WESPAC IX 2006
The 9th Western Pacific Acoustics Conference
Seoul, Korea, June 26-28, 2006

BETTER LIFE THROUGH BUBBLES AND BIOMEDICAL ULTRASOUND

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ABSTRACT

Many environmental, biological, and engineered fluidic systems invariably involve bubbles suspended in a liquid. These bubbles can have a profound impact on the mechanical and acoustical properties of the multi-phase medium. When exposed to moderate-to-high amplitude acoustic forcing, bubbles can respond nonlinearly – a process known as acoustic cavitation. Cavitating bubbles can lead to a range of physical effects, including microstreaming, collapse microjets, inertially confined cavity collapses, and an associated host of mechanical and chemical effects. In this paper we provide a brief survey of linear bubble acoustics and cavitation effects. We provide examples of how these phenomena can be put to positive use in applications related to biomedical ultrasound imaging and high-intensity ultrasound therapy.

KEYWORDS: Bubbles, cavitation, ultrasound, biomedical, HIFU

INTRODUCTION

Bubbles, in their various forms, are invariably found in virtually all fluidic systems, ranging from the oceans to biological organisms to human engineered systems of all kinds. These cavities consist of pockets of gas and/or vapor that can be short lived, as in boiling bubbles that cool and condense when they rise, or enduring, as in gas bubbles stabilized against dissolution by surface layers [1] or caught in cracks on hydrophobic surfaces [2]. The presence of bubbles can have both beneficial and deleterious effects, depending the situation at hand. For example, bubbles generated by breaking waves on the sea surface are projected into the water column where they dissolve; thereby promoting air-sea gas transfer that is critical to marine life. However, these very same bubbles are excellent sources of sound upon formation [3], a fact that increases the level of ambient noise in the water column and can compromise the efficacy of passive sonar systems. On the *other* hand, bubble-generated ambient noise can be used as a non-invasive probe of ocean surfaces processes such as precipitation [4], wind speed [5], and breaking wave distributions [6], to name but a few. Similar examples of the schizophrenic nature of the physical/biological effects of bubbles and acoustic cavitation (defined below) exist in industrial and biomedical ultrasound. For example, regulatory agencies mandate that ultrasound imaging machines must not promote cavitation activity due to the potential for biological damage. However, acoustic cavitation is considered desirable in certain therapeutic ultrasound systems, where bubbles can assist in tissue heating and promote tissue ablation.

Friend or foe, bubbles are a factor that must be dealt with when dealing with liquid systems, particularly when acoustic wave propagation is involved. If properly managed, bubble activity can reap significant benefits; understanding the nature of the bubble or cavitation field is key. Indeed, bubble behavior is germane to a number of important industrial, biomedical, and environmental processes [7]. In the sections to follow, we present a brief primer on acoustically relevant bubble behavior and the physical effects associated with said activity. This will be followed by a few examples of how bubbles can be used in conjunction with sound and ultrasound to enhance humankind's ability to achieve positive outcomes in biomedical ultrasound imaging and therapy. The list of examples is not intended to be exhaustive, but rather to provide a "snapshot" of the broad range of interesting acoustical and physical phenomena associated with the ubiquitous bubble.

A PRIMER ON BUBBLE AND ACOUSTIC CAVITATION

The role played by bubbles in the acoustics of liquid media is best subdivided into two categories, (a) low-amplitude linear response and (b) large amplitude nonlinear behavior. Furthermore, bubble activity can be modeled in terms of individual bubble behavior and the mechanical behavior of bubble swarms and bubbly liquids. We briefly address these general classes of behavior in the context of the physical effects they produce. The discussion is necessarily brief, and the reader is advised to consult the references for additional details.

