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TOPICAL REVIEW

Acoustic holography in biomedical applications

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Abstract

Acoustic holography can be used to construct an arbitrary wavefront at a desired 2D plane or 3D volume by beam shaping an emitted field and is a relatively new technique in the field of biomedical applications. Acoustic holography was first theorized in 1985 following Gabor's work in creating optical holograms in the 1940s. Recent developments in 3D printing have led to an easier and faster way to manufacture monolithic acoustic holographic lenses that can be attached to single-element transducers. As ultrasound passes through the lens material, a phase shift is applied to the waves, causing an interference pattern at the 2D image plane or 3D volume, which forms the desired pressure field. This technology has many applications already in use and has become of increasing interest for the biomedical community, particularly for treating regions that are notoriously difficult to operate on, such as the brain. Acoustic holograms could provide a non-invasive, precise, and patient specific way to deliver drugs, induce hyperthermia, or create tissue cell patterns. However, there are still limitations in acoustic holography, such as the difficulties in creating 3D holograms and the passivity of monolithic lenses. This review aims to outline the biomedical applications of acoustic holograms reported to date and discuss their current limitations and the future work that is needed for them to reach their full potential in the biomedical community.

1. Introduction

Holography is the process of recording an interference pattern by recording both the phase and amplitude of a wave and then reconstructing this interference pattern in a 3D volume (Hariharan 2002). Holography was first introduced in optics by Gabor in 1948 as a way of reconstructing interference patterns recorded from a coherent light source to form a 3D visible image (Gabor 1948). To record and reconstruct an optical hologram, a light beam is split into two, using a beam splitter. One beam is reflected by the object which is to be reconstructed by the hologram, onto a photographic plate, whilst the other falls directly onto the plate (Andrulevičius 2011). The two beams then interfere with each other, and the interference pattern is recorded on the photographic plate. The hologram can then be reconstructed using the same two beams from opposite directions (Andrulevičius 2011). At the time, Gabor's work was used mainly for microscopy. However, as technology advanced, new holography methods were developed for applications in security (Grigaliunas *et al* 2005), data storage (Hesselink *et al* 2004), and other areas (Gabor 1948, Andrulevičius 2011, Dhirubhai *et al* 2015).

Similar holographic principles were later applied in acoustics when Maynard *et al* theorized near-field acoustic holography in 1985 (Maynard *et al* 1985). This breakthrough allowed better characterization of acoustic properties of materials and elastic properties of submerged objects (Sternini *et al* 2020). Acoustic holography is a method of generating distributions of pressure in 3D volumes using sound waves, for example using sound waves in air or using ultrasound in water.

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Ultrasound has been studied for many decades due to its ability to seamlessly propagate through biological tissues and has been used in multiple biomedical applications, such as in ultrasound imaging (Wells 2006), high intensity focused ultrasound (HIFU) (Maloney and Hwang 2015, ter Haar and Coussios 2007), or physiotherapy (Robertson 2002).

In the biomedical field, acoustic holograms using ultrasound have many applications, including providing an appealing alternative for conventional focused ultrasound (FUS) therapies (Burgess *et al* 2011, Fishman and Frenkel 2017, Gorick *et al* 2022). FUS is a useful tool for minimally invasive surgery; it is a tightly focused beam of ultrasound which allows small areas to be targeted (Lynn *et al* 1942, Fishman and Frenkel 2017). FUS has been used clinically for non-invasive ablation of benign and malignant tumours (Kennedy 2005), uterine fibroids (Kong *et al* 2014), and breast cancer (Roubidoux *et al* 2014). It has been widely used for histotripsy which uses the mechanical effects of HIFU to ablate tissue and treat diseases such as blood clots, prostate cancer, and neurological diseases (Xu *et al* 2021, 2024). It is also being used to induce localized bio-effects, such as non-invasive and safe opening of the blood–brain barrier (BBB) to deliver drugs to the brain (Choi *et al* 2010, Marty *et al* 2012, Englander *et al* 2021). BBB opening for drug delivery using FUS has been used in multiple pre-clinical studies (Gorick *et al* 2022) and clinical trials to treat central nervous system pathologies such as Alzheimer's disease (D'Haese *et al* 2020) and brain tumours (Anastasiadis *et al* 2021).

Ultrasound can be delivered to the body using single-element transducers and phased array transducers (PATs); a single-element transducer can only target one location at a time and has a fixed focal volume. However, it is relatively simple and has a low associated cost (Antoniou and Damianou 2024). PATs on the other hand can target locations sequentially within a wider region but are very complex and expensive compared to single-element transducers. However, they are more precise and can allow real-time electronic steering, by independently controlling multiple ultrasound sources in phase and amplitude (Payne *et al* 2011). Acoustic holograms provide a more precise and cheaper alternative to phased arrays and can be combined with either a single-element or a multi-element transducer.

Acoustic holography has a very wide range of applications, including 3D ultrasound imaging (Kruizinga *et al* 2017), contactless power transfer (Bakhtiari-Nejad *et al* 2018), creation of Bessel beams (Jiménez *et al* 2016a, Jiménez-Gambín *et al* 2019a), contactless manufacturing (Melde *et al* 2018, 2023), and generation of self-bending ultrasound beams (Jiménez-Gambín *et al* 2019b).

