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To cite this article: Xingyu Bai *et al* 2024 *Int. J. Extrem. Manuf.* **6** 062001


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Topical Review

Design and micromanufacturing technologies of focused piezoelectric ultrasound transducers for biomedical applications

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Received 28 February 2024, revised 4 April 2024

Accepted for publication 12 July 2024

Published 24 July 2024



CrossMark

Abstract

Piezoelectric ultrasonic transducers have shown great potential in biomedical applications due to their high acoustic-to-electric conversion efficiency and large power capacity. The focusing technique enables the transducer to produce an extremely narrow beam, greatly improving the resolution and sensitivity. In this work, we summarize the fundamental properties and biological effects of the ultrasound field, aiming to establish a correlation between device design and application. Focusing techniques for piezoelectric transducers are highlighted, including material selection and fabrication methods, which determine the final performance of piezoelectric transducers. Numerous examples, from ultrasound imaging, neuromodulation, tumor ablation to ultrasonic wireless energy transfer, are summarized to highlight the great promise of biomedical applications. Finally, the challenges and opportunities of focused ultrasound transducers are presented. The aim of this review is to bridge the gap between focused ultrasound systems and biomedical applications.

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Keywords: piezoelectric ultrasonic transducers, focusing techniques, preparation method, biomedical applications

1. Introduction

Ultrasonic transducer is an electronic device that converts ultrasonic waves into electrical energy and vice versa. According to the working principle, ultrasonic transducers can be divided into electric field types, like capacitive and piezoelectric, and magnetic field types, such as magnetostrictive transducers [1–5]. The earliest notable ultrasonic transducer was a sandwich transducer designed by Langevin in 1917 [6]. The transducer was made of quartz crystal as a piezoelectric material. In 1933, the magnetic field type ultrasonic transducer, which used magnetostriction, first appeared [7]. Due to the advantages of high strength and high power, magnetostrictive transducers caused a wave of research at that time [8]. From the 1950s, the development of ferroelectric ceramics like barium titanate (BT) and lead zirconate titanate (PZT) solidified the dominant role of piezoelectric transducers, a position they maintains today, continually evolving with new materials and technologies [9].

Piezoelectric ultrasonic transducers without beam focusing have a certain degree of natural focusing properties due to their physical structure, which has been widely used in the medical field [10]. However, general piezoelectric transducers can only produce a wider ultrasound field, which may limit its effectiveness in applications requiring high accuracy. Focused transducers are capable of producing extremely narrow beams and are more specialized for tasks requiring high precision, such as in certain diagnostic and therapeutic procedures [11–15]. In ultrasound imaging, focused beamforming techniques and methods will affect the resolution of imaging [16–18]. In order to control smaller cells in ultrasonic tweezers, the sound wave emitted by the transducer preferably generates a sufficiently high radiation force at the focal point [19, 20]. In ultrasound therapy, low-intensity focused ultrasound (LIFU) and high-intensity focused ultrasound (HIFU) were used to modulate nerve and tumor ablation, respectively [21–24].

In recent years, there have been many reports on the review articles surrounding the application of focusing technology in the medical field, summarizing the important role played by focused ultrasound transducers in various diseases. Meng *et al* [25] provided an overview of focused ultrasound for the treatment of brain diseases. Bachu *et al* [26] highlighted the mechanism and clinical application of HIFU. Javid *et al* [27] emphasized the use of focused ultrasound in transcranial neuromodulation. While the above reviews all focus on the application of focused ultrasound, there is also a need for more detailed discussions on the transducer design and manufacturing processes to facilitate the development of better performing transducers for more applications. The key challenge in focused ultrasound transducers lies in the selection of appropriate materials and focusing techniques. It is necessary to solve the problem of how to process brittle and hard materials such as piezoelectric ceramics

and piezoelectric single crystals [28–31]. In addition, it is also important to avoid acoustic impedance mismatches between the sections. It has been reported that focused ultrasound transducers based on piezoelectric materials have been put into clinical applications and play an important role in nervous system diseases, tumors, and chronic diseases. There is an urgent need to summarize and analyze the preparation and design of focused ultrasound transducers in different application scenarios.

In this review, we provide a comprehensive overview of the latest progress of focused ultrasound transducers, especially the preparation methods of each part and the latest applications. Here, we mainly target related applications in the medical field, including ultrasound diagnosis, ultrasound therapy, ultrasound wireless energy transfer, and ultrasound acoustic tweezers. The first section introduces the basic characteristics of ultrasound and the biological effects of ultrasound on human body in detail. Subsequently, the second section summarizes the relevant functional materials of the focusing transducer. The third section critically examines four distinct focusing techniques and discusses their respective merits and limitations. Finally, the applications of piezoelectric focusing transducer in medical field are summarized in detail. The summary and prospect section gives the future development direction of the focused ultrasound transducer and its application in emerging fields. Figure 1 presents a systematic overview of this review.

