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# Primary Radiation Force to Ultrasound Contrast Agents in Propagating and Standing Acoustic Field

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**Abstract**

Primary radiation force on ultrasound contrast agents (UCA) in a propagating and standing acoustic field was explored. A specific ultrasound contrast agent Albunex® and Optison® were chosen for simulation. The model was developed based on a shelled bubble model proposed by Church. The numerical simulation suggests that bubble translational motion is more significant in therapeutic ultrasound due to higher intensity and long pulse duration. Even a single cycle of a propagating wave of 4 MPa at 1 MHz can cause a bubble translational motion of greater than 1 μm which is approximately one tenth of capillary. Hence, UCA characteristics can be significantly changed in therapeutic ultrasound without rapid bubble collapses.

***Keywords:*** *Acoustic Radiation force, Ultrasound Imaging, Ultrasound Therapy, Ultrasound Contrast Agent, Density of Contrast Agent Characteristics*

## I. Introduction

Ultrasound contrast agent (UCA) has been an active research topic in both diagnostic and therapeutic ultrasound. Linear and nonlinear effects of UCA to an acoustic field can increase the contrast in the ultrasound image, so that it has been adapted for cardiac and vascular diagnosis [1]. Additionally, radiation force to UCA from ultrasound imaging sound field and its effects showed a plausibility of a targeted ultrasound imaging [2, 3]. In therapeutic ultrasound, low amplitude oscillation of UCA in an acoustic field increases thermal deposition [4, 5]. UCA can also nucleate cavitation, so that a combination of mechanical and thermal damage can be induced at a highly localized area even at a low power level of ultrasound [6-8]. In addition, UCA can provide means to correct aberration by creating a pseudo point sound source with nonlinear beam mixing for therapeutic ultrasound [9].

In order to understand the dynamics of UCA, UCA models have been developed based on microbubble models during the 1990s. de Jong, *et al* have proposed the shell elasticity parameter and shell friction to explain the shell layer effect of a specific UCA, Albunex® [10]. Church has more rigorously derived a general shelled bubble model from the conservation of momentum equation [11]. Individual UCA microbubble's activities can be more successfully explained with these models in a low amplitude acoustic field. On the other hand, the effect of a small population of microbubbles in liquid medium has been researched in terms of the effective wave number [12-14]. From the effective wave number, attenuation coefficient and phase velocity can be calculated as a function of void fraction and frequency.

Although the developed models provide deep insight into bubble dynamics as a single bubble and a population of bubbles respectively, there is still lack of information regarding bubble translational motion due to an applied radiation force. Radiation force is

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generally ignored in acoustics since it is relatively small compared to other components such as reflection and transmission. However, radiation force can changes the local concentration of UCA as P.A. Dayton, *et al* have shown [2]. In addition, the radiation force effect on UCA has a potential of targeted ultrasound imaging.

In order to induce radiation force, a proper bubble model needs to be selected. Among numerous bubble models to express albumin based shelled bubble, Church's model was selected, since other models underestimate the bubble shell effect which shows critical roles in damping and shell stability under sonication. Hence, radiation force model in propagating and standing wave is developed based on Church's UCA model. The numerical evaluation is conducted for a specific UCAs, Albunex® and Optison®, whose basic parameters are publicly available. The average translation distance of a bubble at each cycle of the wave is also calculated with consideration of drag force. Even though this method was developed from a specific UCA, this method could be applied to the other UCAs as long as the basic parameters are known.

## II. Methods

### 2.1. Linearization of a shelled bubble model and the steady state response

Church's model provides a nonlinear bubble oscillation [11]. In order to calculate the radiation force, the model was simplified further and linearized in a radius-force frame [15]. As shown in equation (1), the linearized model is the formation of the linear forced damped oscillator [16].