This review will outline the biomedical applications of acoustic holograms reported to date, such as BBB opening, hyperthermia, cell patterning, tissue patterning, and holographic acoustic tweezers. It will also discuss the current limitations and prospects of acoustic holography in the biomedical field.

1.1. What are acoustic holograms?

To design a holographic lens, the required phase profile for a target can be calculated computationally and can then be converted to height values to form the lens topography. The transmission hologram or holographic lens can be manufactured by 3D printing or use of a mould. The surface of the lens encodes the phase information to reconstruct the desired wavefront. To create a hologram image, the lens is placed in front of a single-element transducer and an acoustic wave propagates through the lens material. When ultrasound passes through the lens, each of its voxels acts as an elastic column of the hologram, and vibrates longitudinally as a Fabry–Perot resonator, applying a phase shift to the passing wave (Jiménez *et al* 2016b). This produces an interference pattern which creates the desired waveform at the image plane. This process is shown in figure 1 (Melde *et al* 2016).

A hologram can be used with a single-element transducer, like in figure 1, which offers an advantage over the more complex and costly PATs used in biomedical ultrasound. However, phased array-based acoustic holograms are also a powerful tool for controlling ultrasound fields and offer the ability to actively control the hologram in real-time for many applications, including ablation correction (Hertzberg and Navon 2011), tissue ablation (Glickstein *et al* 2024), and ultrasound imaging (Ilovitsh *et al* 2018). These holograms use an array of transducers which are individually controlled to focus the acoustic waves in an arbitrary location. For example, Hertzberg *et al* used this technique for multi-focal targeting in a tissue phantom with the view to perform patterned neuromodulation (2010). Other groups have developed this with deep learning methods to provide more computationally efficient and highly accurate holograms (Schein *et al* 2023, Wang *et al* 2023).

Acoustic holograms also scale better with a higher information density (i.e. the number of pixels a hologram contains) than phased arrays. The information density is limited by the 3D printer's resolution capabilities. For example, a lens with an aperture of 50 mm printed with resolution 100 μm would have 192 000 acoustic elements, which is much higher than the elements possible in PATs (Melde *et al* 2016). The resolution of the pressure field, and therefore the complexity and cost, of a phased array scales with the number of independent inputs. Arrays of 1024 elements have been constructed, but this is still an order of

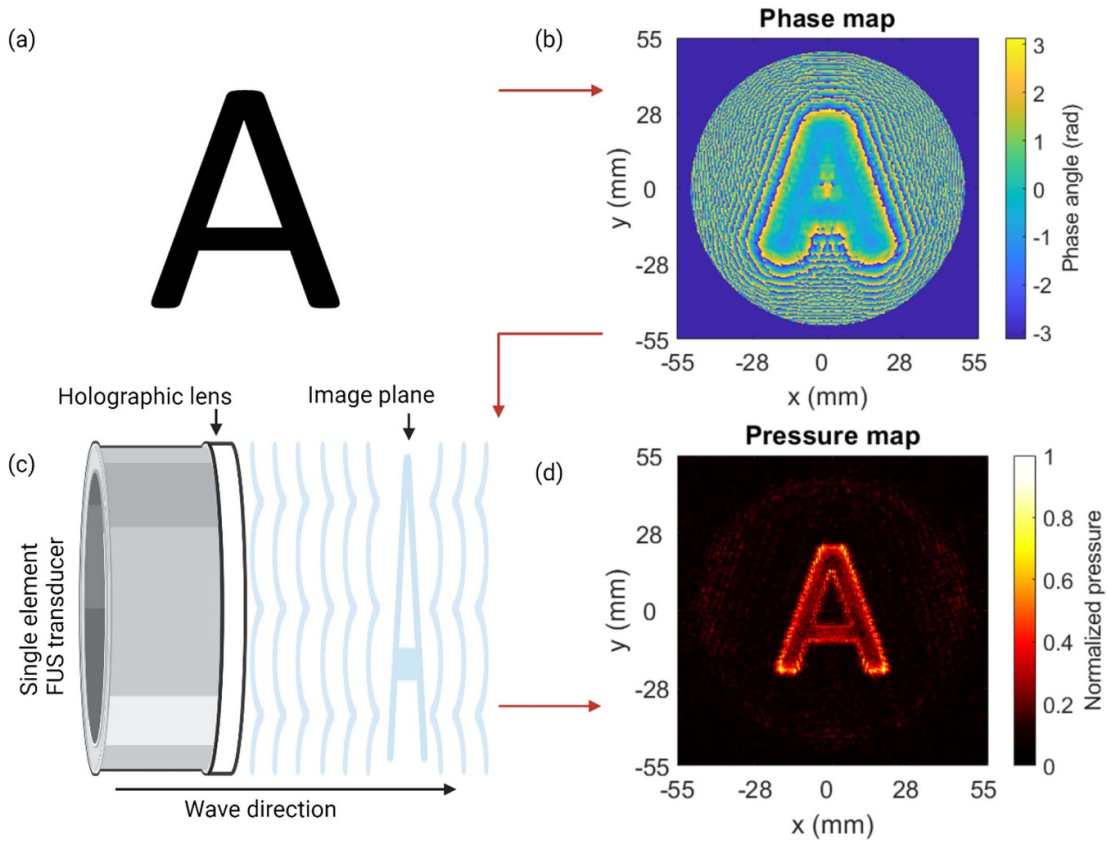


Figure 1. Overview of the acoustic holography method to reconstruct an arbitrary image with a phase-only hologram. (a) Target acoustic image, (b) computed phase distribution at the holographic plane at the transducer surface, (c) arbitrary acoustic image generation on the image plane following transmission of a planar ultrasound wave through a holographic lens, and (d) reconstructed image created by the acoustic hologram.