Linear acoustics of a single bubble. The small-amplitude response of an acoustically-driven spherical bubble is described by a damped simple harmonic oscillator equation:

$$\ddot{r} + 2b\dot{r} + \omega_{res}^{2} r = -\frac{P_a}{\rho R_o} e^{-i\omega t} \quad \text{where} \quad R(t) = R_o + r(t) \quad and \quad r(t) << R_o \ . \qquad (1)$$

Here $R(t)$, R_o, and $r(t)$ are the instantaneous, equilibrium, and perturbed radii of the bubble, P_a is the acoustic pressure amplitude, b is a damping term that accounts for viscous, thermal, and radiation loss, and ω_o is the resonance frequency of the oscillator [8]. Ignoring surface tension, this is given by the well known Minneart relationship [9]:

$$\omega_o = \frac{1}{R_o}\sqrt{\frac{3\gamma P_o}{\rho}} \ . \qquad (2)$$

where P_o is the ambient pressure, γ is polytropic exponent for the gas and ρ is the density of the liquid. This simple model serves to illustrate the fact that a bubble, when impulsively excited by some acoustic or hydrodynamic disturbance, will "ring" like a bell at a frequency given by

Eq. (2); thus bubbles can be noisy beasts when placed in an acoustically active environment. The larger the bubble, the lower its' resonance frequency. Moreover, the bubble as a scatterer of sound displays a rather pronounced resonance response at ω_o. This so called "giant monopole resonance" makes the bubble an extremely effect sound scatter, an effect that makes it an ideal agent for enhancing echo contrast in ultrasound imaging of blood and certain tissue structures *in vivo*.

For an air bubble undergoing adiabatic pulsations in water at standard temperature and pressure, Eq. (2) can be written as

$$f_o R_o = \frac{1}{2\pi}\sqrt{\frac{3\gamma P_o}{\rho}} \approx 3.25\ Hz - m \quad . \tag{3}$$

Thus, millimeter bubbles resonate in the kHz frequency range whereas micron bubbles are most acoustically active in the MHz frequencies. It is important to note that the resonance-size air bubble in water possess a radius that is only 1/500th of the acoustic wavelength.

Linear acoustics of a bubble swarm. The dominant effect that a swarm of small bubbles has on the mechanical properties of a liquid is to make the mixture far more compressible while minimally impacting the mixture density. By "small bubbles" we mean bubbles that are less than resonance size, and the net effect is to depress the mixture soundspeed to a level lower than that of either the liquid or the gas alone. This is described by the so-called Woods equation:

$$c_{eff} \approx \sqrt{\frac{P_o}{\beta(1-\beta)\rho}} \quad \text{where} \quad \beta = \frac{V_g}{V_g + V_l} \quad . \tag{4}$$

This expression for the effective sound speed of the mixture is accurate to within 1.2% for free-gas volume fractions (VF), β, ranging from 0.2% to 94% [10]. A plot of sound speed versus VF is given in Fig. 1. It is evident that even a very small concentration of bubbles can dramatically alter the acoustical properties of the mixture. Figure 1 also suggests that measurements of low-frequency sound speed can serve as a sensitive tool for measuring spatially averaged volume fractions in multi-phase flows. In addition, the reader is directed to refs [7] and [10] for detailed descriptions of a number of extremely interesting effects that set in at frequencies at and above the bubble resonance frequency. These include acoustic scattering from bubble swarms, greatly pronounced sound speed dispersion, and enhanced dissipation – all of which impact sound probation in bubbly liquids.

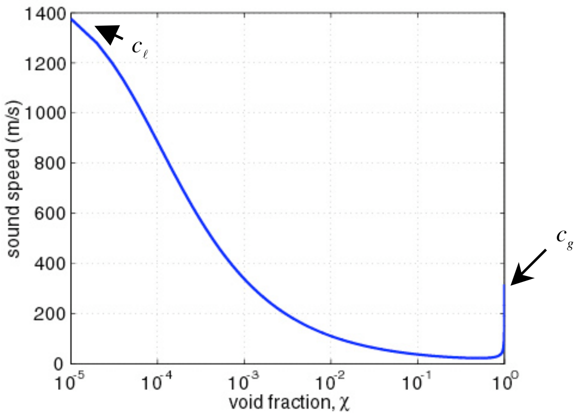

Figure 1. The effective sound speed versus VF for air bubbles in water c_l and c_g are the speed of sound in water and air respectively.

