Bubbles with shock waves and ultrasound: a review

Siew-Wan Ohl¹, Evert Klaseboer¹ and Boo Cheong Khoo²

¹Institute of High Performance Computing, 1 Fusionopolis Way, 16-16 Connexis North, Singapore 138632, Republic of Singapore
²Department of Mechanical Engineering, National University of Singapore, Block EA 07-08, 9 Engineering Drive 1, Singapore 117575, Republic of Singapore

The study of the interaction of bubbles with shock waves and ultrasound is sometimes termed ‘acoustic cavitation’. It is of importance in many biomedical applications where sound waves are applied. The use of shock waves and ultrasound in medical treatments is appealing because of their non-invasiveness. In this review, we present a variety of acoustics–bubble interactions, with a focus on shock wave–bubble interaction and bubble cloud phenomena.

The dynamics of a single spherically oscillating bubble is rather well understood. However, when there is a nearby surface, the bubble often collapses non-spherically with a high-speed jet. The direction of the jet depends on the ‘resistance’ of the boundary: the bubble jets towards a rigid boundary, splits up near an elastic boundary, and jets away from a free surface. The presence of a shock wave complicates the bubble dynamics further. We shall discuss both experimental studies using high-speed photography and numerical simulations involving shock wave–bubble interaction. In biomedical applications, instead of a single bubble, often clouds of bubbles appear (consisting of many individual bubbles). The dynamics of such a bubble cloud is even more complex. We shall show some of the phenomena observed in a high-intensity focused ultrasound (HIFU) field. The nonlinear nature of the sound field and the complex inter-bubble interaction in a cloud present challenges to a comprehensive understanding of the physics of the bubble cloud in HIFU. We conclude the article with some comments on the challenges ahead.

1. Introduction—how bubbles can help the advance of biotechnology

Cavitation bubbles appear ‘naturally’ in the human body when our joints crack. It is proposed that the ‘fluid cavitation is responsible for the cracking noise’ [1]. The cavitation bubbles in our bodily liquids are generated from the dissolved gas in the liquid. As noted by the ‘father’ of microscopy, Anthoni van Leeuwenhoek (paraphrasing in English), ‘...a large quantity of bubbles came out of the water, rose, and even more appeared when I gently tapped on the glass...’ when he described the use of an ‘air-pump’ to study the presence of air in water and blood [2]. When there is an external excitation, such as a shock wave or an ultrasound field, cavitation bubbles are nucleated from gas pockets in the liquid. In most cases, these bubbles also contain water vapour.

Cavitation bubbles are not stationary. They oscillate (usually strongly) in volume. They are found ubiquitously on moving ship propellers, underwater explosions and in shock wave lithotripsy treatment for the disintegration of kidney stones. A schematic of the spherical oscillation of a cavitation ‘explosion’ bubble is shown in figure 1. The radius–time curve shows the variation of the radius of the bubble in time as it oscillates (figure 1a). The bubble expands (from 1 to 3) because of a high initial internal pressure, and reaches a maximum size at 4. It then collapses (from 5 to 7) to a minimum volume (figure 1b). This bubble behaviour is strongly nonlinear, i.e. the bubble spends much more time...
The bubble dynamics change when there is a nearby boundary. In particular, the loss of spherical symmetry can result in the formation of high-speed liquid jets traversing the bubble. A typical example is given in figure 2, which shows the non-spherical collapse of a bubble near a rigid plate. Initially, the bubble expands almost spherically (figure 2a). The top side of the bubble near the plate is flattened as the bubble approaches its maximum size (the last three outermost curves in figure 2a). From its maximum size (outermost curve in figure 2b), the bubble collapses. As the bubble shrinks, it moves towards the plate, and develops a jet which transverses the bubble (inner eight curves in figure 2b). The jet then impacts on the top bubble wall and eventually on the plate. The speed of this water jet is very high, usually around 100 m s\(^{-1}\), and is independent of the bubble size. Figure 2c shows an experimental observation of the same bubble collapse. The bubble is at its maximum size in the first frame on the left. It then collapses and moves towards the plate on top. The last frame shows the bubble at its minimum size at the plate (probably with a jet).

The jet in a collapsing bubble could also be observed when a shock wave moves across a stationary or a cavitation bubble. This jet develops in the direction of the travelling wave. The jet speed in this case is often supersonic (a few km s\(^{-1}\)). The physics involved in the bubble–shockwave interaction can be rather complex (especially with regard to reflection of shock waves, both outside the bubble and internally), but the jet speed will be analysed in greater detail in §2.

Another similarly complex phenomenon is the bubble dynamics in a strong ultrasound field. When a HIFU transducer is placed near or in a water tank, bubble clouds are generated in the water. These clouds move, expand and collapse in the sound field. They are driven by acoustic radiation forces (Bjerknes forces [3,4]). It is possible that similar structures appear in the human body during treatment with HIFU.

HIFU is already clinically used for the treatment of prostate cancer, uterine fibroids and bone metastasis. It has also been tested for treating other tumours such as kidney, liver, pancreatic and bladder tumours. HIFU is currently being tested for treating essential tremor and Alzheimer’s disease. Most clinical HIFU equipment uses high frequency (in megahertz) at low intensity. The main advantage of HIFU in medical treatment is its non-invasiveness. Treatment can be administered extracorporeally without surgery. Also the treatment area can be highly selective as HIFU has potentially a focal region of a few millimetres in length [5]. The bubble generated by HIFU at the focal region could also be used for imaging during the treatment. This is because the bubble (with its air core) has different acoustic impedance from its surrounding tissues.

