Introduction to Antibubbles. Proceedings of the 38th Scandinavian Symposium on Physical Acoustics, Geilo 1– 4 February 2015. Editor: Rolf J. Korneliussen, ISBN: 978-82-8123-015-6

Introduction to Antibubbles

Kristoffer Johansen[a], Spiros Kotopoulis[a,b], and Michiel Postema[a,c,*]

[a]*Department of Physics and Technology, University of Bergen, Allégaten 55, 5007 Bergen, Norway*
[b]*National Centre for Ultrasound in Gastroenterology, Haukeland University Hospital, Jonas Lies vei 65, 5021 Bergen, Norway*
[c]*Department of Physics, University of Witwatersrand, 1 Jan Smuts Avenue, Johannesburg, South Africa*
[*]*Contact author: Michiel.Postema@ift.uib.no*

Bubbles are emptiness, microscopic clouds surrounded by the world. Born by chance with a violent and brief life, collapsing in a union with the infinite [1]. Remarkably similar to the life of a human being. However, there are some discrepancies when comparing the life of a bubble, and that of a human being. For example, the nature of the acoustically active bubble is described by the language of mathematics, where understanding the behaviour of bubble dynamics has been a goal for physicists for centuries [2]. However, not only physicists have been enchanted by the intrinsic beauty encompassed in the simplicity of a bubble. Throughout history bubbles have been a symbol in art.

From the antique, the Greek rhetorician and novelist Lucian of Samosata (ca. 117–180 AD) wrote with his typical characteristic wit when describing human life: " *I've thought of a simile to describe human life as a whole (...) You know the bubbles that rise to the surface below a waterfall–those little pockets of air that combine to produce the foam? (...) Well, that is what human beings are like. They're more or less inflated pockets of air (...) but sooner or later they're bound to go pop. [3]*" Using bubbles as a metaphor to describe human life has given bubbles an iconographic role in Western culture.

Fortunes in economics can be created by chance. Some oscillate in size during their lifespan, analogously to acoustically active bubbles in the physical world, which oscillate when excited by an acoustic wave. Under the right conditions fortunes may grow non-linearly, and suddenly collapse into nothingness. Some fortunes can even leave a permanent impact on the world in which they were created. Once again an analogy to the life and death of the acoustically active bubble can be made. Namely, under the right acoustic conditions bubbles oscillate highly non-linearly, and in some acoustic regimes they collapse. The collapse of the acoustically active bubble can give rise to several phenomena, *i.e.*, acting as a source of shock waves [4] or the creation of microjets with destructive power [5,6].

Shock waves emitted by acoustically active bubbles during multiple collapses are periodic in nature, provided there is a strong acoustic field [4]. However, it is interesting to note that the same periodicity of bubbles collapsing and sending out shock waves throughout society, can be appreciated in economics [7]. Moreover, collapsing fortunes in economics are often depicted as bubbles [8]. There is nothing to support a continued existence of what has been created, and the bubble becomes unstable. A recent example is the subprime lending and collapse of the housing market in the USA [9]. Where two separate interconnected economic bubbles grew out of proportion, lacking structural foundation, and terminating in a collapse in both markets, sending shock waves around the world. It is important here to note that bubbles in economics interact, and as they interact a larger bubble is formed which behaves differently compared to how the two bubbles behave separately.

Conversely, the analogues phenomenon can be observed for acoustically active bubbles. When two bubbles oscillate in phase as a result of an acoustic excitation they will experience a force of mutual attraction, this is due to secondary radiation forces [10]. As the bubbles approach each other they will start to interact, where they will either coalesce [11] or cluster together forming microfoam [12]. A cluster of microfoam is essentially just a greater bubble composed of several smaller bubbles interacting. Both of the two respective phenomena mentioned above change the dynamics of the complete system with respect to the initial behaviour when separated. Indeed, similar to what is observed in economics when bubbles develop and interact over time.

