sizes (considered in the current study).

Note that in the current study, some assumptions and simplifications were made. In the present work, the results were obtained only for one isolated bubble. Bubble–bubble interactions can affect the bubble dynamics [49] and, correspondingly, the inertial cavitation threshold. Both radial and translational motions of bubbles are well known to be affected by the viscoelasticity of the surrounding medium [49]. However, the inclusion of bubble interactions may greatly increase the complexity of the problem and needs further investigation.

We used the linear Westervelt equation in the acoustic model. At high intensities, the effects of nonlinear wave propagation become important and lead to a distortion of the waveform. Higher harmonics are generated due to the nonlinear distortion [39], and a shock wave can form [50,51]. These nonlinear harmonics may affect the values of the predicted threshold pressures. This study included a comprehensive parametric investigation of the inertial cavitation threshold in which both frequencies were varied, and it found the optimal frequencies. The optimal threshold pressures in different media were lower than 1.5 MPa.

When one frequency in dual-frequency excitation was fixed, the
predicted threshold pressures were slightly higher (less than 2 MPa for the radius criterion and less than 3 MPa for the bubble collapse speed criterion). For these acoustic pressures, nonlinear propagation effects are not important and were neglected in the current study [39]. Thus, nonlinear propagation effects may influence the results reported in the current study only for single-frequency acoustic signals.

6. Conclusions

The inertial cavitation threshold for a dual-frequency acoustic driving signal in various viscoelastic media was studied numerically. The Gilmore-Akulichev-Zener model was employed to describe the bubble dynamics in soft tissue. A full parametric study of the inertial cavitation threshold and its dependency on the acoustic signal mode, signal frequency, initial radius, and viscoelastic tissue properties was performed. In this study, the optimal inertial cavitation threshold and the corresponding optimal frequencies were found simultaneously for different initial bubble radii. Overall, for both threshold criteria, approximately 3 billion simulation runs to find the inertial cavitation threshold were completed. To accelerate the calculations and obtain the results within a reasonable time, the high-speed processing power of GPUs was exploited with the CUDA C language.

The inertial cavitation thresholds obtained have distinct values for the two criteria investigated. The bubble collapse speed criterion gives higher thresholds than the radius criterion. The optimal frequencies for the dual-frequency excitation were calculated. Using the optimal combination of frequencies, it was possible to reduce significantly the threshold pressure relative to a single-frequency signal. With the optimal dual-frequency excitation, the thresholds were almost independent of the initial size of the bubble. In contrast, for the single-frequency signal, the thresholds depend significantly on the initial bubble radius. Moreover, when using the optimal frequencies in the dual-frequency signal, the tissue elasticity had a much stronger effect on the threshold than the tissue viscosity. Further experiments are required to verify the results obtained. The results presented in the current paper may be useful for the further development of the dual-frequency excitation approach. The effects of bubble–bubble interactions will be investigated further in future work.

CRediT authorship contribution statement

Tatiana Filonets: Conceptualization, Methodology, Writing – original draft, Software, Data curation, Visualization. Maxim Solovchuk: Conceptualization, Methodology, Writing – original draft, Validation, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Comparison of the optimal and minimum thresholds

Figs. A.1 and A.2 demonstrate the difference between the optimal and minimum threshold pressures for different initial bubble sizes. In Figs. A.1 and A.2 the differences between the optimal and minimum threshold pressures for the various initial bubble sizes are shown for two different cavitation criteria. White area represents the area where there is no difference between the optimal and minimum threshold pressures. This area much prevails over the colored area. Besides, in most of the cases from the colored area, the difference between the optimal and minimum threshold pressures is smaller than 0.06–0.1 MPa. Only in several cases (among 1.5 billion parameter combinations) for extremely high elasticity values around 1 MPa, the difference can reach 0.16–0.25 MPa. Please also note that without optimization the threshold pressure can reach up to 8–10 MPa.

Thus, it can be concluded that the predicted optimal threshold pressures are equal or very close to the minimum threshold pressures in the whole investigated range of the bubble radii. Therefore, the corresponding optimal frequency combinations (Figs. 9 and 11) have also a minor dependency on the initial bubble radius.