As a side note, a special type of bubble, known as an ultrasound contrast agent (UCA), has been developed for imaging purposes. These bubbles have a shell (made of lipid or polymers) and a gas core (air or a heavy gas such as octafluoropropane). The shell prevents the bubble from dissolving, and the gas core provides the acoustic impedance required for the imaging. Apart from imaging, UCA is applied in other research areas such as targeted drug delivery. Drug-loaded UCAs are transported to the tumour site, and ultrasound or a shock wave is applied to excite the UCA for the delivery of the drug. Interested readers are referred to recent reviews on
2. Bubbles interacting with shock waves

A shock wave is basically a very large localized pressure perturbation, as shown in figure 3. It travels with a velocity slightly greater than the speed of sound (approx. 1500 m s$^{-1}$). The most common use of such a shock wave is in lithotripsy, the disintegration of kidney stones. Once such a shock wave hits a bubble, it is found that a jet is generated in the same direction as the travel direction of the shock wave.

Field and co-workers [9–12] conducted many experiments studying this interaction in the late 1980s and 1990s. In their experiments, the shock wave was generated by an impact striker which generated a shock pressure in the gigapascal range. The gas bubbles were trapped in a two-dimensional gelatin gel. The gel liquefied as soon as the shock wave went through it. The observation of the shock was done using Schlieren shadowgraphs combined with high-speed photography. It was observed that the shock wave induced the collapse of the gas bubbles with accompanying high-speed jets (a few hundred metres per second) in the direction of the travelling shock wave, as seen in figure 4. They also studied the shock wave impacting on several bubbles arranged in a row or an array (a primitive ‘bubble cloud’). In certain cases, a shielding effect of the outer bubbles on the inner bubbles in an array was observed.

Figure 3. Example of a typical shock wave as used in several medical applications; shock wave pressure as a function of time. The pressure first briefly attains a very high value (approx. 40 MPa), then it becomes very low (approx. $-8$ MPa). Water can sustain such a negative pressure only for a very short time. The positive part of the shock wave has a time duration of approximately 1 $\mu$s, and, as the shock speed is approximately 1500 m s$^{-1}$, the spatial extent is about 1.5 mm.

UCA [6,7]. A clear distinction should be made, however, between endogenous cavitation nuclei, which we study in the rest of this article, and artificially introduced nuclei, such as the UCA.

Another method of targeted drug delivery still under research is the use of acoustics to vaporize a droplet which could block blood flow to a tumour or deliver lethal drugs to cancer cells [8]. Many other interesting topics are undoubtedly worth mentioning, but, due to length constraints, this review will not be exhaustive. This paper is organized in the following manner: we begin with the subject that is most well understood, namely bubble–shockwave interaction (§2). In §3, some of the intriguing phenomena observed in HIFU are shown and discussed. Section 4 deals with some comments and thoughts on the challenges ahead, followed by conclusions in §5.

Figure 3: 20150019

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[10] (for more discussion on shielding effects in bubble clouds see §3.2). It must be kept in mind, though, that these are essentially static ‘holes’ instead of bubbles generated with a laser, spark or by ultrasonic means. Nevertheless, these experiments are important from a historical point of view.

In Japan, Tomita et al. [13] investigated the collapse of multiple gas bubbles on a boundary by a shock wave. They placed two air bubbles on a gelatin block. The bubbles interacted with a travelling shock generated by an explosive. The bubbles collapsed by jetting into the gelatin. They found that, beyond a critical separation, the bubbles collapsed without influencing each other. Another group at Tohoko University studied the interaction of gas bubbles with shock waves generated by an explosive [14]. They found that, if the bubbles were close enough to each other, the direction of their jets during collapse was influenced by the adjacent bubble in such a way that the jets did not follow the direction of travel of the shock waves, but slanted towards the centre of the two bubbles. The group also studied the interaction of shock waves with a bubble on different surfaces (aluminium foil, gelatin, rat liver and rat abdominal aorta) [15]. High-speed photography was used to observe the bubble collapse after its interaction with a shock wave generated by the explosion of a silver azide pellet. The bubble on the aluminium foil was found to jet through the foil as it collapsed (figure 5a). On the other surfaces, the authors observed bubble migration and oscillation after the shock wave travelled through. Eventually the bubble collapsed, and penetrated into the surfaces (figure 5b). They also analysed the tissue damage caused by the collapsing bubble.

The interest in bubble shock wave interaction grew with the recognition of the crucial role of bubbles in extracorporeal shock wave lithotripsy (ESWL). It was understood that the collapse of the bubbles induced by the shock waves causes the formation of microjets, which impinge on the renal stones and facilitate their disintegration [16]. Coleman et al. [17] reported that the jets from the collapse of cavitation bubbles generated by an extracorporeal shock wave lithotripter were violent enough to puncture thin foils and to deform metal plates. In Germany, the research group led by Lauterborn studied the interaction of lithotripter-generated shock waves with air bubbles [18]. They placed a small bubble (between 0.1 and 0.9 mm in radius) on a thin plastic foil. As the shock travelled through the bubble, it collapsed and penetrated the foil with a high-speed jet (between 400 and 800 m s$^{-1}$). Ohl & Ikink [19] imaged the jetting of micrometre-sized gas bubbles interacting with a lithotripter shock wave. From their observation, the small bubbles (generated by pulsed electrolysis) collapse with micrometre-sized jets in the travel direction of the shock waves, as seen in figure 6. They postulated that the mechanism could be potentially exploited for drug or gene delivery into cells.