$$m_{rad} R_e \ddot{x} + c R_e \dot{x} + k_s R_e x = -4\pi R_e^2 P_A \cos\omega t \tag{1}$$

$$\text{where } m_{rad} = 4\pi R_e^3 \rho$$

$$k_s = 4\pi R_e \left( 3\kappa P_0 + 12 G_s \frac{d_{s_e}}{R_e} \right)$$

$$c = 4\pi R_e \left( 4\eta_L + 12\eta_S \frac{d_{s_e}}{R_e} \right)$$

$x$, $R_e$, $P_A$, $P_0$, $\rho$, $\kappa$, $G_s$, $d_{s_e}$, $\eta_L$, $\eta_S$, and $\omega$ are the radial displacement ratio of the bubble radius, the equilibrium bubble radius, the applied pressure amplitude, the ambient pressure, the liquid density around bubble, the polytrophic exponent of a gas, the shear modulus of bubble shell, the shell equilibrium thickness, the shear viscosity of liquid, the shear viscosity of shell, and the operating frequency, respectively. Since this model is strictly based on Church's model, the actual displacement of the bubble wall is not specific as x but as $R_e x$. Accordingly, velocity and acceleration are $R_e\dot{x}$ and $R_e\ddot{x}$ respectively.

The linearized equation was modified for the additional damping effects such as acoustic and thermal damping based on the Prosperitti' s damping model as shown in equation (2) [17].

$$c_{tot} = c + c_{ac} + c_{th} \tag{2}$$

$$\text{where } c_{ac} = \delta_{ac}\sqrt{k_s m_{rad}}$$

$$c_{th} = \delta_{th}\sqrt{k_s m_{rad}}$$

$\delta_{ac}$ and $\delta_{th}$ are the acoustic damping and thermal damping from Prosperitti's damping model. Hence, in equation (1) was updated with $c_{tot}$ accordingly.

Due to the strong damping effect, the transient response to the applied sound field is nominal, so that the steady state response of the bubble was induced as shown in equation (3), from the updated linear equation (1) [16].

$$R_e x = C\cos(\omega t - \xi) \tag{3}$$

$$\text{where } C = \frac{4\pi R_e^2 P_A}{\sqrt{m_{rad}^2(\omega_0^2 - \omega^2)^2 + \omega^2 c_{tot}^2}}$$

$$\omega_0^2 = \frac{k_s}{m_{rad}}$$

$$\tan(\xi) = \frac{\omega c_{tot}}{m_{rad}(\omega_0^2 - \omega^2)}$$

C indicates the amplitude of the bubble wall displacement and $\xi$ represents phase lag of the bubble response to the incident acoustic field.

## 2.2. Radiation Force in Propagating Wave

Since the time averaged radiation force over a cycle is the net force over the period, the time averaged force was induced based on the linearized bubble model as shown in equation (4).

$$\bar{F}_{trav} = -\langle V \nabla P \rangle \tag{4}$$

$$= \frac{3}{2} V_e k P_A C \sin(\xi)$$

$$= \frac{6\pi R_e V_e k P_A^2 \omega c_{tot}}{\left(m_{rad}^2(\omega_0^2 - \omega^2)^2 + \omega^2 c_{tot}^2\right)}$$

where V is the instantaneous volume of the bubble, P is the instantaneous pressure, $V_e$ is the equilibrium volume of bubble, and k is the wave number of the incident wave, respectively. If we rearrange equation (4) with relationships of $\delta_{tot} = \frac{c_{tot}}{m_{rad}\omega_0}$ and $\delta_{tot} = \frac{2\beta_{tot}}{\omega_0}$, then we have

$$\bar{F}_{trav} = \frac{2\pi P_A^2 R_e}{\rho c_s \omega} \frac{2\beta_{tot}/_{\omega}}{[(\omega_0/\omega)^2-1]^2+\left(2\beta_{tot}/_{\omega}\right)^2} \tag{5}$$

where $\beta_{tot}$ is dimensionless damping coefficient

Equation (5) is identical with the time averaged radiation force calculated from the compressible liquid model in the reference [2]. The final form of time averaged radiation force in propagating wave is identical due to the linearization of the model. Although the radiation force seems identical in formula, the actual value of the calculated radiation force is different. It is due to the calculation of the damping strongly depends on the model.