magnitude less than a 3D-printed hologram (Cox *et al* 2019). Modern 3D printers can achieve 20 μm resolution, which can be used throughout the typical frequency range of ultrasound applications. For example, BBB opening, and neuromodulation applications are typically conducted at sub-MHz frequencies (Melde *et al* 2016, Ferri *et al* 2019b), therefore acoustic holograms are a promising alternative to PATs in such applications.

Another key advantage of acoustic holograms is their ability to be used for aberration correction. Aberrations, such as those produced by the skull, are caused by inhomogeneities in the material and degrade the focusing quality for transcranial applications (Pinton *et al* 2012, Kyriakou *et al* 2014). Acoustic holograms can account for these aberrations, increasing the energy delivered to the target area and reducing out-of-target volume treated by the ultrasound beam, hence offering an improved focus quality (Maimbourg *et al* 2018, Ferri *et al* 2019b).

2. Holography method

2.1. Acoustic hologram design

To create an acoustic hologram a single-element transducer is coupled with an acoustic lens and ultrasound is propagated through it to create the desired wavefront in the target volume.

The following steps provide an example of how to create a phase-only acoustic hologram that focuses ultrasound on a desired volume.

1. When there are large inhomogeneities in a medium, the acoustic properties need to be obtained before designing the acoustic hologram. For example, for applications in the body, a CT scan of the area of the body to be targeted can be obtained and used to derive the speed of sound and density of the medium using empirical linear relationships (Mast 2000). When designing holograms in free-field or homogeneous media this step is not necessary.
2. Establish the simulation grids and acoustic maps by performing a 3D linear interpolation on the acoustic properties.

3. Perform the time reversal method using back-propagation simulations, where the acoustic source is defined as the target volume (Bacot *et al* 2016). Other methods, such as the iterative angular spectrum approach, can also be used for this step (Melde *et al* 2016, Schoen and Arvanitis 2020). Software such as *k*-wave (Treeby and Cox 2010) or SimSonic (Bossy 2012) can be used to perform this numerical simulation.
4. For a phase-only hologram, the phase information at the desired frequency at the holographic plane (normally defined as the exit plane of the transducer) is recorded. However, holograms can be designed retaining the phase and amplitude information for a more energy efficient lens (Brown 2019).
5. Using an interpolation method, the corrective acoustic lens profile can be calculated from the complex conjugate of the phase information, which accounts for the temporal inversion in the simulations.
6. The lens can then be manufactured and coupled to a transducer. The varying height of the lens elements produces the required phase shift to passing sound waves to cause the interference pattern, forming the intended hologram at the image plane or volume. The phase shift is dependent on the acoustic properties of the lens material, which must be acquired before the design process and must be sufficiently different from the properties of water to allow a large enough phase change for even the shorter height values.

Maimbourg *et al* manufactured the local lens thickness using 3D printed casting moulds, which were fastened to a single-element transducer. The silicone lens was cast using commercial silicone, and the mould was removed leaving a silicone acoustic lens attached to the transducer. The transducer could then generate a signal which would pass through the lens and the skull, generating a focus in the desired brain area (Maimbourg *et al* 2018). However, other studies have been successful by 3D printing the holographic lens directly (Zhang *et al* 2018, Andrés *et al* 2022a).

Whilst the Gerchberg–Saxton algorithm described here is a widely used and effective method for phase-only holograms, other methods such as the pseudo-inverse algorithm (Ebbini and Cain 1989) or the conjugate field method (Ibbini and Cain 1989) have been used for hologram generation. The pseudo-inverse algorithm is often computationally more efficient and faster to solve compared to the Gerchberg–Saxton algorithm, which is best suited for simpler, low noise problems. The conjugate field method provides a more general algorithm that can be used with a wider range of constraints but is often much slower to converge on a stable solution, particularly for phase only problems, which the Gerchberg–Saxton algorithm is best suited to.

Recently, the use of machine learning has also been combined with hologram design methods, and deep learning-based frameworks have been used to improve the computational speed and accuracy of acoustic hologram design compared to the methods discussed in this section (Lee *et al* 2022).

2.2. Acoustic hologram measurement

Pressure fields generated by acoustic holograms can be measured using conventional equipment such as microphones and hydrophones. This makes the recording and reconstruction process easier and simpler than optical holograms because a reference beam does not need to be recorded (Muthaporn 2021). As an example, figure 2 shows an *ex vivo* experimental setup, where a human skull fragment is positioned in a custom holder with the transducer and lens attached. An arbitrary waveform generator is used to produce a signal which is amplified and applied to the FUS transducer. A needle hydrophone is then used to measure the acoustic pressure field so that it can be recorded using a digital oscilloscope and displayed on the PC (Maimbourg *et al* 2018). The needle hydrophone can be moved incrementally, and pressure values measured at each position to build up a raster scan of the pressure distribution.