From these examples it can be appreciated that bubble dynamics in physics has clear analogies to bubble dynamics in economics. Linear and non-linear oscillations [13], primary radiation forces [10], secondary radiation forces, fragmentation [14], coalescence [11], microfoam formation [12], shock wave emission [4], and microjetting [5,6] are all important phenomena in bubble-physics, serendipitously direct equivalents can be found in economics when trying to understand the life and death of a bubble.

Although it is interesting to understand the iconographic role of bubbles in Western culture, that is not the prime objective of this thesis. This thesis is based on three published articles:*Acoustically Active Antibubbles* [15], *Ultrasonic Driven Antibubbles Encapsulated by Newtonian Fluids for Active Leakage Detection* [16], and *Acoustic Filtering of Particles in a Flow Regime* [17]. Overall the objective of this thesis is to derive the fundamental equations of antibubble dynamics. Starting from the simplest system that can be imagined, an antibubble with no shell in an ideal fluid, to solving the most complex system, the spatio-temporal dynamics of antibubbles with a shell in Newtonian viscous surrounding fluid. The results are analysed with respect to applying antibubbles for clinical diagnostic imaging, targeted drug and gene delivery, and active leakage detection from subsea production facilities. Furthermore, motivated by our understanding of how sound fields interact with microscopic particles, a separate study is conducted, where we utilise this strong interaction to create an acoustic filter for streaming fluids contaminated by microscopic particles.

Ultrasound contrast agents consist of microscopically small gas bubbles, encapsulated by elastic shells. These agents are commonly used in clinical diagnostic imaging to enhance the acoustic contrast between blood and other tissues to improve the quality of ultrasonic images [18]. Furthermore, ultrasound contrast agents are employed in therapy as a vehicle for targeted drug and gene delivery. This process is defined as sono dynamic therapy, the transient formation of micron-sized pores in cell membranes induced by ultrasound in combination with microbubbles [19]. This technique shows promise in cancer treatment as it allows increased localised drug delivery [20,21]. Nevertheless, during sono dynamic therapy treatment, patients are still affected by systemic side effects as the chemotherapeutics are still systemically delivered. An ideal solution to this problem would be to encapsulate a therapeutic load into a delivery tool and to release it at the desired location.

Many attempts have been made to incorporate chemotherapeutics into microbubbles [22]. The most common technique is to embed or bond a therapeutic load into the microbubbles' shell [23,24]. However, adding a thick viscoelastic layer to a microbubble greatly impedes its oscillation amplitude, making it challenging to disrupt and release its therapeutic load at low acoustic amplitudes. A solution would be to incorporate the therapeutic load into the gas core of the microbubble. Such antibubbles should allow for easy manipulation and disruption in sound fields [25]. Figure 1 presents a schematic drawing of an antibubble.

Stable, micron-sized antibubbles have already been produced. These have a load volume of approximately half the entire bubble volume, significantly higher than with any other loading method [26,27]. Figure 2 shows a microscopy image of an antibubble.

Using harmonic imaging methods in combination with ultrasound contrast agents, it is possible to effectively evaluate whether patients have leakage of blood from veins and arteries as a complication after surgery [28,29]. Antibubbles, who carry the same properties as ultrasound contrast agents, should in principle be applicable in a completely different field. Thus, translating the knowledge from clinical diagnostic ultrasound, it is hypothesised that acoustically driven antibubbles can be used for active leakage detection from subsea production facilities [16].