Under the assumption of an inviscid and irrotational liquid, drag force is given as shown in equation (6) [15]. The liquid shear viscosity is on the order of 1/1000 compared to the shell viscosity, so that the inviscid medium assumption can be justified with the given bubble model including the liquid medium shear viscosity. Hence, the average translation distance of the bubble whose initial velocity is zero during a cycle of propagating wave can be expressed as equation (6).

$$F_{drag} = \frac{2\pi}{3} \rho R_e^{\,3} a_t \tag{6}$$

$$= \frac{m_{rad}}{6} a_t$$

$$\bar{L}_{trav} = \frac{1}{2}\left(\frac{5}{6}\bar{F}_{trav}/m_{rad}\right)\left(\frac{2\pi}{\omega}\right)^2 \tag{7}$$

$$= \frac{10\pi^3 R_e V_e k P_A^2 c_{tot}}{m_{rad}\,\omega\left(m_{rad}^2(\omega_0^2 - \omega^2)^2 + \omega^2 c_{tot}^2\right)}$$

where $a_t$ indicates the acceleration of bubble.

## 2.3. Radiation Force in Standing Wave

If two identical waves travel with amplitude of $P_A$ along the z axis at the opposite direction, the standing wave is $2P_A \sin(kz)\cos(\omega t)$. Hence, the radiation force can be expressed as equation (8).

$$\bar{F}_{stand} = \frac{6\pi R_e V_e k P_A^2 m_{rad}(\omega_0^2-\omega^2)}{\left(m_{rad}^2(\omega_0^2-\omega^2)^2+\omega^2 c_{tot}^2\right)} \sin(2kz) \tag{8}$$

Hence, the average translation distance of the bubble whose initial velocity is zero with drag force can be expressed as equation (9).

$$\bar{L}_{stand} = \frac{10\pi^3 R_e V_e k P_A^2(\omega_0^2-\omega^2)}{\omega^2\left(m_{rad}^2(\omega_0^2-\omega^2)^2+\omega^2 c_{tot}^2\right)} \sin(2kz) \tag{9}$$

## 2.4. Parameters

In order to obtain the average radiation force and the average translation distance numerically, basic parameters are required and calculations need to be conducted accordingly. The basic bubble parameters

Table 1. main parameters of Albunex®

| | |
|---|---|
| Shell density ($kg/m^3$) | 2700 |
| Shear viscosity of Albunex® ($Ns/m^2$) | 2.2 |
| Surface tension of inner surface (N/m) | $40 \times 10^{-3}$ |
| Surface tension of outer surface (N/m) | $5 \times 10^{-3}$ |
| Estimated Shear Modulus (Pa) | $120 \times 10^{6}$ |
| Inner Radius (m) | $3.4 \times 10^{-6}$ |
| Shell Thickness (m) | $15 \times 10^{-9}$ |
| Specific Heat of gas (J/kgK) | 1000 |
| Thermal conductivity of gas | 0.024 |
| Gas density ($kg/m^3$) | 1.3 |
| Polytrophic exponent of gas | 1.4 |

used for this analysis were from reference [10], [18], and [19]. Table 1 shows the primary parameters of Albunex®. Since Optison® is closely related to Albunex®, it is assumed that the difference between two is simply the radius size and the mean radius of Optison® is assumed to be 1.7 μm.

In the calculation of the damping coefficient, the shell thickness was estimated as 5% of bubble radius as in reference [18]. The calculated damping constants of Albunex® and Optison® are approximately 4.7 and 6.9 respectively.

The operating frequency of 0.1 – 10 MHz was used for the calculation, since this regime includes most of ultrasound imaging frequencies. In addition, the amplitude is generally low for ultrasound imaging, so that the amplitude is set to 0.5 MPa.

For therapeutic ultrasound, the operating frequency is generally around 1 MHz in order to treat deep tissue. The operating amplitude ranges from 0.1 to 5 MPa at a frequency of 1 MHz. The natural microbubbles can be unstable and can cause transient cavitation at the high pressure acoustic field such as 5 MPa. However, the engineered microbubbles such as Albunex® has a stiff shell, so that the $2^{nd}$ harmonic components appears only approximately 10% of the fundamental component with the incident pressure condition of 5 MPa at 1 MHz based on the de Jong's model [10]. Therefore, this range was assumed as the linear regime.