2. Device physics

2.1. Ultrasound basics

There are many basic characteristic parameters describing ultrasonic wave, such as sound speed, wavelength, period, frequency, energy density, sound intensity, and sound pressure. However, sound intensity is usually used more because of its temporal and spatial characteristics [32]. First, the spatial distribution of sound intensity is not uniform. For the sound field generated by the planar transducer, the maximum peak intensity of the general central axis is 4 times the average sound intensity. Second, the sound intensity is also uneven in time. No matter continuous wave or pulse wave, there are time peak (TP) and time average (TA). Common sound intensity expressions are discussed below.

Spatial peak time Peak sound intensity I_{SPTP} (also known as maximum instantaneous sound intensity) is generally used to describe the sound intensity corresponding to the sound pressure at the spatial peak point of the pulse wave (P_m^2 as shown in figure 2). According to the conversion formula of sound pressure and sound intensity, $I_{SPTP} = P_m^2 / \rho c$ can be obtained [33], where the density and sound velocity are respectively represented. The spatial peak pulse means sound intensity I_{SPTA} is the energy transmitted per unit area of a pulse divided

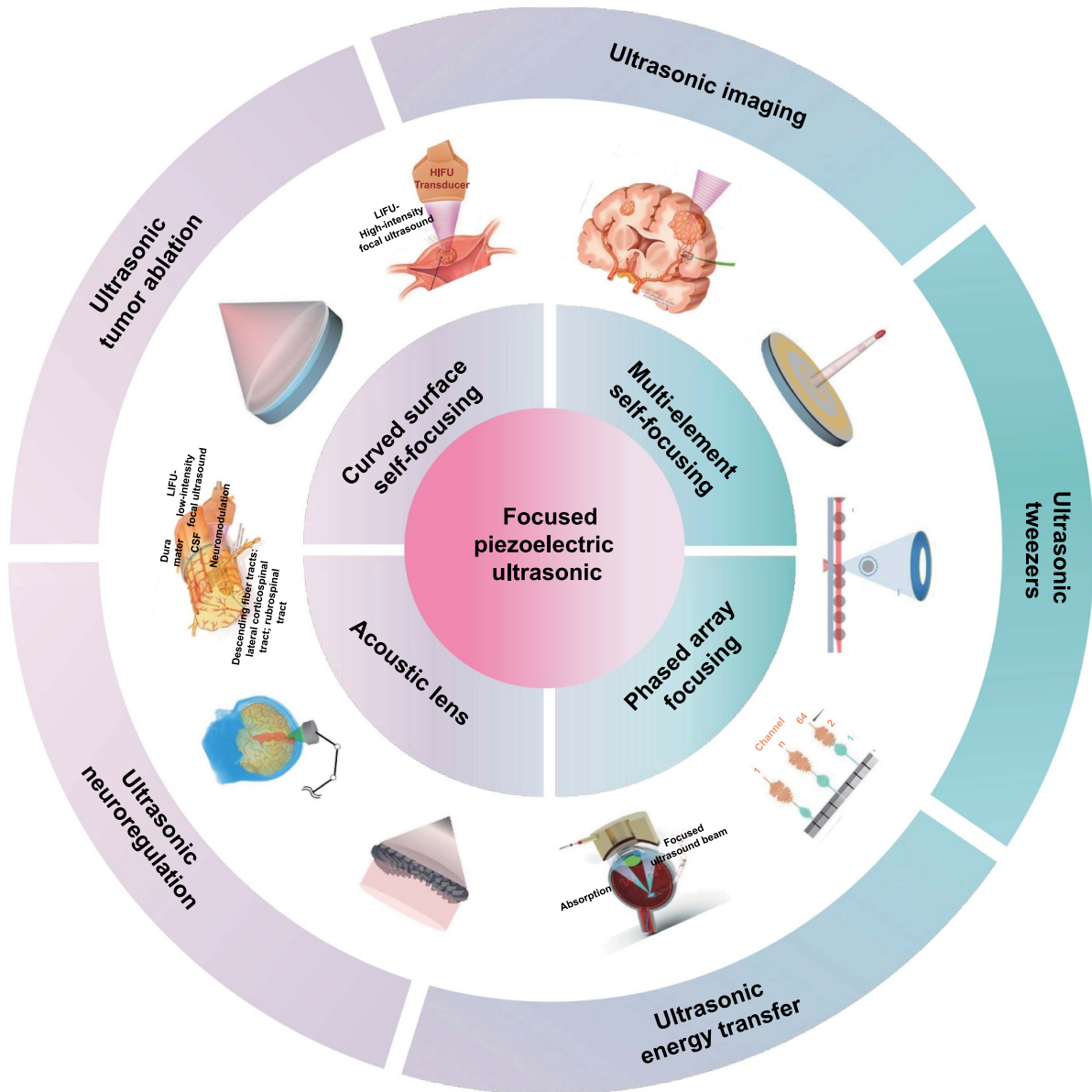


Figure 1. Systematic outline of this review. We summarize the focusing techniques of piezoelectric ultrasound transducers and their application.

by the pulse duration (T_1 in figure 2). Continuous wave is generally described by the mean value of spatial peak time sound intensity I_{SPTA} , which is numerically equal to $P_0^2/2\rho c$ [33], P_0 is the sound pressure amplitude.

2.2. Focused ultrasound

As discussed above, the distribution of sound intensity in space and time is not uniform. In fact, the sound field generated by the non-focusing transducer can be divided into near field and far field regions. The sound wave in the near field region fluctuates greatly, and the sound intensity in the far field region tends to be stable [34]. The boundary between the two regions is the natural focus of the non-focusing transducer. For the sound field generated by the focusing transducer, there are still far

field and near field regions, but the sound beam at the focus becomes extremely narrow and the sound intensity becomes extremely strong.