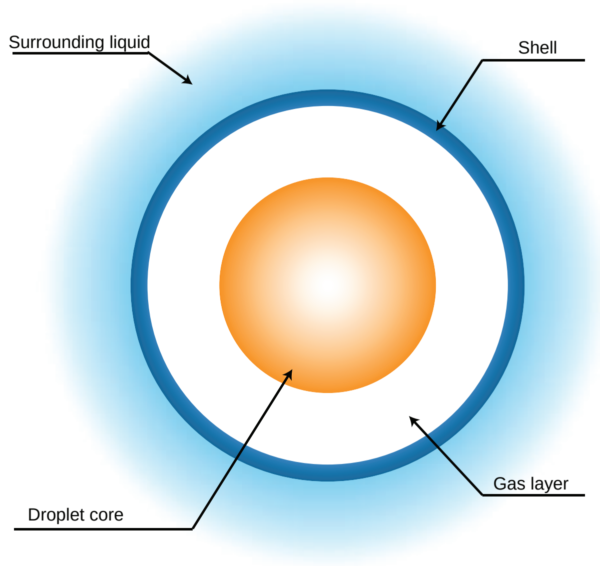

Figure 1: Schematic drawing of liquid (light blue) containing and antibubble cosisting of a droplet core (brown), surrounded by a gas layer (white) and with a thin shell (dark blue).

Recently, it has been proposed to locate offshore hydrocarbon production facilities subsea instead of at the surface [30]. Locating production facilities subsea is not only to decrease cost, but also to initiate production of hydrocarbons at greater depths. Furthermore, several of the new production fields in the Northern Hemisphere are placed in Arctic climates. Therefore, low temperatures are becoming a major challenge. Hence, using subsea production plants to extract hydrocarbon in such region solves several problems.

However, when establishing subsea production plants, it is essential to secure appropriate maintenance surveillance. An up-and-coming method is ultrasound-based active leakage detection [31]. This is achieved by studying the composition of sound scattered back to the ultrasound source. Knowing that gas bubbles scatter sound more effectively than solid objects or liquids, it is possible to differentiate them [29,31]. In oil exploration, the flow coming up from the reservoir is a mixture of water, oil and gas. Therefore it can be assumed that leaks from subsea production facilities inhibit the three components necessary for the production of antibubbles [32]: gas, a hydrophobic liquid, and water containing plenty of surface-active agents. Mixing under the right conditions might create a gas cavity with a droplet core of a hydrophobic liquid, and a thin shell of surface-active agents. It is therefore of interest to understand, from a theoretical point of view, how antibubbles with an encapsulation behave in a sound field. Increased understanding could lead to improved active leakage detection, clinical diagnostic imaging and targeted drug and gene delivery.

Lord Rayleigh was the first to publish on the radial pulsation of a gas cavity when subjected to an external pressure change [33], Plesset also contributed to the development of what today is known as the Rayleigh-Plesset equation [34]. The pioneering work done by these researchers were motivated towards understanding the dynamics of the cavitation phenomenon observed on ship propellers [33].

All current models for bubble dynamics, both uncapsulated and encapsulated have their origin in the Rayleigh-Plesset equation for a free gas bubble. Antibubbles are fundamentally

Figure 2: Optical microscopy image of antibubble with single core.

different from gas bubbles because of an incrompressible droplet core in the centre of the bubble. Nevertheless, the first mathematical model for an acoustically active antibubble is derived during the work on this thesis. This Rayleigh-Plesset-like equation enables us to study differences in oscillator behaviour compared to gas bubbles, both with and without an encapsulating shell [15].

Although many papers have been written on the dynamic behaviour of free and encapsulated microbubbles, especially on ultrasound contrast agents [35], only two paper has been published on acoustically active antibubbles [15,16]. Here the term microbubbles is defined as gas bubbles with a diameters less than 10 μm.

References

[1] A. Prosperetti, "Bubbles," *Phys. Fluids*, vol. 16, no. 6, pp. 1852–1865, 2004.

[2] T.G. Leighton, *The Acoustic Bubble*. Academic Press, London, 1994.

[3] Lucian of Samosota, "Charon of the Inspectors, in Works," *Harvard University Press, Cambridge MA*, vol. 2, p. 434, first print 1915, reprinted 1991.