At Duke University, Sankin et al. [20] studied the lithotripter shock wave interaction with an oscillating bubble generated by a laser. They found that, if the shock wave reached the oscillating bubble during its collapse phase, the resultant collapse was more intense (larger shape deformation and jet velocity) than if the shock wave reached the bubble at its expansion phase. They further extended the study to include an elastic boundary on which the gas bubble was attached [21]. They confirmed that the maximum jet penetration was achieved when the shock wave arrived during the bubble collapse.
phase. They suggested that this phenomenon could be exploited for targeted drug delivery and gene transfection.

Shock wave–bubble interaction was also studied using laser-generated shock waves. Kodama & Tomita [22] reported that the shock wave generated by a collapsing laser-bubble caused an air bubble attached to a gelatin gel to collapse with a strong jet which penetrated the gelatin. Many other studies involving the use of laser bubbles include the investigation of shock waves emitted by a single bubble [23,24], the interaction of two laser bubbles [25,26], the collapse of a laser-generated bubble near a rigid boundary [27,28], an elastic boundary [29,30] and a free surface [31,32].

There are a number of interesting simulation studies that are worth mentioning. An early work by Church [33] modelled the bubble by the Gilmore–Akulichev formulation (essentially an extension of the Rayleigh–Plesset formulation for spherical bubbles in appendix A). The ESWL wave was considered as a pressure wave that changed in time. Very high pressure (up to 10 MPa) was considered. Some 10 years later, Zhu & Zhong [34] also used the Gilmore formulation to calculate the bubble response when it interacted with an ESWL field. They considered three different pressure profiles as generated by different lithotripters. The main drawback of these models is that they can only be applied to spherical bubbles, while all the above experiments clearly show deviation of sphericity in the form of jets in the shock wave direction.

A more advanced model and simulation technique was developed at the University of Southampton, UK [35–37], in this century. A numerical simulation code based on the free-Lagrange formulation to solve the Euler equations was developed. The travelling shock and the bubble collapse are captured by the mesh which changes its connectivity as the bubble deforms. The group first developed a two-dimensional version, and then extended it to an axial symmetrical version. Their results showed the reflection of shock waves inside the bubbles, and dynamic stress loading on nearby solid materials. In [37], the authors validated their code by comparing with an arbitrary Lagrangian Eulerian (ALE) simulation reported in Ding & Gracewski [38], who used the ALE method to solve the Euler equations for the simulation of a shock wave interaction with an air bubble. Both weak (less than 30 MPa in peak pressure) and strong (up to 2 GPa in peak pressure) shocks were investigated. They noted that, for weak shocks, the bubble remains quasi-spherical, while for...
strong shocks a jet appears in the bubble. The shock was mod-
elled as a step pressure (as compared with an ESWL shock
wave profile, as in figure 3). A bubble of initial radius 1.0 mm collapsed with a high-speed jet (2200 m s⁻¹) in the
travel direction of the shock wave. However, full domain
simulations such as these above are computationally very
expensive, especially if they are being extended to full three-
dimensional simulations (for example, to model the interaction
of two or more bubbles with a shock wave [39]).

In Singapore, an active group of people is involved in
bubble dynamics studies, which essentially started as a
spin-off from underwater explosion-related work [40] in
which the prediction of jets in collapsing bubbles is essen-
tial. Klaeboer et al. [41,42] attempted to simulate the bubble–
shock wave interaction using the boundary element method
(BEM), where only the surface of the bubble is meshed as
an alternative to the above-mentioned numerical methods.
A typical simulation is shown in figure 7, where the shock
wave is modelled as a travelling step pressure. In [41], the
code was validated by comparing with the simulation results
from previous papers [36,38]. It was found that the BEM code
successfully captured the bubble deformation and collapse.
The high-speed jet upon bubble surface impact (2000 m s⁻¹
by BEM) was comparable to the previous reported values
(2200 m s⁻¹ for ALE and 2250 m s⁻¹ for free-Lagrange). How-
ever, in BEM, the model is based on potential flow. There was
no travelling or reflected shock wave inside the bubble. Never-
theless, the simulation captured most of the bubble dynamics
because the phenomenon of bubble shock wave interaction is
governed by inertia (potential flow can predict the jet and its
speed accurately). Klaeboer et al. [42] modified their model
to include a lithotripter shock wave and compared the results
with experimental observations [20]. They reported good
agreement between the collapse times of the bubbles and the
pressure peaks measured (water hammer pressure in the simu-
lation). They concluded that the BEM model is capable of
predicting jet shape and velocity (as well as other parameters)
during bubble collapse after interacting with a shock wave. The
biggest advantage of the model is that it is computationally
very efficient.

A group at the University of California, Berkeley, used a
boundary integral method code to study the interaction of
shockwave and bubble near rigid surfaces [43,44]. They con-
sidered the reflection and interface of the shock wave at the
rigid boundary. They found that the reflection of the shock
wave at the wall affected the bubble collapse. Constructive
interference of the waves enhanced the expansion and sub-
sequent collapse of the bubble. On the other hand,
destructive interference suppressed the bubble collapse. Also
in California, Johnsen & Colonius [45,46] developed a high-
order quasi-conservative scheme to solve the Euler equations.
Their simulation captured the travelling shock and the highly
deformed interface of the bubble. As in the free-Lagrange
method, the simulation runs beyond bubble jet impact. They
showed the rebound of the collapsed bubble, and the emission
and reflection of shock waves during the collapse.