Although hydrophone measurements are the gold standard for evaluating the spatial distribution of pressure fields, they are time consuming, require large data storage, and cannot be used *in vivo*. Other methods to measure pressure fields include thermochromic detectors which can be used to measure the acoustic intensity across multiple image planes (Zhang *et al* 2020), or acoustic cavitation patterns (Kim *et al* 2021). Imaging with MRI can also be used *in vivo* to measure the effects of acoustic holograms, such as measuring the BBB opening and performing thermometry to see an increase in tissue temperature, and it has been used widely in FUS experiments to guide the treatment in real-time (Hokland *et al* 2006, Lipsman *et al* 2013).

Errors can be the cause of many of the limitations in acoustic holography. Sapozhnikov *et al* detail how to take measurements using acoustic holography, and which errors are important to control and consider (2015). Field sampling errors are caused by errors inherent to the acoustic holography technique, such as timing and positioning uncertainties. Sapozhnikov *et al* also discuss geometrical errors which are due to uncertainties of the positions in which measurements are taken. Temperature errors are caused by acoustic holography's dependency on properties of the propagation medium, such as speed of sound and the density of the medium which alter with temperature. If the temperature changes during a measurement, the acoustic

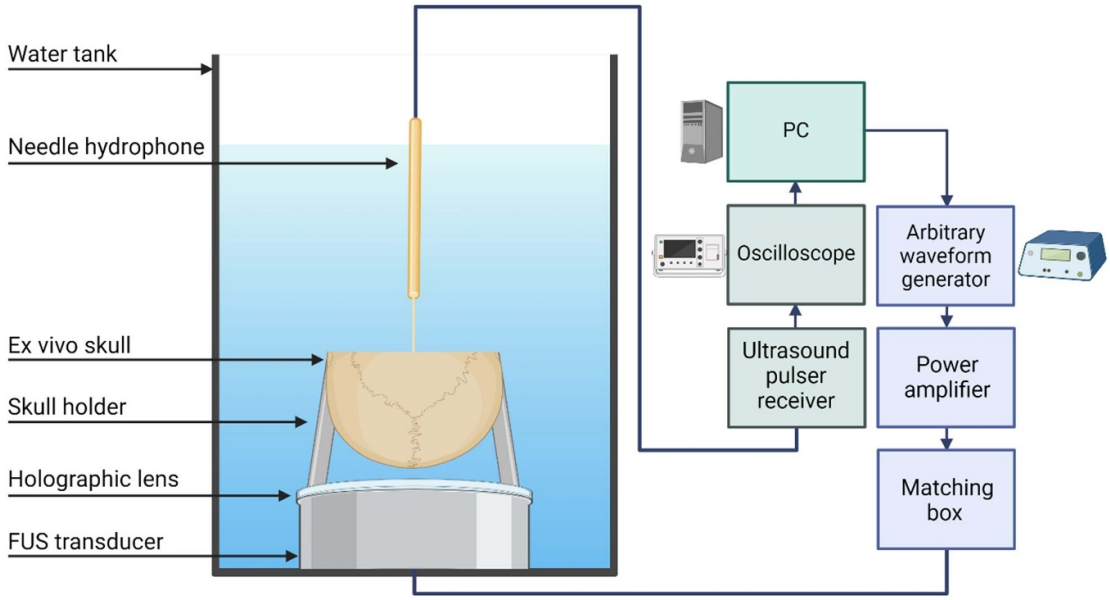


Figure 2. Experimental setup used to generate a hologram image through an ex vivo human skull fragment and measure it using a needle hydrophone, which is used to produce a pressure profile of the image plane following a raster scan.

field may also change. It is suggested the temperature uncertainty should be ±1 °C to avoid an error greater than 1% (Sapozhnikov *et al* 2015).

3. Applications of holograms

Acoustic holography could prove to be a powerful technique in biomedical applications; techniques such as particle control, cavitation patterning, cell patterning, and hyperthermia could provide treatments to a range of pathologies. Figure 3 shows some of the medical applications of acoustic holograms.

3.1. Cavitation

3.1.1. Cavitation patterning

Acoustic cavitation is a phenomenon that can be used for local therapeutic effects *in vivo* and in other biomedical applications. It is the process of creating and collapsing endogenous bubbles, or driving exogenous bubbles (for example, systemically administered microbubbles) into volumetric oscillations in a liquid medium using the alternating phases of ultrasound waves (Pouliopoulos *et al* 2020a, McCune *et al* 2021). The dynamics of acoustic cavitation can be monitored using passive cavitation detection (PCD) (Tung *et al* 2010, Haworth *et al* 2012, 2015) or passive acoustic mapping (Jones *et al* 2015, Arvanitis *et al* 2017, Pouliopoulos *et al* 2020b, Kamimura *et al* 2021). Acoustic holograms have also been combined with these monitoring systems where a lens has been used to steer the directivity of a PCD and compensate for any aberrations between the PCD and cavitation location, so that cavitation can be locally monitored externally from the system (Lamothe *et al* 2024).

The use of acoustic holography for cavitation patterning could allow more precise targeting of the ultrasound beam and an arbitrarily shaped cavitation field (Kim *et al* 2021). Kim *et al* used microbubble destruction patterns in a gelatine phantom block in a 2D plane to demonstrate this (2021). They demonstrated the advantages of acoustic holography for cavitation patterning: improved resolution of the targeted beam, reduced cost due to the simple manufacturing of a 3D printed lens, and a simple setup, as only a single transducer is required. Whilst their work is significant by demonstrating this technique in 2D, it could be further developed to create precise 3D cavitation patterns with multi-focal planes (Kim *et al* 2021).