[4] K. Johnston, C. Tapia-Siles, B. Gerold, M. Postema, S. Cochran, A. Cuschieri, and P. Prentice, "Periodic shock-emission from acoustically driven cavitation clouds: a source of the subharmonic signal." *Ultrasonics*, vol. 54, no. 8, pp. 2151–2158, 2014.

[5] P. Prentice, A. Cuschieri, K. Dholakia, M. Prausnitz, and P. Campbell, "Membrane disruption by optically controlled microbubble cavitation," *Nat. Phys.*, vol. 1, no. 2, pp. 107–110, 2005.

[6] M. Postema, A. van Wamel, F. J. ten Cate, and N. de Jong, "High-speed photography during ultrasound illustrates potential therapeutic applications of microbubbles," *Med. Phys.*, vol. 32, no. 12, p. 3707, 2005.

[7] J. J. van Duijn, “The long wave in economic life,” *Economist (Leiden).*, vol. 125, no. 4, pp. 544–576, 1977.

[8] C. Perez, “The double bubble at the turn of the century: technological roots and structural implications,” *Cambridge J. Econ.*, vol. 33, no. 4, pp. 779–805, 2009.

[9] M. Coleman, M. LaCour-Little, and K. D. Vandell, “Subprime lending and the housing bubble: Tail wags dog?” *J. Hous. Econ.*, vol. 17, no. 4, pp. 272–290, 2008.

[10] P. A. Dayton, K. E. Morgan, A. L. S. Klibanov, G. Brandenburger, K. R. Nightingale, and K. W. Ferrara, “A preliminary evaluation of the effects of primary and secondary radiation forces on acoustic contrast agents,” *IEEE Trans. Ultrason. Ferroelectr. Freq. Control.*, vol. 44, no. November, pp. 1264–1277, 1997.

[11] M. Postema, P. Marmottant, C. T. Lancée, S. Hilgenfeldt, and N. de Jong, “Ultrasound-induced microbubble coalescence.” *Ultrasound Med. Biol.*, vol. 30, no. 10, pp. 1337–1344, 2004.

[12] S. Kotopoulis and M. Postema, “Microfoam formation in a capillary.” *Ultrasonics*, vol. 50, no. 2, pp. 260–268, 2010.

[13] A. Prosperetti, “Bubble phenomena in sound fields: part two,” *Ultrasonics*, vol. 22, no. 3, pp. 115–124, 1984.

[14] M. Postema, A. van Wamel, C. T. Lancée, and N. de Jong, “Ultrasound-induced encapsulated microbubble phenomena.” *Ultrasound Med. Biol.*, vol. 30, no. 6, pp. 827–840, 2004.

[15] S. Kotopoulis, K. Johansen, O. H. Gilja, A. T. Poortinga, and M. Postema, “Acoustically Active Antibubbles,” *Acta Physica Polonica A*, vol. 127, no. 1, pp. 1115–1118, 2015.

[16] K. Johansen, S. Kotopoulis, and M. Postema, “Ultrasonic driven antibubbles encapsulated by newtonian fluids for active leakage detection,” *IAENG*, 2015, in press.

[17] K. Johansen, T. Yddal, S. Kotopoulis, and M. Postema, “Acoustic filtering of paricles in a flow regime,” in *IEEE Int. Ultrason. Symp. Proc.*, 2014, pp. 1436–1439.

[18] C. Dietrich, Ed., *EFSUMB–European Course Book*. EFSUMB, London, 2012.

[19] M. Postema and O. Gilja, “Ultrasound-directed drug delivery,” *Curr. Pharm. Biotechnol.*, vol. 8, no. 6, pp. 355–361, 2007.

[20] S. Kotopoulis, A. Delalande, M. Popa, V. Mamaeva, G. Dimcevski, O. H. Gilja, M. Postema, B. r. T. Gjertsen, and E. McCormack, “Sonoporation-enhanced chemotherapy significantly reduces primary tumour burden in an orthotopic pancreatic cancer xenograft.”*Mol. Imaging Biol.*, vol. 16, no. 1, pp. 53–62, 2014.