The jetting phenomenon can be analysed in simple terms,
from a physics point of view. Our analysis shows that the col-
lapse time and jet speed can be predicted. The theoretical
collapse time for a spherical bubble as derived in appendix
A is:

\[ t_{\text{collapse}} \sim \frac{R_0}{\sqrt{\frac{\rho}{p_{\text{ref}}}}} \]  

Here \( \rho \) is the density of water (1000 kg m⁻³) and, if \( p_{\text{ref}} \) is taken
to be 0.528 GPa, one gets 1.4 µs (with \( R_0 = 1.0 \text{ mm} \)). Numeri-
cally, a larger value for the collapse time of the bubble of
1.76 µs was obtained for the simulation of figure 7. This can
easily be explained by the fact that the jet must traverse slightly
more than the bubble radius alone (as the right-hand side of the
bubble in figure 7 has not shrunk as much as the left-hand side
with the jet). The pressure pulse that was applied in figure 7
was 0.528 GPa. This is a very high pressure and the corre-
sponding shock speed is larger than the speed of sound at
1950 m s⁻¹ [41]. The shock front has travelled a distance of
1950 × 1.75 × 10⁻⁶ = 3.4 mm during that time. Similarly, as
was the case for a spherical bubble, the jet speed is also
independent of the bubble radius and is given by

\[ u_{\text{jet}} = \frac{c}{\sqrt{\frac{p_{\text{ref}}}{\rho}}} \]  

where the constant \( c \) assumes a value of about 2.5. Here, this
would be \( c \sqrt{\frac{p_{\text{ref}}}{\rho}} \approx 2 \text{ km s}^{-1} \). This is consistent with the
observed jet speed of about 2 km s⁻¹.

To summarize, the shock wave essentially acts as a
sudden pressure rise, causing the bubble to collapse in a
very similar manner to a spherical bubble. But as the pressure
rise starts earlier at one side of the bubble, this side collapses
first. The other side of the bubble only starts collapsing later
(when the shock wave in water has arrived there). This results
in a jet travelling in the direction of the shock wave. Note that
the case of figure 7 (done with a BEM) uses the same par-

eters as those in Ding & Gracewski [38] (see their
fig. 12). Their finite volume method obtained a collapse
time of 1.60 µs and a jet speed of 2.2 km s⁻¹; these values
are not far off those obtained with the above theory.
However, for weak shock waves, due care must be taken. For example, Ding & Gracewski [38] (see their fig. 8) took a bubble with $R_0 = 0.1$ mm subjected to a shock wave of 20.5 MPa. The bubble collapsed in 0.75 μs, which is in good agreement with equation (2.1), which gives 0.69 μs. However, no jet was observed in the bubble. This can actually be explained relatively simply, as the shock wave moves over the bubble relatively fast, i.e. the shock wave has travelled a distance of $1500 \times 0.69 \times 10^{-6} = 1.1$ mm; thus 10 times the bubble radius. This means that the front and back of the bubble feel the shock wave almost at the same instant, resulting in an (almost) spherical bubble collapse.

Another point worth mentioning is that, if the shock wave is relatively narrow, the bubble does not feel the maximum shock wave pressure during the whole collapse, resulting in larger values for the collapse time than equation (2.1) and lower jet speeds than those of equation (2.2) (as the effective $p_{\text{red}}$ is much smaller). The typical shock wave shown in figure 3 has a ‘width’ of about 1.5 mm.

An interesting alternative application of lithotripter technology was recently found [47] by the discovery of ‘particle shooting’ when relatively rough micrometre-sized particles are subjected to the negative part of a shock wave. Rapidly growing cavitation bubbles that form on the surface of such particles cause the particle to accelerate. A microparticle was successfully ’shot’ into a skin-like jelly material with this method. The technique could be used for non-invasive ultrasonic drug delivery (see [47] for more details). However, for weak shock waves, due care must be taken.

3. Bubbles interacting with an ultrasound field

### 3.1. One bubble interacting with an ultrasound field

The first use of HIFU can be traced back to the late 1930s [50] with the invention of focused ultrasound and its first biological application in the early 1940s by Lynn et al. [51] in which ‘focused ultrasound could be applied in any selected direction, to a predetermined depth, in the tissues of living animals’. The underlying physics of HIFU is usually explained as ‘conversion of mechanical energy into heat, and through inertial cavitation’ [52], where the cavitation consists of rapidly collapsing bubbles. Several applications have been developed [53, 54], and research on the use of HIFU is still ongoing [55]. However, the physics and exact mechanisms involved are not yet well understood.

First of all, the nucleation process is still much of a mystery (especially in human tissues). But also, the interplay of the thousands of bubbles that usually occur in HIFU, the creation of bubble clouds and their movement is not clear. Therefore, instead of investigating a many-bubble system, we will firstly...
concentrate on a single bubble interacting with a sound wave. This will highlight some of the phenomena involved.