References

[1] G. Ter Haar, C. Coussios, High intensity focused ultrasound: Physical principles and devices, Int. J. Hyperth. 23 (2) (2007) 89–104, https://doi.org/10.1080/02656700601186138.
[2] J.E. Kennedy, G.R. ter Haar, D. Cranston, High intensity focused ultrasound: surgery of the future? Brit. J. Radiol. 76 (909) (2003) 590–599, https://doi.org/10.1259/bjr/17150274.
[3] I.S. Elhelf, H. Albahar, U. Shah, A. Otso, E. Cressman, M. Almekkawy, High intensity focused ultrasound: The fundamentals, clinical applications and research trends, Diagnost. Interventional Imaging 99 (6) (2018) 349–359, https://doi.org/10.1007/j.dlidi2018.03.001.
[4] Z. Iradifar, Z. Iradifar, D. Chapman, P. Babyn, An introduction to high intensity focused ultrasound: Systematic review on principles, devices, and clinical applications, Journal of Clinical Medicine 9 (2), doi:10.3390/jcm9020460.
[5] M.A. Solovchuk, T.W. Sheu, M. Thiert, W.-L. Lin, On a computational study for investigating acoustic streaming and heating during focused ultrasound ablation of liver tumor, Appl. Therm. Eng. 56 (1) (2015) 62–76, https://doi.org/10.1016/j.applthermaleng.2013.02.041.
[6] L.A. Shehata, Treatment with high intensity focused ultrasound: Secrets revealed, Eur. J. Radiol. 61 (3) (2015) 534–541, https://doi.org/10.1016/j.ejrad.2011.01.047.
[7] M.A. Solovchuk, M. Thiert, T.W. Sheu, Computational study of acoustic streaming and heating during acoustic hemostasis, Appl. Therm. Eng. 124 (2017) 1112–1122, https://doi.org/10.1016/j.applthermaleng.2017.06.040.
[8] A. Gassellhuber, M.R. Dreher, A. Partanen, P.S. Yarmolenko, D. Woods, B.J. Wood, D. Haemmerich, Targeted drug delivery by high intensity focused ultrasound mediated hyperthermia combined with temperature-sensitive liposomes: Computational modelling and preliminary in vivo validation, Int. J. Hyperth. 28 (4) (2012) 337–348, https://doi.org/10.3109/02656736.2012.677930.
[9] V. Frenkel, Ultrasound mediated delivery of drugs and genes to solid tumors, Adv. Drug Delivery Rev. 60 (10) (2008) 1193–1208, ultrasound in Drug and Gene Delivery. doi:10.1016/j.addr.2008.03.007.
[10] R. Holt, R. Boy, Bubble dynamics in therapeutic ultrasound, Research Signpost Ch. 6 (2005) 108–229.
[11] F. cry, N. Sanghi, R. Foster, R. Bührle, C. Hennige, Ultrasound and microbubbles: their generation, detection and potential utilization in tissue and organ therapy–experimental, Ultrasound Med. Biol. 21 (9) (1995) 1227–1237, https://doi.org/10.1016/0301-5629(98)04256-7.
[12] M. Ashokkumar, The characterization of acoustic cavitation bubbles – an overview, Ultrasound. Sonochem. 18(4) (2011) 864–872, european Society of Sonochemistry (ESS12). doi:10.1016/j.ultraschon.2010.11.016.
[13] S. Yasui, Acoustic Caviation and Bubble Dynamics, Springer International Publishing (2018), https://doi.org/10.1007/978-3-319-68257-2.
[14] M. A. A. Ashokkumar, J. Lee, V. Iida, K. Yanai, T. Konzka, T. Tuziuti, A. Towata, The detection and control of stable and transient acoustic cavitation bubbles, Phys. Chem. Chem. Phys. 11 (2009) 10118–10121, https://doi.org/10.1039/b915731h.
[15] P.-K. Choi, Sonoluminescence and acoustic cavitation, Jpn. J. Appl. Phys. 56 (7S1) (2017) 07JA01, https://doi.org/10.7567/jjap.56.07ja01.
[16] R.J. Wood, J. Lee, M.J. Bussemaeber, A parametric review of sonochemistry: Control and augmentation of sonochemical activity in aqueous solutions, Ultrason. Sonochem. 38 (2017) 351–370, https://doi.org/10.1016/j.ultsonch.2017.03.030.

[17] C.C. Coussios, R.A. Roy, Applications of acoustics and cavitation to noninvasive therapy and drug delivery, Annu. Rev. Fluid Mech. 40 (1) (2008) 395–420, https://doi.org/10.1146/annurev.fluid.40.113006.102116.

[18] J. Laberde, C. Boyer, J. Callagione, A. Gerard, Acoustic bubble cavitation at low frequencies, Ultrasonics 36 (1996) 589–594, https://doi.org/10.1016/S0041-624X(97)00010-5.

[19] E. Zilonova, M. Solovchuk, T. Sheu, Simulation of cavitation enhanced temperature elevation in a soft tissue during high-intensity focused ultrasound thermal therapy, Ultrason. Sonochem. 53 (2019) 11–24, https://doi.org/10.1016/j.ultsonch.2018.12.006.

[20] P.Z. He, R.M. Xia, S.M. Duan, W.D. Shou, D.C. Qian, The affection on the tissue lesions of difference frequency in dual-frequency high-intensity focused ultrasound (hiuf), Ultrason. Sonochem. 13 (4) (2006) 339–344, https://doi.org/10.1016/j.ultsonch.2005.05.008.

[21] H.L. Liu, W.S. Chen, J.-S. Chen, T.-C. Shih, Y.-Y. Chen, W.-L. Lin, Cavitation-enhanced ultrasound thermal therapy by combined low- and high-frequency ultrasound exposure, Ultrason. Sonochem. 32 (5) (2006) 759–767, https://doi.org/10.1016/j.ultsonch.2006.01.010.