3.1.2. Brain applications

BBB opening is one example of how cavitation can be used for medical applications in the brain. The BBB surrounds cerebral blood vessels within the brain, and tightly regulates the exchange of ions, molecules, and cells between the blood and brain. This protects the brain tissue from pathogens, but it also inhibits

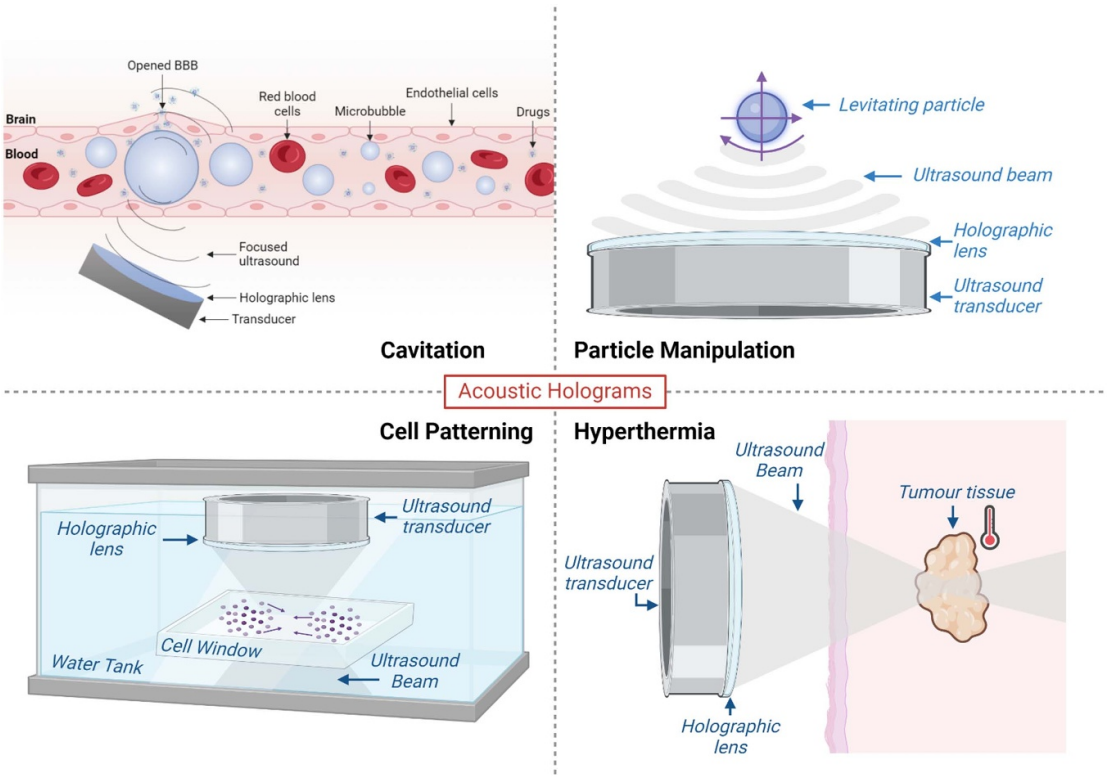


Figure 3. Biomedical applications of acoustic holograms, including cavitation for BBB opening, particle manipulation, cell patterning, and hyperthermia.

lifesaving treatments and therapeutic molecules from being delivered to the brain (Abbott *et al* 2010, Daneman and Prat 2015).

FUS used with circulating microbubbles is a promising method used to open the BBB to allow drug delivery to the brain; it is non-invasive, non-ionising, reversible, and localized (Hynynen *et al* 2006, Konofagou 2012, Pouliopoulos *et al* 2020c). A low-frequency ultrasound beam is used as this reduces skull attenuation (Pichardo *et al* 2011); MHz frequencies can be used on small animals, but sub-MHz frequencies phased arrays are being developed for clinical applications to account for the thicker human skull and the greater penetration depths required (Clement *et al* 2000, McDannold *et al* 2010, Liu *et al* 2014). The FUS beam is used to oscillate microbubbles causing acoustic cavitation. This causes mechanical forces to be applied to the tight junctions of the BBB which can open it temporarily (Papademetriou and Porter 2015, Beccaria *et al* 2020, Wei *et al* 2021). FUS treatments have been shown to be safe and efficient in preclinical studies in mice (Hu *et al* 2022a), rabbits (Hynynen *et al* 2005), and nonhuman primates (Marquet *et al* 2011, McDannold *et al* 2012).

Acoustic holograms combined with microbubbles offer a safe, non-invasive, and low-cost method to open the BBB which could aid in the treatment of many brain pathologies, such as Alzheimer's disease (Burgess *et al* 2011, Lipsman *et al* 2018), Parkinson's disease (Magara *et al* 2014), and other neurodegenerative diseases (Karakatsani *et al* 2021, Noel *et al* 2021).