## III. Results

According to the UCA descriptions, the size of most microbubble in UCA is on the order of 1 to 5 μm in diameter and the number of microbubbles in 1 ml is on the order of $10^{8}-10^{10}$ [20, 21]. Since the recommended maximum dosage of UCA is under 5 ml, the average distance between two bubbles in an average adult male, weighing 80 kg, is approximately 300 μm at the maximum dosage [20, 21]. Hence, it can be assumed that the individual bubble is located far enough from other bubbles.

As shown at the Figure 1–a), bubble reaction to a propagating acoustic field reaches the peak at the resonance frequency which is approximately 3.8 MHz. The peak radiation force of UCA model is approximately 0.030 $\mu$N. The result shows approximately 30 times smaller than that of Dayton's expectation. It is due to the difference in the damping estimation [2]. The damping constant for Albunex® of 0.15 is used in the reference, but the calculated damping constant from the continuous momentum model is over 4.5.

On the other hand, radiation force in standing wave is zero at the resonance frequency as can be seen in Figure 1–a). In addition, the direction of the radiation force is inverted at the resonance frequency. If the bubble's resonance frequency is lower compared to the standing wave frequency, then it is forced to move toward the node. And if the bubble's resonance frequency is higher, then it is forced to move toward the antinode. In addition, the radiation force is peaked around 1 MHz which is generally ultrasound surgery operating frequency and the peak amplitude of the radiation force in standing acoustic field is approximately a half of the maximum radiation force in propagating acoustic field.

Optison® (GE Healthcare, USA) is another commercially available UCA closely related to Albunex ®. One of the main differences between two products is the size distribution of microbubbles. Since Optison® is composed of smaller microbubbles, the