[22] T.D. Khokhlova, M.S. Canney, V.A. Khokhlova, O.A. Sapozhnikov, L.A. Crum, M. R. Bailey, Controlled tissue emulsification produced by high intensity focused ultrasound shock waves and millisecond boiling, J. Acoust. Soc. Am. 130 (5) (2011) 3496–3510, https://doi.org/10.1121/1.3626152.

[23] B. Petit, Y. Bohren, E. Gaud, P. Busat, M. Arditii, F. Yan, F. Tranquart, E. Allemann, Sonothrombolysis: The contribution of stable and inertial cavitation to clot lysis, Ultrason. Sonochem. 41 (5) (2015) 1402–1410, https://doi.org/10.1016/j.ultsonch.2014.12.007.

[24] D. Suo, S. Guo, W. Lin, X. Jiang, Y. Jing, Thrombolysis using multi-frequency high intensity focused ultrasound at MHz range: an in vitro study, Phys. Med. Biol. 60 (18) (2015) 7403–7418, https://doi.org/10.1088/0031-9155/60/18/7403.

[25] D. Suo, Z. Jin, X. Jiang, P.A. Dayton, Y. Jing, Microbubble mediated dual-frequency high intensity focused ultrasound thrombolysis: An in vitro study, Appl. Phys. Lett. 110 (2) (2017), 023703, https://doi.org/10.1063/1.4973857.

[26] F. Hegedüs, K. Klápcsík, W. Lauterborn, U. Parlitz, R. Mettin, Gpu accelerated study of a dual-frequency driven single bubble in a 6-dimensional parameter space: The active cavitation threshold, Ultrason. Sonochem. 67 (2020), 105007, https://doi.org/10.1016/j.ultsonch.2020.105007.

[27] M. Wang, Y. Zhou, Numerical investigation of the inertial cavitation threshold by solving the westervelt equation for the investigation of acoustic streaming and nonlinear propagation effects, J. Acoust. Soc. Am. 134 (5) (2013) 3931–3942, https://doi.org/10.1121/1.4821201.

[28] M. Solovchuk, T.W.H. Sheu, M. Thiriet, Multiphysics modeling of liver tumor ablation by high intensity focused ultrasound, Commun. Comput. Phys. 18 (4) (2015) 1050–1071, https://doi.org/10.4208/cicp.171214.200715s.

[29] C.C. Coussios, R.A. Roy, Applications of acoustics and cavitation to noninvasive therapy and drug delivery, Annu. Rev. Fluid Mech. 40 (1) (2008) 327–358, https://doi.org/10.1146/annurev.fluid.40.113006.102116.

[30] D.B. Khismatullin, Resonance frequency of microbubbles: Effect of viscosity, Phys. Rev. E 99 (2019), 023109, https://doi.org/10.1103/PhysRevE.99.023109.

[31] R.E. Apfel, C.K. Holland, Gauging the likelihood of cavitation from short-pulse, low-duty cycle diagnostic ultrasound, Ultrason. Sonochem. 17 (2) (1991) 179–185, https://doi.org/10.1016/0967-0504(91)90125-G.

[32] D.B. Khismatullin, Resonance frequency of microbubbles: Effect of viscosity, J. Acoust. Soc. Am. 116 (3) (2004) 1463–1473, https://doi.org/10.1121/1.1778835.

[33] R. Gaudron, M.T. Warner, E. Johnsen, Bubble dynamics in a viscoelastic medium with nonlinear elasticity, J. Fluid Mech. 766 (2015) 54–75, https://doi.org/10.1017/jfm.2015.7.

[34] S. Behnia, A.J. Sojahrood, W. Soltanpoor, O. Jahanbaksh, Suppressing chaotic oscillations of a spherical cavitation bubble through applying a periodic perturbation, Ultrason. Sonochem. 16 (4) (2009) 502–511, https://doi.org/10.1016/j.ultsonch.2008.12.016.

[35] M. Solovchuk, M. Solovchuk, T.W.H. Sheu, Dynamics of bubble-bubble interactions experiencing viscoelastic drag, Phys. Rev. E 99 (2019), 023109, https://doi.org/10.1103/PhysRevE.99.023109.

[36] M.A. Diaz, M.A. Solovchuk, T.W. Sheu, A conservative numerical scheme for modeling nonlinear acoustic propagation in thermoviscous homogeneous media, J. Comput. Phys. 363 (2018) 200–230, https://doi.org/10.1016/j.jcp.2018.02.005.

[37] M.A. Diaz, M.A. Solovchuk, T.W. Sheu, High-performance multi-gpu solver for describing nonlinear acoustic waves in homogenous thermoviscous media, Comput. Fluids 173 (2018) 195–205, https://doi.org/10.1016/j.compfluid.2018.03.008.