[21] S. Kotopoulis, G. Dimcevski, O. H. Gilja, D. Hoem, and M. Postema, “Treatment of human pancreatic cancer using combined ultrasound, microbubbles, and gemcitabine: a clinical case study.” *Med. Phys.*, vol. 40, no. 7, 2013.

[22] M. Postema and O. Gilja, “Contrast-enhanced and targeted ultrasound,”*World J. of Gastroenterol.*, vol. 17, no. 1, pp. 28–41, 2011.

[23] D. J. May, J. S. Allen, K. W. Ferrara, and S. Member, “Dynamics and fragmentation of thick-shelled microbubbles,” *IEEE Trans. Ultrason. Ferroelectr. Freq. Control.*, vol. 49, no. 10, pp. 1400–1410, 2002.

[24] M. J. Shortencarier, P. A. Dayton, S. H. Bloch, P. A. Schumann, T. O. Matsunaga, K. W. Ferrara, and S. Member, "A method for radiation-force localized drug delivery using gas-filled lipospheres," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control.*, vol. 51, no. 7, pp. 822–831, 2004.

[25] M. Postema, F. ten Cate, G. Schmitz, N. de Jong, and A. van Wamel, "Generation of a droplet inside a microbubble with the aid of an ultrasound contrast agent: first result," *Lett. Drug Des. Discov.*, vol. 4, no. 1, pp. 74–77, 2007.

[26] A. T. Poortinga, "Long-lived antibubbles: stable antibubbles through pickering stabilization." *Langmuir*, vol. 27, no. 6, pp. 2138–2141, 2011.

[27] J. E. Silpe, J. K. Nunes, A. T. Poortinga, and H. A. Stone, "Generation of antibubbles from core − shell double emulsion templates produced by micro fluidics," *Langmuir*, vol. 29, no. 28, pp. 8782–8787, 2013.

[28] P. J. Bendick, P. G. Bove, G. W. Long, G. B. Zelenock, O. W. Brown, and C. J. Shanley, "Efficacy of ultrasound scan contrast agents in the noninvasive follow-up of aortic stent grafts." *J. Vasc. Surg.*, vol. 37, no. 2, pp. 381–5, 2003.

[29] P. J. Frinking, A. Bouakaz, J. Kirkhorn, F. J. ten Cate, and N. de Jong, "Ultrasound contrast imaging: current and new potential methods," *Ultrasound Med. Biol.*, vol. 26, no. 6, pp. 965–975, 2000.

[30] J. Moreno-Trejo and T. Markeset, "Mapping Factors Influencing the Selection of Subsea Petroleum Production Systems," in *Adv. Prod. Manag. Syst. Value Networks Innov. Technol. Manag.* Springer, 2012, pp. 242–250.

[31] D. Miller, "Ultrasonic detection of resonant cavitation bubbles in a flow tube by their second-harmonic emissions," *Ultrasonics*, vol. 19, no. 5, pp. 217–224, 1981.

[32] H. C. S. Dorbolo and N. Vandewalle, "Fluid instabilities in the birth and death of antibubbles," *New J. Phys.*, vol. 5, no. 161, pp. 1–9, 2003.

[33] L. Rayleigh, "On the pressure developed in a liquid during the collapse of a spherical cavity," *Philos. Mag.*, vol. 34, no. 200, pp. 94–98, 1917.

[34] M. Plesset, "The dynamics of cavitation bubbles," *ASME J. Appl. Mech.*, vol. 16, pp. 277–282, 1949.

[35] A. A. Doinikov and A. Bouakaz, "Review of shell models for contrast agent microbubbles." *IEEE Trans. Ultrason. Ferroelectr. Freq. Control*, vol. 58, no. 5, pp. 981–993, 2011.