Maimbourg *et al* describe how an acoustic lens can be set up with an aberrant or absorbing layer to correct aberrations in the head (2018) and Andrés *et al* demonstrated how targeting the hologram through the temporal bone window can produce a sharp focal spot, whilst reducing temperature rise compared to thicker skull bones (2022). Recently, Jiménez-Gambín *et al* furthered this work to correct for aberrations and create a hologram image inside the skull (2019b). They then used an acoustic hologram coupled with a single-element FUS transducer to induce a highly localized bilateral BBB opening in mice (Jimenez-Gambin *et al* 2022), rats (He *et al* 2022), and non-human primates (Jimenez-Gambin *et al* 2024). This method can be used as a low-cost alternative to open the BBB and deliver drugs, or to perform highly controlled neuromodulation of desired neural pathways (Pouliopoulos *et al* 2022, He *et al* 2023, Kook *et al* 2023).

3.2. Particle control and levitation

Another important application of acoustic holography is the ability to manipulate millimetric or sub-millimetric objects, ranging from liquids, to solids, and living cells (Gu *et al* 2020). Particle manipulation has important applications in fields such as pharmaceutics, due to its ability to not alter or damage cells.

Particle levitation can be achieved because sound waves exert acoustic radiation forces that in turn can be used for acoustic levitation (Hoshi *et al* 2014, Baresch *et al* 2016, Andrade *et al* 2020). With recent developments, acoustic levitation can now also rotate and translate particles. The transportation and merging of multiple drops in 2 dimensions was achieved by Foresti *et al* (2013), and Ochiai *et al* were able to control objects in 3 dimensions (Hoshi *et al* 2014, Ochiai *et al* 2014, Andrade *et al* 2020).

Phase surfing is one way to use acoustic holograms for particle manipulation; a particle on the water-air interface can be manipulated using the radiation forces present in an acoustic hologram. Cox *et al* placed a small foam disk on a water surface and, by physically moving the hologram and the focal point along the water, the disc was moved by 14.4 mm (2019). This study also demonstrates how a more complex hologram can be used with no additional manufacturing or electrical challenges, and the same setup is used with a more complex acoustic field that phased arrays would not be able to achieve without a significant increase in array elements (Cox *et al* 2019).

Despite the progress made in acoustic levitation in the past decade, it is still limited to academic research applications. In (Andrade *et al* 2020), some of these technical challenges restricting acoustic levitation from being able to manipulate objects with the same abilities as industrial robots, or to produce amorphous drugs with enhanced solubility are discussed. Further research is needed into the dynamics of acoustically levitating particles to be able to increase the manipulation speed achieved so far of 8.75 m s^{-1} for lightweight particles (Hirayama *et al* 2019). Further understanding levitation dynamics will also allow dampening of undesired oscillations of solid levitated objects (Andrade *et al* 2020).

3.2.1. Holographic Acoustic Tweezers

Holographic Acoustic Tweezers (HATs) are equivalent to previously reported Holographic Optical Tweezers. A HAT system uses acoustic radiation forces to manipulate matter without touching it. This can be done in air, water, or theoretically in biological tissues. It could be used to create displays where objects are levitated (Fushimi *et al* 2019), help with assembly processes on the micrometre and centimetre scale (Melde *et al* 2018), or in biomedical applications to help disease diagnosis, manipulation of kidney stones, etc (Marzo and Drinkwater 2019).

Marzo and Drinkwater demonstrated the ability of HATs to manipulate multiple particles simultaneously in 2D and 3D spaces, using an array of emitters coupled with an acoustic hologram. This could be done with an accuracy of ± 1 mm in 2D and ± 5 mm in 3D manipulation (Marzo and Drinkwater 2019). The particles remained stable after repositioning, and after one hour there was no noticeable movements. They also presented an iterative back-propagation algorithm used to define the emission phases of the array, which were then used to create the functional HAT (Marzo and Drinkwater 2019).

3.3. Cell patterning

Cell patterning is a particularly useful technique in cell-based applications and its process is shown in figure 4. Ma *et al* showed how cells can be patterned in 3D in a biocompatible hydrogel using acoustic holograms. Cells are initially randomly dispersed in a 2D pattern, and when an acoustic field is projected onto them, acoustic radiation forces and acoustic streaming flows cause convection. This is due to the acoustic wave being absorbed by the fluid particles, which causes an imbalance in the Reynolds stresses. A net body force is exerted on the fluid, which creates a time averaged flow and particles in the fluid are pulled towards areas of high pressure (Ma *et al* 2020). The cell pattern can then be immobilized using a collagen solution so that the assembly is transferable. It is shown that the cells remain viable for at least one week after the cell patterning, meaning this technique could be used very effectively in biomedical applications (Ma *et al* 2020).

Cell patterning with holography has potential to be used in tissue engineering, a technique for creating biomimetic microstructures, and functional cell assemblies, as discussed by Ghanem *et al* (2023). Being able to create complex 3D cell cultures with regular patterns could have significant impact in the field of drug screening, genetic engineering, and *in vitro* toxicological tests (Ma *et al* 2020). Existing methods for cell patterning include bioprinting, where cell-encapsulating materials are used to 3D print complex cell arrangements (Ozbolat *et al* 2016, Daly *et al* 2021). However, long printing times limit this technique, because cells at the start of the printing process become altered from the newly extruded cells. Acoustophoresis is another technique to create cell patterns; it uses acoustic radiation forces to control cells and is an effective way to overcome the limitations of conventional cell patterning techniques, which include time, material choices, and cell resolution (Lin *et al* 2012). It is also shown that acoustophoresis achieves higher cell aggregation than other 3D printing methods (Kang *et al* 2018).