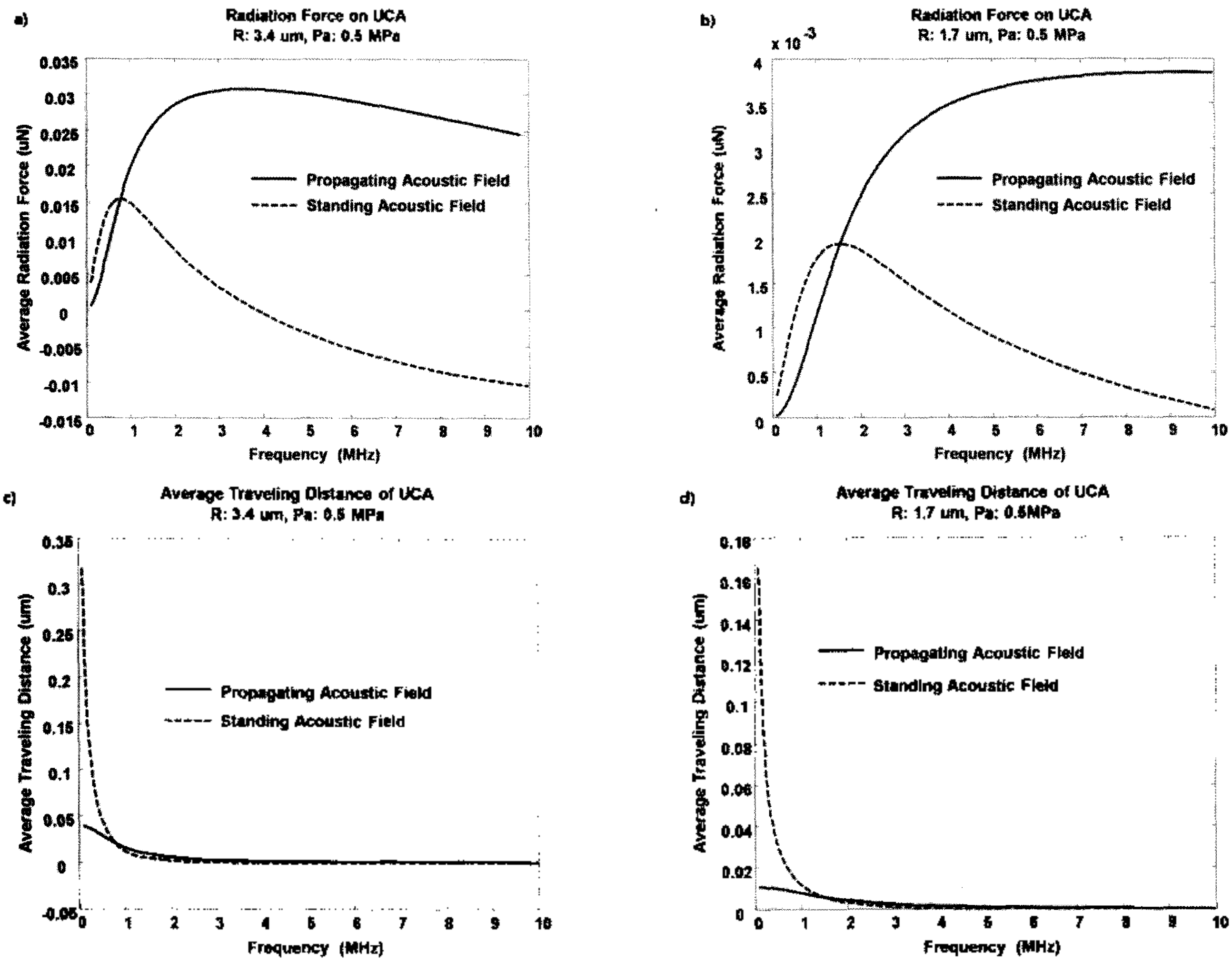


Figure 1. Radiation Force and Average Translation Distance of UCA with respect to frequency. The mean radius of Albunex® is around 3.4 μm and the mean radius of Optison® is 1.5~ 2.25 μm.

radiation forces to Optison® will be more close to Figure 1-b). Interestingly enough, the smaller bubble also shows the peak radiation force in standing wave around 1 MHz.

As can be seen in Figure 1-c) and 1-d), the average translation distance in a cycle of incident acoustic field deceases fast as frequency increases. It is mainly because the time period becomes shorter as frequency increases. It might seem deceptive but this condition matches well to the general ultrasound imaging condition. Since an imaging pulse is generally composed of 3-5 cycles of the wave, the pulse duration proportionally decreases as frequency increases. By comparison of Figure 1-c) and 1-d), we can also notice the average translation distance in a cycle is proportional to the size of bubble at the low frequency in both propagating and standing acoustic field.

Figure 2 shows the simulation results related to therapeutic ultrasound condition. As can be seen in the Figure 2, radiation force in both propagating and standing waves is proportional to the square of input pressure. Accordingly, the average translation distances are also proportional to the square of input pressure. It can be easily induced from equations (4), (7), (8), and (9). One thing can be noticed in the Figure 2, both the radiation force and average translation distance seem to proportional to the radius of bubble in a low frequency condition. Therefore, we can predict that Albunex® is more strongly affected by radiation forces than Optison® in therapeutic ultrasound. We can also notice that the local