Nonlinear bubble behavior. Acoustic cavitation refers to the driven response of a gas and/or vapor cavity to acoustic forcing. It is generally refers to energetic response to large-amplitude forcing, as opposed to the linear process described above. Equation (1) proves inadequate and a more complete description of the radial dynamics of an acoustically driven bubble is required:

$$\left(1-\frac{\dot{R}}{c}\right)R\ddot{R}+\frac{3}{2}\dot{R}^2\left(1-\frac{\dot{R}}{3c}\right)=\left(1+\frac{\dot{R}}{c}\right)\frac{P\left(\dot{R},R,t\right)}{\rho}+\frac{R}{\rho c}\frac{\partial P\left(\dot{R},R,t\right)}{\partial t} \text{ , where}$$

$$P\left(\dot{R},R,t\right)=\left[\left(P_o-P_v-\frac{2\sigma}{R}\right)\left(\frac{R_o}{R}\right)^{3\kappa}+P_v\right]-P_o-\frac{2\sigma}{R}-\frac{4\mu\dot{R}}{R}-P_a\sin\omega t \ . \tag{5}$$

Here, σ, P_v, μ, c, and ρ are the surface tension, vapor pressure, viscosity, sound speed, and density of the surrounding medium, respectively [11]. The governing equations are highly nonlinear and the resulting bubble motion is rich in complexity, exhibiting all manner of (sub)harmonic response and some rather unusual physical effects that can dramatically alter the mechanical, thermal, and even chemical properties of the host medium. Some of these effects are described below, and for the purpose of this article, we limit the discussion to the more general aspects of the problem. The reader is directed to Refs. [7] and [11] for a broader discussion; the latter reference is noteworthy in that it addresses the role that nonlinear bubble behavior can play in therapeutic ultrasound.

Stable cavitation. Cavitation activity falls loosely within two categories: stable cavities that persist over hundreds or thousands of acoustic cycles, and inertial cavities that can self destruct in a cycle or two. Stable cavitation is characterized by more or less repetitive oscillations about an equilibrium radius that may or may not change over time due to dissolution or growth by a process known as rectified diffusion [7,11]. Probably the most important facet of stable cavitation is the formation of small-scale fluid flows known as cavitation microstreaming [7,12], an effect that is greatly enhanced by the excitation of surface waves on the bubble. These flows occur over scales comparable the bubble dimensions, and are considered one of the key ways that cavitation near sold boundaries promote surface cleaning. Stable cavitation can also promote heat generation due to viscous losses in the boundary layer on the surface of the pulsating bubble [11]. In short, stable cavitation provides a means for converting acoustical energy into mechanical (streaming) and thermal (heating) energy over length scales comparable to the bubble size, *i.e.* much smaller than an acoustic wavelength.

Inertial cavitation. If you drive a stable cavity at sufficiently large pressure amplitudes, the rarefaction portion of the acoustic pressure cycle causes it to grow to a size for which the internal pressure drops to the vapor pressure. During the ensuing compressive phase, the growth is arrested and the vapor-filled bubble proceeds to collapse like a Rayleigh cavity. By the time the gas pressure builds up to the point where is dynamically significant, the bubble wall velocity approaches supersonic speeds and the collapse continues, driven by the inertia of the onrushing liquid (hence the name *inertial cavitation*). If this occurs far from any boundaries (or other bubbles), the gas is profoundly compressed, resulting in intense heating and pressure. Chemical reactions ensue and light is generated from the radiative re-combination of chemical species [13]. Microstreaming can also result, particularly if the bubble is not destroyed upon collapse and rebounds. In addition to heating, acoustic shock waves are generated that can impact boundaries and alter the propagation media in the immediate vicinity of the bubble through mechanical stress and heating due to visco-thermal absorption.

If the inertial collapse occurs near a boundary, things get even more interesting. The asymmetry in the flow field results in the formation of a liquid jet that pierces the bubble and impacts the boundary. Figure 2 shows a photograph of jet formation during the collapse of a vapor bubble in a 60 Hz sound field in glycerin-water mixture at an ambient pressure of 0.05 bar. Although this frequency is low and the bubble somewhat large (order 2 mm), the general features are indicative of what one might encounter at ultrasonic frequencies, were jet velocities and impact pressures can exceed several hundred meters per second and 100's of MPa respectively [7,14]. The net effect is impulsive forcing of the interface that can cause significant erosion. Also shown in Fig. 2 is an electron micrograph of the surface of a 2-mm thick brass plate submerged in water and exposed to 25 shocks from a Dornier extracorporeal shick wave lithotripter [14]. The eroded site has a diameter on the order of 20 μm and was caused by the impact of a high-speed liquid jet formed by a collapsing bubble.