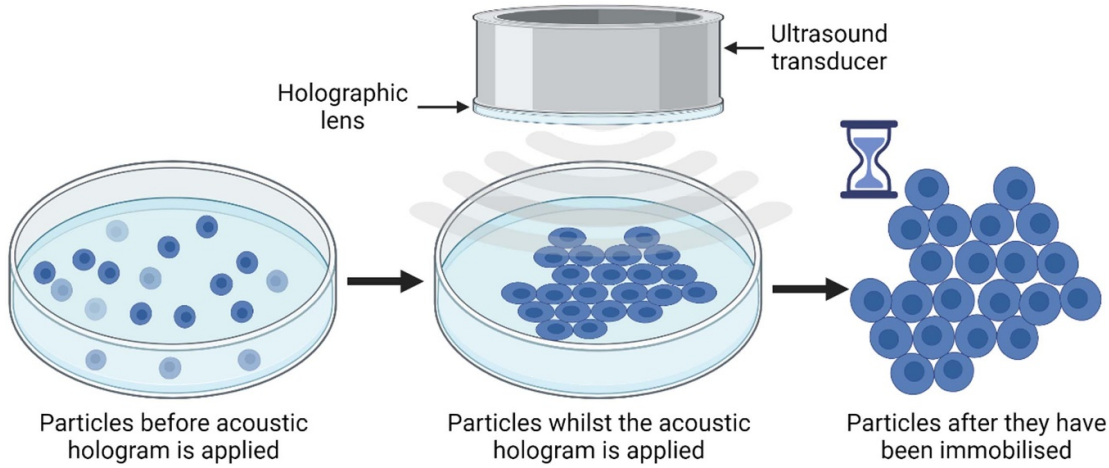


Figure 4. Acoustic holograms can be used for cell patterning to distribute cells into an arbitrary pre-determined pattern which can be fixed for use.

Acoustic holography offers an opportunity to create more complex cell patterns, whilst providing a better representation of biological tissue cell patterns. However, it is important to consider that the acoustic radiation force is weaker on biological cells than polymer materials and cell patterning is therefore more difficult than particle manipulation (Ma *et al* 2020, Melde *et al* 2023).

3.4. Acoustic vortex beams

Conventional ultrasound beams have linear momentum which can be used effectively for non-invasive techniques, targeted drug delivery, or imaging. A vortex beam has the added component of orbital momentum which can be transferred to liquids and solid objects, hence exerting mechanical torque on the medium. This has applications in contactless particle manipulation, however, a more significant advantage for the biomedical field, is the ability of acoustic vortices to propagate deeply through opaque media like biological tissues (Jiménez-Gambín *et al* 2020).

Acoustic vortices can be focused through an *ex vivo* skull using acoustic holograms (Jiménez-Gambín *et al* 2020). By producing acoustic vortices with holograms, acoustic images can be generated at the therapeutic target whilst mitigating skull aberrations, offering a much simpler and more effective technique than phased-array systems for vortex generation. An acoustic vortex beam can transfer angular momentum to tissues; however, its full range of uses remains to be investigated (Jiménez-Gambín *et al* 2020). Further research should be conducted into the ability of acoustic vortex beams to non-invasively target blood clots, torque exertion in the brain, and acoustic-radiation-force-based biomedical applications.

3.5. Hyperthermia

Hyperthermia is a well-established treatment technique for cancer; by increasing the temperature of tumour tissue to 40 °C–43 °C the cells are killed due to cell necrosis and tissue ablation (Wust *et al* 2002, Escoffre and Bouakaz 2015, Mouratidis *et al* 2019). Whilst other techniques exist such as electromagnetic or conductive heating (Kok *et al* 2020), HIFU provides a non-invasive technique to deliver hyperthermia (Tillander *et al* 2016), where the mechanical energy of the wavefront is transferred to the cells causing their temperature to increase (Hynynen 1995).

Previously, Andrés *et al* proved the ability of holograms to provide spatially controlled heating in gelatin-milk phantoms and *ex vivo* liver tissue (2022b). Most recently, Andrés *et al* furthered this work by targeting multiple tumour spheroids simultaneously and by expanding and relocating the hyperthermia volume using holographic lenses in tissue mimicking phantoms (2023). They achieved iso-thermal doses of hyperthermia over a 6 mm wide region and found the treatment of tumour spheroids with holographic lenses is more damaging to tumour cells than heating using polymerase chain reaction used in previous studies (Mouratidis *et al* 2015, Brüningk *et al* 2020). This has the potential to reduce the number of treatments a patient needs for a large area and can provide low cost and personalized hyperthermia cancer treatments. These holographic lenses also have the potential to shape the hologram to the specific tumour region, allowing for more localized and precise treatments.

Further refining of the experimental setup and phantom model of the tumour spheroids are needed, and *in vivo* studies must be performed before clinical use (Andrés *et al* 2023). However, acoustic holograms could

be used very effectively to target the entire tumour volume or a smaller portion (e.g. the peritumoral region) of a tumour to ablate larger volumes than HIFU can currently treat.