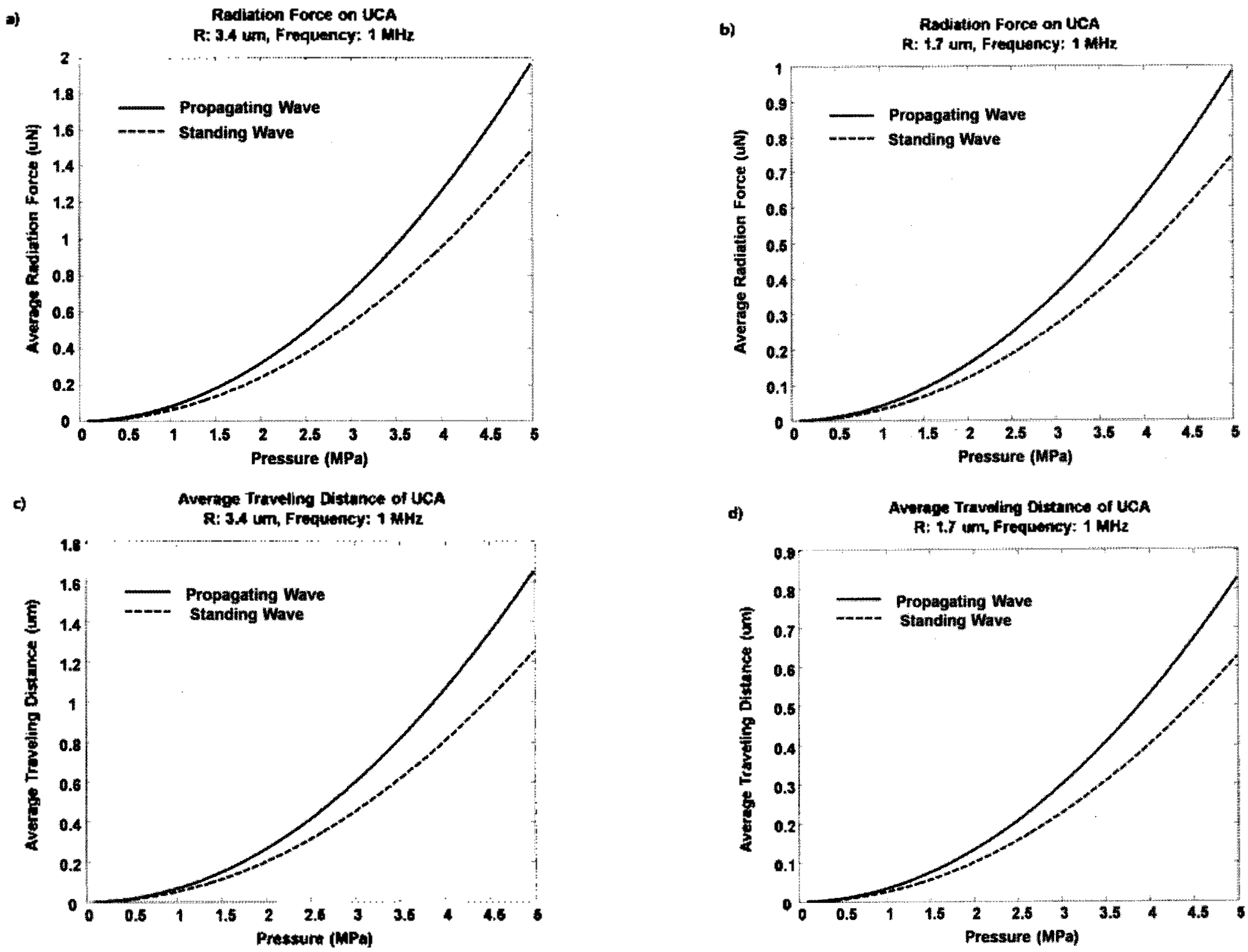


Figure 2. Radiation Force and Average Translation Distance of UCA with respect to input pressure.

bubble distribution will be changed quickly in therapeutic ultrasound. For an example, a simple cycle of 4 MPa sound pressure at 1 MHz can move a bubble approximately 1 μm which is approximately a tenth of capillary diameter.

## IV. Discussion

As mentioned above, ultrasound imaging machines utilize a pulse duration of 3–5 cycles (0.6–1 μsec at 5 MHz) in order to obtain a high resolution image. Therefore, it is unlikely to show a standing wave effect in most cases. This indicates that the radiation force and the resultant bubble translational motion are predominantly determined by the incident propagating acoustic field in ultrasound imaging cases.

On the other hand, therapeutic ultrasound has applied relatively long pulses whose duration is on the order of 10–100 msec. in order to achieve sufficient biological effect such as destruction of cancer cells and increase of local temperature. In addition, the delivered high energy can easily cause a cavitation effect at the highly localized area. Since a large bubble or high density of small bubbles can cause a strong reflection due to acoustic impedance mismatch, it is likely that a strong standing wave could be sustained in front of the created bubbles area. Hence, UCA away from focus of HIFU transducer could be affected by radiation force of standing wave. In addition, the radiation force of standing wave is also a sinusoidal function of location and its direction is toward to node due to the small UCA size compared to operating frequency. Therefore, micro–

bubbles of UCA close to node and antinode of standing wave are more strongly affected by its radiation force.