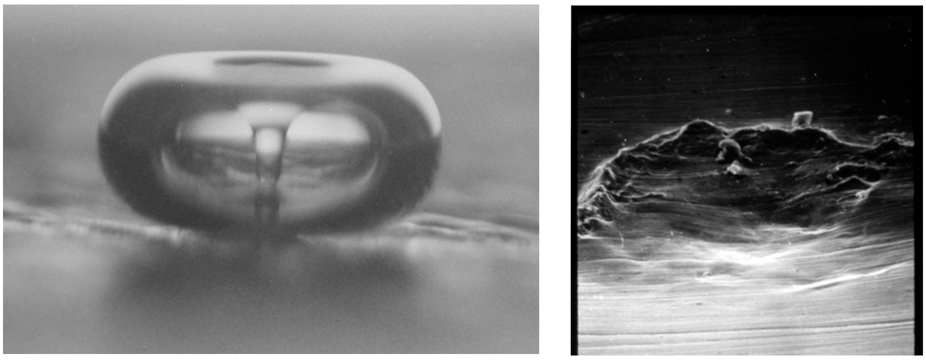

Figure 2. Left: jet formation during the collapse of a bubble near a boundary in a 60 Hz sound field (courtesy of L.A. Crum and previously published in [15]). Right: a cavitation "pit" on the surface of a brass plate exposed to lithotripter shock waves (unpublished photo courtesy of L.A. Crum, Univ. of Washington; related photos from the same study are published in [15]).

BUBBLES, CAVITATION, AND BIOMEDICAL ULTRASOUND

As a way of illustrating the significance of bubble and cavitation, we discuss the role that bubbles and cavitation can play in two different biomedical application areas: diagnostic ultrasound contrast enhancement, and high intensity focused ultrasound therapy.

Diagnostic ultrasound contrast agents. The ability to ultrasonically image blood flow, tissue variability, and tissue interfaces depends critically in the acoustical contrast presented by the moving medium or targeted tissue relative to the surrounding environment. This contrast is manifested in two ways. First, changes in the spatially dependent acoustic impedance results in backscatter. Unfortunately, most tissues possess roughly the same sound speed and density as water, thus the variations between tissue types and between tissue and blood tend to be small. This limits image contrast and the ability for sonographers to delineate tissue types. A second source of contrast results from volume scattering from microstructure in the tissue. With this, sonographers can identify fluid filled lesions as well as regions where tissue microstructure is either enhanced or diminished.

The addition of bubbles to blood and/or tissue provides a means for enhancing contrast owing to the elevated backscatter cross section of individual bubbles, particularly when driven near resonance. These bubbles are typically injected systemically, possess radii on the order of 1 μm or less, and are stabilized against dissolution by surface skins and coatings [15]. They can enhance the backscatter contrast of the blood phase and thus make it easier to image acoustically remote regions, such as the chambers of the heart. Since they track the blood flow they enhance the physician's ability to detect turbulence and can signal abnormal flow patterns associated with stenoses and improper valve function. By observing where bubbles tend to collect, one can use contrast imaging to detect blood pooling from internal bleeding and identify regions of abnormally high vasculature, such as tumors.

Contrast imaging can also help image aspects of tissue health as well. For example, blood perfusion is critical to tissue health in several organs, and the slow flow associated with perfusion is virtually impossible to image without the added echogenecity brought on by microbubbles in the blood.

The inherent nonlinearity of driven bubble response provides yet another means for detecting bubbles with imaging ultrasound. Harmonic imaging is a modality in which tissue is exposed to ultrasound at a frequency f and backscatted information is collected at $2f$. It is in part a consequence of the nonlinearity of the tissue, which can be greatly enhanced by the introduction of bubbles; recall the nonlinear nature of Eq. (5). Other physical effects, such as transient contrast extinction, have been exploited to further image blood flow properties. Moreover, a variety of novel signal processing techniques, such as pulse inversion, have been developed specifically to exploit the unique scattering features of contrast microbubbles. Indeed, the techniques employed and physical characteristics of the commercially available contrast agents are quite varied and too numerous to address here. A comprehensive description of these techniques and associated clinical applications is provided in the excellent text by Szabo [16].