4. Limitations of acoustic holograms

While acoustic holograms have a wide range of uses in medicine, there are limitations that currently hinder their widespread use. Most work has been done with 2D plane holograms, and the development of precise 3D acoustic holograms is still ongoing. Melde *et al* have begun this work for matter assembly (2023). However, 3D holograms are more complex; they require multiple lenses and a high frequency transducer which prohibits their use in medical applications. The applications discussed in section 3 would benefit from and, in some cases, only work if they could be used in 3D volumes. For example, cavitation patterning therapies would be more effective and faster in a 3D field with multiple focal planes (Kim *et al* 2021).

Acoustic holographic lenses are also limited as they are passive devices, unlike dynamic PATs, where each transducer can be individually controlled or electronically activated (Ahmad *et al* 2005). This means that the features of the hologram cannot be altered, and the ultrasonic beam cannot be steered accurately in real time with a single-element transducer. Several studies have attempted to overcome this; for example, stackable holograms contain multiple pressure patterns which can be recreated from a single transducer (Brown *et al* 2020). Programmable acoustic holograms were also designed and tested, where different acoustic fields were produced depending on the speed of sound of the propagating medium (Xu *et al* 2023). Reconfigurable metasurface holograms for optics have also been developed; the phase profile can be controlled by altering the environment the material is in, such as the temperature or hydrogen levels (Li *et al* 2019, Wang *et al* 2021). Binary acoustic metasurfaces to generate holograms have also been developed, allowing dynamic beam steering, but further work is needed to improve the materials used and the complexity of the beams generated (Hu *et al* 2022b). Some investigation into mechanically moving the transducer and acoustic lens around the focal position has been conducted, but the feasibility of this technique in its applications needs to be confirmed (Maimbourg *et al* 2020). Lens passivity also makes them patient-specific when applied for transcranial therapies due to the difference in aberrations caused by different skull anatomies (Choi *et al* 2007). However, the low cost of printing lenses means that individual lenses can feasibly be printed for each patient or treatment target.

During wave transition through the lens material, acoustic energy is lost due to acoustic absorption. This causes an inefficiency in the lens which is dependent on its material properties, and which has not yet been thoroughly investigated. A lot of studies use normalized results and, since most medical applications will require ultrasound to be delivered at a certain threshold pressure, it is important that these physical losses in the lens materials are investigated and reduced as much as possible.

Similarly, thermal rising in the acoustic lens due to thermal dissipation during ultrasound propagation is another important limitation dependant on material selection. This can alter the speed of sound in the lens, which would alter the acoustic hologram image. It could also cause the acoustic lens to act as a thermal lens, which could affect the patient undergoing treatment (Maimbourg *et al* 2018). These effects need to be studied further to determine a safe limit on temperature rise; the use of different materials could help overcome this limitation. Ferri *et al* began this work by investigating the use of different materials for acoustic lenses and the effect different polymers have on the quality of the hologram (2019a).

Most lenses have been designed for a narrowband working frequency or exclusively for high frequency, which is not compatible with many medical applications, particularly those inside the body. Recent work has established that acoustic lenses may be designed for both broadband and narrowband applications (Chen *et al* 2023). However, whilst these composite metamaterials hold much promise, they have only been designed and tested for acoustic silencing applications and would need further development to be suitable for medical applications (Chen *et al* 2023).

Acoustic holography studies so far for medical applications have been performed *in vitro*, in mice, and in non-human primates, but further studies are needed before it can be used on patients. It is much simpler to achieve an accurate and secure setup for *in vitro* experiments, as seen in (Maimbourg *et al* 2018), where elastic bands or other positioning equipment were used to hold the skull in place. Therefore, research into the error margins acceptable for the use of acoustic holography in therapeutic ultrasound applications is needed. Maimbourg *et al* suggest the use of thermoplastic masks or neuronavigation guidance (Pouliopoulos *et al* 2020c) could help ensure the precision of the targeting in clinical transfers.

In vivo environments also differ from *in vitro* environments in that their temperature fluctuations, liquid viscosity (blood vs water), and blood flow rates cannot be easily reproduced. This will need to be considered carefully in future studies as acoustic holograms are brought into clinical use.

There are also limitations in the measurement techniques used for acoustic holograms; whilst they can be very precise, needle hydrophones are slow to operate over large areas. This prolongs the process of developing

an acoustic hologram, as the hologram must be measured outside the brain before it can be used in therapeutic ultrasound treatments. There is therefore a need for fast and accurate techniques to measure the holographic quality in 3D. Lamothe *et al* have begun investigations into using acoustic holograms to assist PCD measurements which could allow for accurate, real-time, and localized monitoring of acoustic cavitation which would help to resolve this problem (2024).

5. The future of acoustic holograms

Acoustic holography has an exciting future and has the potential for use in a multitude of industrial and biomedical applications. This review discussed the potential of acoustic holography for precise drug delivery into the brain to target specific areas for treatment, and for particle control and levitation, which could be used for assembly techniques. Acoustic holography is the next step on from holographic optical tweezers demonstrated in the design of HATs. Acoustic holograms could also be used as a cell patterning technique, and for other biomedical applications, such as hyperthermia treatments for cancer cells. However, further research and testing are needed before acoustic holograms are safely used in clinical applications.

Data availability statement

No new data were created or analysed in this study.

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