Our HIFU experimental set-up is shown in figure 9. The HIFU is generated by a bowl-shaped piezo-electric transducer. It is supported by a holder and has been waterproofed. It has a resonant frequency of 250 kHz. The transducer is submerged in a water tank of approximately 300 mm$^3$. It is driven by an amplifier to which a signal generator is connected.

When a bubble is placed in a weak low-frequency ultrasound field generated by the HIFU set-up in figure 9, it does not stay spherical but instead starts to undergo shape oscillations. An example is shown in figure 10. The bubble of radius 0.3 mm is created by electrolysis at the tip of an electric wire. Then an ultrasound field of 15 kHz is applied from below. The images are captured by a high-speed camera with 150 000 frames s$^{-1}$. The bubble starts to oscillate after a short delay of about 40 frames (approx. 267 ms). The oscillation period is about 20 frames (approx. 133 ms), thus the oscillation frequency is approximately 150 Hz.

3.2. Bubble clouds, streamers and comets

At high driving voltage, a HIFU transducer in water produces a high pressure at its focal point which in turn generates bubble clouds. The dynamics of these bubble clouds is a major challenge from a modelling point of view [58]. The sound field is nonlinear (i.e. the amplitude of the sound wave is so large that the linearization of the fluid dynamics equations is no longer valid), and the bubbles undergo complex interactions such as collision and coalescence. Nevertheless, there is still a strong motivation to understand the acoustic bubble clouds as they are perhaps responsible for the mechanisms behind the success of the use of HIFU for medical treatment.

A similar set-up as depicted in the previous section has been used here. When the transducer is driven strongly (387 Vpp), streams of bubbles are observed to form above the transducer (figure 12). The bubbles in the streams are small, and the largest bubbles have radii of about 60 μm. It is noted that these bubbles are smaller than the resonant bubble size ($R_{\text{res}} = 150$ μm) (see appendix A for discussion on resonant frequency). They seem to have been initiated from or near the surface of the transducer. They travel upwards towards the focal point of the transducer, which is about 5 cm above the transducer centre.

A similar structure is mentioned in [56]. Cylindrical transducers placed at the bottom and the top of a glass cylinder are used to generate an axially focused ultrasound field. The created structures consisting of the observed bubbles are termed ‘streamers’ (figure 12); it is argued that the bubbles nucleate on ‘motes’ which are solid particles or gas pockets (impurities in the water). The primary Bjerknes force [57,59] drives the streamer bubbles (less than resonant size) to the focal pressure antinode.

Lauterborn and co-workers studied the streamers generated by a cylindrical transducer operating at 20 kHz with experimental observations [60,61] and numerical analysis [59,62–64]. The group termed the streamers ‘acoustic Lichtenberg figures’ (very similar to figure 12). In [61], a simple model of a two-phase mixture interacting with a travelling sound wave was presented. The pressure amplitude of the sound field depends on the location in space, and consequently also the resulting radial bubble oscillations. The result showed the evolution of the bubble concentration and sound field pressure distribution over time. Parlitz et al. [59] reported a new particle model for the bubble cloud. The bubble oscillations were calculated using the formulation from [65], which includes compressibility. The sound field is modelled using the wave equation from [66]. The results showed that the nonlinear bubble oscillation causes the movement of big and small bubbles (relative to the resonant bubble size) to pressure node and antinode to be less predictable. The authors also mentioned the complications from the secondary Bjerknes force, the added mass and the drag force. However, both added mass and drag force were not included in the calculation.

While the above mentioned model [63] attempts to predict the individual behaviour of each bubble, a totally different approach consisting of averaging the behaviour over many bubbles as a ‘mixture model’ has been proposed. For example, D’Agostino & Brennen [67] have reported the development of
a one-dimensional bubble cloud simulation where the sound field was modelled as a Gaussian-shaped pressure distribution. The authors analysed the mode oscillation of a bubble cloud. There are limitations to this model, for instance the bubble cloud is spherical and interactions between the bubbles are not considered. Subsequently more complex models were developed (for example for vapour bubbles [58]). Doinikov [68] showed a Lagrangian formalism model which is capable of modelling the radial and translational motion of a bubble in a three-dimensional cluster in an ultrasound field. The interaction between the bubbles is considered up to the third order. However, the calculation requires the bubbles to be far apart. Pelekasis et al. [69] presented a two-bubble model based on Keller & Miksis [65]. The model considers compressibility. The authors used the calculation to study the attraction and repulsion of the two bubbles (of different sizes) in a sound field of various sound amplitudes.

An attempt to simulate a bubble cloud behaviour is presented in figure 13. The model is based on the numerical framework developed in [70]. Contrary to the above models, the bubbles are no longer always spherical and can now develop jets. No ultrasound is applied; instead, the
bubbles oscillate because of an initially high internal pressure ('explosion' bubbles). The model is based on the BEM where only the bubble surfaces are meshed. There are 362 nodes on each bubble. All 37 bubbles are initiated with the same high initial pressure of 36 MPa (figure 13a). During the growth stages (figure 13b,c), the outer bubbles grow bigger than the inner ones due to a shielding effect. Also, the outer bubbles collapse earlier (last frame). They all jet towards the centre of the cloud while the inner bubbles have yet to collapse. This simulation shows the complex dynamics and interaction of individual bubbles in a bubble cloud. Note that all the bubbles in this particular simulation have been placed deliberately in the same plane, yet the shielding behaviour is already clearly observable. For bubbles in a random three-dimensional configuration (as in a real bubble cloud), this shielding effect will also be present (the bubbles in the centre are then shielded from all sides).