Even though this small movement due to radiation force seems negligible in general, it can cause significant effects in human body. It is because UCA is limited within blood vessel. In case the blood vessel is parallel to the beam direction, it will accelerate/decelerate the UCA movement according to the blood stream direction. If the blood vessel is perpendicular to beam direction, UCA will be pushed toward distal vessel wall where flow speed is very slow. This effect will changes the local concentration of UCA and the reaction between bubbles will increase drastically since the average distance between bubbles becomes small. This secondary radiation force effect will be discussed in successive presentation in detail.

The experimental results from reference [2] are obtained from very high concentration of UCA. The bubble concentration was between 20% - 60% for the optical observation. Considering the distribution, the distance between bubbles rather small for any free oscillation model can be used. This indicates that the symmetric oscillation of bubble may not be proper at this level of the concentration anymore.

The numerical estimation of radiation force from Church's model is approximately one order smaller than that of a compressible liquid model suggested in reference [2]. Since a compressible liquid model adapted shell shear viscosity, high shell shear modulus, and heavy shell density effects into a single parameter of compressibility, it is rather underestimates shell effect to damping which causes a bubble to oscillate with smaller amplitude as can be seen in figure 3. Over 90% of damping is due to shell in Church's bubble model. In order to validate the simulation, a series of experiments are under preparation.

Nonlinear effect can be significant in high intensity ultrasound and in high frequency ultrasound. If the localized high frequency components increased the radiation force can be increased significantly since

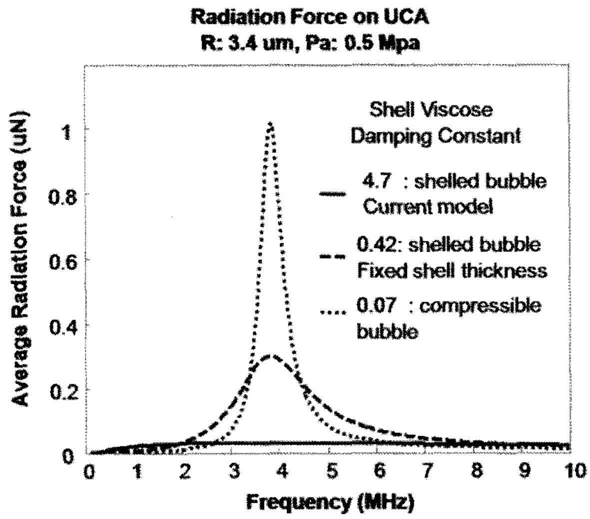


Figure 3. Radiation Force with respect to frequency. Even though individual models share the identical final equation format, the estimated equivalent shell damping constants are different according to the models. Based on the shelled bubble model with the fixed ratio between shell radius and shell thickness, the estimated equivalent shell viscose damping constant is calculated to be 4.7. On the contrary, the equivalent shell viscose damping constant from compressible bubble model is approximately 0.07.

the bubble size is not small compared to the wave length anymore. In order to calculate the radiation force including the nonlinear oscillation of bubble, the radiation pressure model need to be modified accordingly.

In this presentation, the pressure limit of the incident field is set to be 5 MPa at 1 MHz based on the N. de Jong's nonlinear UCA model. However, limit of linear regime totally depends on the bubble model. Hence, experimental validation is required to confirm the limit of linear regime.

## V. Summary

Radiation force in propagating and standing acoustic field were calculated for a specific contrast agent Albunex® and Optison®. The resultant average translation distance with consideration of the drag force was also calculated. The result shows that radiation force effect is more significant with therapeutic ultrasound due to longer pulse duration and higher pressure field. Hence, UCA characteristics can be significantly changed even without rapid collapse of UCA in therapeutic ultrasound.


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