Bubbles and high intensity focused ultrasound (HIFU). High intensity focused ultrasound is rapidly becoming a leading modality for effecting minimally invasive therapy. Exposure to HIFU ideally results in the formation of an ellipsoidal thermal lesion caused by rapid heating of tissue brought on by visco-thermal absorption. In many instances, tissue temperature is elevated to the point where boiling bubbles appear, and the resulting scattered ultrasound can generate a malformed "tadpole shaped" lesion that grows towards the source transducer. In some instances, the HIFU field can generate inertial cavitation that can serve to accelerate tissue heating and mechanical disruption. Whether these effects are desirable depends in the specific application, but it is clear that controlling cavitation in HIFU applications requires an understanding of bubble activity at these very high acoustic pressures. As an illustrative example, we briefly describe the ways in which bubbles can enhance HIFU heating.

Figure 3 is a plot of peak temperature rise in an agar-graphite tissue phantom induced by a 1-sec exposure to 1 MHz HIFU, plotted as a function of incident pressure amplitude [17]. Measurements were obtained using a thermocouple cast into the phantom and positioned in the focal plane, approximately 0.5 mm off the acoustic axis. The solid line is the predicted temperature rise computed using the Pennes bioheat transfer equation with heating terms derived from visco-thermal absorption. There is good agreement between measurement and prediction for incident pressures up to 1.2 MPa, at which point there is a marked increase in the temperature elevation over an above that predicted from theory. Coincident measurement of noise emissions using a passive cavitation detector revealed that the onset of enhanced heating coincided precisely with the onset of inertial cavitation activity. This served as clear evidence of the efficacy of bubble enhanced heating, and subsequent modeling shows that the source of this enhanced energy deposition is the absorption of broad band acoustic emissions from inertial cavitation collapses [11].

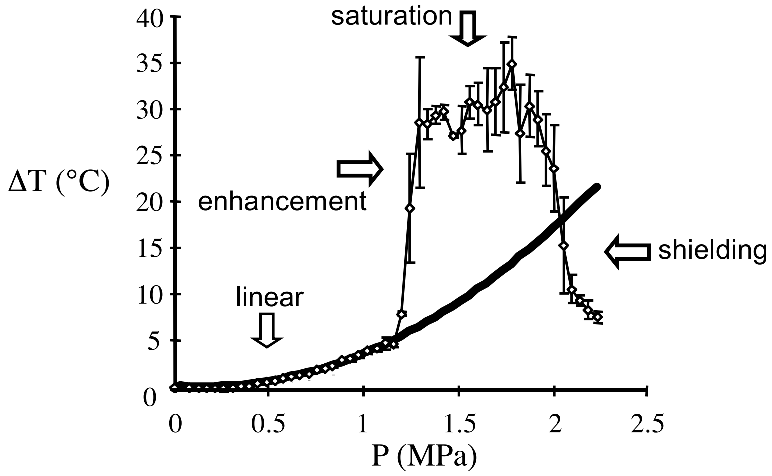

Figure 3. The effect of cavitation activity on the temperature elevation in an agar-graphite phantom exposed to 1-sec bursts of 1 MHz high intensity focused ultrasound as a function of incident pressure amplitude. The heavy solid line a model prediction base on visco-thermal heating and the Pennes bioheat transfer equation.

Clinical HIFU therapy rarely employs intensity levels close to the threshold for cavitation activity. Most systems utilize far greater intensities, sometimes reaching thousands of watts per centimeter squared. The consequences of operating at super-threshold pressures are also evident in Fig. 3. The enhancement region is followed by a plateau where added HIFU pressure fails to generate significant enhanced heating, probably due to excess cavitation "softening" the medium. Increase the pressure further, and the temperature elevation *decreases*, presumably because the cavitation field is shielding the focus and redirecting the incident field back towards the source transducer. Subsequent experiments showed that this shielding effect is associated with an increase in cavitation activity and associated heating in the prefocal region. These results suggest that, when it comes to acoustic cavitation and biomedical ultrasound, it is indeed possible to have too much of a good thing.

In order to properly exploit cavitation effects, one must understand the nature of the bubble field and related physical/biological effects. There a many topics related to cavitation and therapeutic ultrasound that have not been discussed here, including exciting potential applications related to tissue ablation and targeted drug delivery and issues involving cavitation nucleation and potential therapeutic roles for ultrasound contrast agents that have not been addressed. The reader is directed to Refs. [11] and [18] for additional information.