The bubble clouds generated by HIFU at a high-voltage amplitude are complicated structures. In order to understand them better, we attempted to photograph the bubble cloud movement in a travelling sound field generated by the HIFU in a burst mode (figure 14). Under this burst mode, 500 cycles of the ultrasound (approx. 2 ms) are applied. The time for each frame in milliseconds is shown at the bottom of the frame. The experimental set-up is similar to that in figure 9. The concave HIFU transducer (Sonic Concepts) has a resonance frequency of 250 kHz, and a diameter of 64 mm. In the water tank, its focal height is about 50 mm. The video was taken with a high-speed camera (Photron FASTCAM SA5) and a long-distance microscope lens (Infinity K2).

As seen in figure 14, the bubbles first appear in a spherical cloud (t = 0). Then the cloud starts to elongate, with the top part of the bubble cloud beginning to spread out (from t = 0.27 ms to t = 1.6 ms). During this process, the bubble cloud looks like a 'comet'. Eventually, the bubbles form an 'umbrella' shape structure. The size of the structure reaches about 2 mm (t = 2.93 ms). It is interesting to note that a typical speed of a 'comet' was 1.5 m s⁻¹ (figure 14), which is many times the rising speed of an individual bubble rising solely because of buoyancy (which would be in the range of mm s⁻¹ or even smaller). Also the expansion of the top bubbles occurs in multiple directions.

Mettin [71] gives a summary of various bubble structures that have been observed in a standing HIFU field. He describes the movement of 'small' and 'large' clusters (up to a few hundred) of bubbles in a standing wave. The structure shown in figure 14 was described as a 'comet' by Mettin [72]. In Crum & Nordling [3], the same structure was termed 'feathery track'. The formation and dynamics of these structures is still not well understood. Figure 15 shows an ensemble of at least four different comets occurring simultaneously. It is seen that there are multiple sources (or comets) as indicated by the arrows. The bubbles generated at these sources move in different directions. It is obvious that the development of numerical capabilities to simulate such complicated behaviour as seen in figure 15 will be a unique challenge.

Apart from the 'umbrella' shape as shown in figure 14, other shapes of bubble clouds have been observed when the HIFU is operating in a burst mode. Figure 16 shows the formation of a ring-shaped bubble cloud. Mettin [71] has reported a stream of bubbles forming a ring-shaped structure. The rings of streaming bubbles in Mettin [71] are thin, probably only a few bubbles in thickness. The ring in figure 16, however, seems to be at least tens, if not hundreds, of bubbles in thickness. Also the bubble cloud is initially spherical. It expands into a ring as the bubbles move upwards.

The dynamics of bubble clouds in a HIFU field is complex. The nucleation sites (sources or comets) are perhaps where the motes (solid particles) or gas pockets are. Each bubble interacts with the primary and secondary Bjerknes
forces. It is also not clear if these bubble clouds are generated when HIFU is applied in clinical treatment. As about 60% of an adult male human (not obese) consists of water, it is conjectured that bubble clouds as described may form at the focal volume of the HIFU transducer when it is applied to the human body (although strictly, to the best of the authors’ knowledge, there is not yet any experimental evidence to show this). One can surmise that the propagation of HIFU waves to the focal region may not be too adversely affected by reflection as the acoustic impedance of the (high water content) tissues can be fairly close to that of water. There are, however, differences between water and tissue; for example, free movement is limited at tissue boundaries. Yet, similar to what is shown in figure 4 on the interaction of gelatin and a shock wave, at high HIFU intensities (near the focal point), it is possible that this tissue liquefies in a similar manner and still exhibits a more fluid-like character. To what extent the results obtained with water can be extrapolated to human tissue thus remains an open question.

The bubble clouds behave differently in the presence of a nearby boundary. Figure 17 shows the formation and movement of a bubble cloud above a membrane in an ultrasound field generated by the HIFU system depicted in figure 9. The sound field frequency is 27 kHz, and the driving voltage is 150 Vpp. Once more we start by investigating the phenomena at a very low frequency (in order to be able to record the phenomena more easily), before turning our attention to the more common HIFU frequencies. The bubble A oscillates and travels towards the membrane ($t = 0$ to 0.4 ms). It is seen to have collapsed and formed a bubble cloud at $t = 0.5$ and 0.55 ms. Then the bubble cloud A moves across the surface of the membrane ($t = 0.7$ ms) and merges with bubble cloud B ($t = 0.75$ ms) to form bubble cloud C ($t = 0.8$ ms). Bubble cloud C continues to oscillate and move across the membrane surface until it encounters bubble D ($t = 1.25$ ms). The bubbles merge to form bubble cloud E ($t = 1.3$ ms). The cloud moves on the surface from $t = 1.7$ to 2.4 ms before it moves out of the frame.

In another experiment, a similar transducer with a higher resonance frequency of 250 kHz was used. An aluminium foil of 10 μm in thickness was placed near the focal point of the transducer about 5 cm from the transducer surface (figure 18). After sonication, small holes were observed in the aluminium foil. Bubble clouds were seen to pass through the holes, and reappear at the other side of the hole. It is very likely that individual bubbles create high-speed jets, which eventually cause sufficient damage to generate the holes on the foil. For both cases shown in figures 17 and 18, the presence of a wall greatly influences the dynamical behaviour of the bubble cloud.

At a lower driving voltage (120–150 Vpp), the bubbles form concentrated circles above the transducer (figure 19). The radii of the bubbles range between 0.25 and 1.0 mm. They are trapped in the pressure node of the standing waves. The separation between the circles is about 3 mm, which is half the wavelength of the standing waves created by the 250 kHz transducer.

In order to stabilize the bubble circles (or rings), a rigid reflector (same bowl shape as the transducer) is placed about 10 cm above the transducer (out of view in figure 19). The bubbles in the circles are not static, but move around in each circle. They may also coalesce, jump between the rings or escape altogether due to buoyancy when the size becomes sufficiently large.

When zooming in on an individual bubble in figure 19, the movement of a single bubble (dotted white line) towards a trapped bubble in the concentrated ring is shown in figure 20. The bubble has been nucleated near the large trapped bubble. It moves in a zigzag manner to the pressure node where the large bubble is trapped. The bubbles eventually coalesce. More small bubbles nucleate, move towards the large bubble, and coalesce with it. The coalescence of the bubbles increases the size of the trapped large bubble gradually. When the trapped bubble reaches a critical size of about 400 μm in diameter, the buoyancy force causes it to float upwards.

At an even lower driving voltage of 80–100 Vpp, the concentrated circles of bubbles disappear. In their place, a stream of bubbles appears to move from the transducer to the top of the water tank (figure 21). These bubbles are nucleated on the transducer surface. They move along the direction of the travelling waves and eventually float to the top of the water surface. There is no standing wave in the tank. This is because the ultrasound reflected from the free surface is too weak to form a standing wave with the ultrasound generated from the transducer. The bubble stream is funnel-shaped with a narrow middle because of the focusing effect of the sound waves from the bowl-shaped transducer.

This ends our discussion on surface oscillations, bubble clouds and streamers which occur during the application of HIFU.

4. Bubble dynamics in bioapplications, achievements and challenges ahead

As discussed in §2, ESWL is now widely accepted as a treatment for kidney stones. Bubble dynamics plays a crucial role here. HIFU is used to treat, for example, prostate cancer. It has been tested for histotripsy (mechanical tissue fractionation
using HIFU) and sonothrombolysis (removal of blood clots using sound waves). Often it is essential in medical treatments to estimate and control collateral damage to nearby tissues. The damage could be caused by cavitation bubble activities or heating of the surrounding tissue [6].

The main question, which is largely unanswered, is whether the phenomena shown above, which all occur in water-based systems, also manifest themselves in the human body when HIFU is applied. The answer to this question is not easy, as the human body is not all fluid. Also because of the high frequency of HIFU, the observation of cavitation or bubbles, even with the high-speed equipment available today, is still a major challenge. This is further complicated by the fact that most bubbles are of a very small size. It could be argued that, at least in tissue with a high water content, many of the above effects are likely to be present in some form or another. Now, if even some of the above phenomena do occur, what would be the effect of the bubbles? For example, would the occurrence of free radicals [74] outweigh the advantages of the non-invasiveness of the therapy?

In an attempt to avoid such potential problems related to HIFU in the human body itself, some research has been conducted using HIFU in a microfluidic environment. A major obstacle was the creation of cavitation bubbles in such systems (owing to a lack of nucleation spots in the small volumes of liquid involved). Tandiono et al. [75] reports the development of an ultrasonic microfluidics platform where strongly oscillating cavitation bubbles are generated. The authors have a gas inlet and a liquid in their microfluidics channel. The gas–liquid interface is excited by an external transducer around 100 kHz (the resonant frequency of the microfluidics system). The surface waves created facilitate the generation of strongly oscillating cavitation bubbles and even sonoluminescence [76]. The developed platform can potentially be used to harvest cell contents, for cell lysis or other treatments [77]. The development of HIFU for microfluidic systems is still at a very early stage though.
New areas in shock wave applications include advanced designs of transducers (electroconductive systems [78] and electromagnetic and piezoelectric sources [79]), development in clinical techniques for maximizing effectiveness of stone fragmentation [80], and minimizing collateral damage to nearby tissues and organs [81]. HIFU remains an interesting area of research. New medical applications currently being tested include the use of HIFU for essential tremor treatment [55], sonothrombolysis [82] and non-invasive detection of tumours [83]. Other areas of interest that could be mentioned are in dentistry applications [84–86], for example for root canal cleaning. Also, the incorporation of UCA microbubbles for therapeutic purposes opens a new field of possibilities apart from imaging. The backscattering from such bubbles could potentially be used for tissue property measurements.

Figure 19. Bubbles in concentric circles above the transducer operating at 250 kHz, driving voltage of 120 Vpp. The standing wave is stabilized by a rigid reflector which is placed about 10 cm above the transducer. The visible bubbles are larger than the resonance radius \( R_{\text{res}} \) (here \( R_{\text{res}} = 12 \mu m \); see appendix A). They move accordingly to the pressure nodes because of the primary Bjerknes force. (Online version in colour.)

Figure 20. The movement of a single bubble (nucleated near the left-hand side of the frame) towards the bubble trapped in the concentric ring. The small bubble has a diameter of 25 \( \mu m \), and the stationary large bubble has a diameter of 300 \( \mu m \). Many small bubbles nucleate (randomly in the water), and move towards the nearest trapped large bubble. Eventually, the large bubbles reach a critical size of about 400 \( \mu m \) in diameter. They will then float upwards due to buoyancy. The trajectory of the small bubble is that of a typical ‘dancing’ bubble as termed by Mettin & Doinikov [73]. (Online version in colour.)