SUMMARY

We present a brief review of the linear acoustics of individual bubbles and bubble swarms, focusing on effects related to scattering, noise, and sound speed dispersion. This is followed by descriptions of the essential features of stable and inertial acoustic cavitation activity and related physical effects, including cavitation microstreaming, collapse microjets, and inertially confined cavity collapse. We conclude by describing how these aforementioned physical effects are exploited by the use of stabilized microbubbles as ultrasound contrast agents and the generation of inertial cavitation to promote tissue heating and disruption by high intensity focused ultrasound. The concluding message: in order to harness bubbles and cavitation activity for positive effect, one must understand the nature of the bubble/cavitation field and the associated physical and biological effects.

REFERENCES

1. D. E. Yount, "Skins of varying permeability: a stabilization mechanism for gas cavitation nuclei," *J. Acoust. Soc. Am.*, **65**, 1429-1439 (1979)

2. R. E. Apfel, “The role of impurities in cavitation threshold determination,” *J. Acoust. Soc. Am.*, **48**, 1179-1186 (1970)

3. H. Medwin and M. W. Beaky, “Bubble sources of the Knudsen sea noise spectra,” *J. Acoust. Soc. Am.*, **86**, 1124-1130 (1989

4. H. Medwin, J. A. Nystuen, P. W. Jacobus, L. H. Ostwald and D. E. Snyder, "The anatomy of underwater rain noise," *J. Acoust. Soc. Am.,* **92**, 1613-1623 (1992)

5. D. D. Lemon, D. M. Farmer and D. R. Watts, “Acoustic measurements of wind speed and precipitation over a continental shelf,” *J. Geophys. Res.*, **89**, 3462-3472 (1984)

6. D. M. Farmer and S. Vagle, “On the determination of breaking wave distributions using ambient sound,” *J. Geophys. Res.*, **93**, 3591-3600 (1988)

7. T. G. Leighton, *The Acoustic Bubble* (Academic Press, London, 1994)

8. A. Prosperetti, “Bubble phenomena in sound fields: part one,” *Ultrasonics*, 69-77, March (1984)

9. M. Minnaert, “On musical air bubbles and sounds of running water,” *Phil. Mag.*, **16**, 235-248 (1933)

10. W. M. Carey and R. A. Roy, “Sound scattering from microbubble distributions near the sea surface," *Ocean Reverberation*, ed. by D. D. Ellis, J. R. Preston and H. G. Urban, (Kluwer Acad., Dordrecht, Netherlands, 25-44, 1993)

11. R. G. Holt and R. A. Roy, “Bubble dynamics in therapeutic ultrasound,” *Bubble and Particle Dynamics in Acoustic Fields: Modern Trends and Applications, 2005*, A. Dionikov, ed. (Transworld Research Network, Kerala, 108-229, 2005)

12. S. Elder, “Cavitation microstreaming,” *J. Acoust. Soc. Am.,* **31**, 54-64 (1958)

13. K. S. Suslick, *et al.*, "Acoustic cavitation and its chemical consequences" *Phil. Trans. Roy, Soc. A*, **357**, 335-353 (1999)

14. L. A. Crum, "Cavitation microjets as a contributory mechanism for renal calculi disintegration in ESWL," *J. Urology*, **140**, 1587-1590 (1988)

15. N. De Jong, A. Bouakaz and P. Frinking, “Basic acoustic properties of micro bubbles,” *Echocardiography*, **19**, 229-240 (2002)

16. T. L. Szabo, *Diagnostic Ultrasound Imaging: Inside Out* (Elsevier Acad., Burington, MA USA, 2004)

17. R. G. Holt *et al.*, “Bubbles and HIFU: the good, the bad, and the ugly,” *Proceedings of the 2nd International Symposium on Therapeutic Ultrasound,* M. A. Andrew, L.A. Crum and S. Vaezy Eds. (American Institute of Physics, pp. 120-131, 2003)

18. M. R. Bailey *et al.*, "Physical mechanisms of the therapeutic effect of ultrasound (a review)," *Acoust. Phys.*, **49**, 369-388 (2003)