5. Conclusion

Fascinating phenomena on bubble shock waves and ultrasound interaction have been shown in this review. Most of the interaction involves complex physics. Considerable progress can still be achieved in our understanding of the interplay between ultrasound, oscillating bubbles and biomaterials, which in return will benefit any potential treatment. Modelling and simulation tools are still far from achieving a complete fundamental understanding of the phenomena involved. This is especially so for the dynamics of streamers and bubble clouds such as those shown in figures 12, 14–18. The purpose of the current article, for these phenomena, far from giving an explanation, is merely to show the phenomena involved, even though we do not understand them fully, or even know under which conditions they appear. The most likely way forward is a gradual improvement in our knowledge by a combination of experimental, numerical and theoretical techniques. Fundamental understanding of bubble HIFU interaction will be facilitated by better high-speed photography techniques and higher computing power. The advantages of the non-invasiveness of sound waves for medical treatments or imaging remain a primary driving force for innovation.

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Appendix A. Basic bubble dynamics theory

Much of the physics involved in oscillating bubble dynamics can be deduced from the equation that describes the evolution of a spherical bubble, the so-called Rayleigh–Plesset
This can easily be verified by back-substitution (see also [89]). Integrating \( \frac{dR}{dt} \), with the help of a gamma-function, Rayleigh then found the Rayleigh collapse time, the time it takes for a bubble to collapse from \( r = R_0 \) to \( r = 0 \) as:

\[
t_{\text{Rayl}} = 0.914R_0 \sqrt{\frac{\rho}{p_{\text{ref}}}}. \quad (A\,4)
\]

A typical ‘time’ for a bubble is thus \( t_0 = R_0 \sqrt{\rho/p_{\text{ref}}} \). For bubbles in water under atmospheric conditions \( p_{\text{ref}} = 10^5 \text{ Pa} \), the term \( \sqrt{\rho/p_{\text{ref}}} \sim 10^{-1} \text{ s m}^{-1} \). From this it can also be deduced that a typical velocity scale for the bubble is \( u_0 = \sqrt{p_{\text{ref}}/\rho} \sim 10 \text{ m s}^{-1} \) (independent of the size of the bubble).

The pressure inside the bubble consists of the sum of two partial pressures, the vapour pressure of the water, \( p_v \) (usually negligible), and the pressure of the non-condensable gas inside the bubble, \( p_g \). Usually this is taken to behave adiabatically (as there is not much time for the bubble to exchange heat with its surroundings), i.e. \( p_g = p_{\text{ref}}(R_0/R)^\gamma \), with \( p_{\text{ref}} \) the initial gas pressure corresponding to \( R_0 \) and \( \gamma \) the ratio of specific heats of the gas (\( \gamma = 1.4 \)).

For mildly oscillating bubbles, equation (A 2) can give us further information about the resonance frequency of a bubble. Assume that the bubble oscillates around a resonance radius \( R_{\text{Res}} \), as \( R = R_{\text{Res}} + \varepsilon \sin \omega t \), with \( \varepsilon/R_{\text{Res}} \ll 1 \). such that \( \frac{dR}{dt} = \varepsilon \omega \cos \omega t \) and \( \frac{d^2R}{dt^2} = \varepsilon \omega^2 \sin \omega t \). Substituting these in equation (A 2) and noting that the first term is of order \( \varepsilon^2 \) while only retaining terms of order \( \varepsilon \):

\[
-\rho R_{\text{Res}} \varepsilon \omega^2 \sin \omega t = p_{\text{ref}} \left( \frac{R_{\text{Res}}}{R_{\text{Res}} + \varepsilon \sin \omega t} \right)^{3\gamma} - p_{\text{ref}} \\
\approx p_{\text{ref}} \frac{3\gamma p_{\text{ref}}}{R_{\text{Res}}} \varepsilon \sin \omega t - p_{\text{ref}}. \quad (A\,5)
\]

This simplifies to (note that \( p_{\text{ref}}/p_{\text{ref}} = \varepsilon^2 \approx 3\gamma p_{\text{ref}} (R_{\text{Res}}/\rho) \); if the angular frequency is replaced by \( \omega = 2nf \), then, finally, the Minnaert resonance frequency [90] for standard water under atmospheric pressure is recovered:

\[
f_{\text{Res}} \approx \frac{1}{2\pi} \sqrt{\frac{3\gamma p_{\text{ref}}}{\rho}} \approx 3 \text{ m s}^{-1}.
\]

This result is very useful when dealing with low-amplitude sound waves interacting with bubbles. For example, a frequency of \( f = 100 \text{ kHz} \) would give \( R_{\text{Res}} = 30 \mu m \) (for higher frequencies surface tension effects become important [6]). If the bubbles in a standing acoustic wave are smaller than \( R_{\text{Res}} \) they will travel to the pressure antinodes, while bubbles larger than \( R_{\text{Res}} \) will move to the pressure nodes instead. A specially designed highly accurate numerical BEM without singularities which was recently developed for sound waves [91] would perhaps be useful for an even better understanding of the scattering phenomena involved in these situations. Surface tension, liquid viscosity and compressibility can be included in more advanced versions of the above shown equations relatively easily.