In the focused ultrasound system, a focal spot is often formed at the focal point, which is due to the diffraction of the sound wave. In most cases, the center of curvature of the transducer surface does not coincide with the focus of the wave. For example, for a curved transducer, except for a spherical surface or a rectangular cylinder, the geometric focus of other shapes does not coincide with the wave focus. This results in the diffraction of the sound wave, forming an axisymmetric solano-shaped sound beam, known as the focal spot. The radius of the focal spot can be expressed as: $r_0 = 1.61\lambda f/R$ [35], where λ is the wavelength, R is the aperture radius of the transducer, and f is the focal length. The focal spot radius determines the

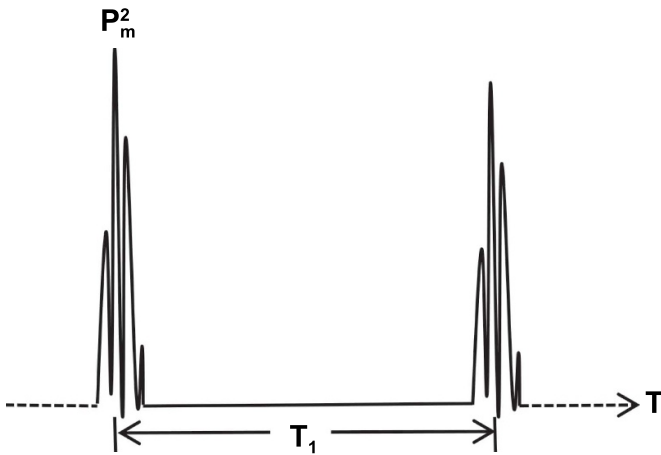


Figure 2. The curve of sound pressure squared (P^2) of a pulse wave with time.

lateral resolution of the system, and the smaller the focal spot radius is, the higher the lateral resolution. Axis resolution is dependent on frequency and bandwidth.

Another distribution characteristic of the focused sound field is the occurrence of a maximum value on the sound axis and many submaximal around it [36]. The acoustic axis direction lobe is called the main lobe, and the two sides of the main lobe are sidelobe. This is due to the interference of the diffraction wave generated by the transducer at the output aperture. By optimizing the structural design of the transducer, the sound field distribution of the main maximum and sidelobe can be improved, and the applicability in different scenes can be improved [37]. For example, in ultrasound ablation, it is best to use an extremely narrow beam with as little sidelobe as possible, while in general low-frequency ultrasound imaging, no special focusing design is required in order to reduce costs [38].

2.3. Ultrasonic biological effect

Since ultrasound is a wave form, it is possible to obtain physiological and pathological information of the organism using self-transmitting and receiving transducers, which is the principle of ultrasonic diagnosis [39]. At the same time, ultrasound is a form of energy, when it spreads in the biological body, it will cause changes in the function, structure and state of the biological system, which is the ultrasonic biological effect [40]. This section details several common ultrasonic biological effects.

Thermal effects. When ultrasonic energy is converted into heat energy in the organism, it is called the thermal effect. Thermal effects can cause a rapid rise in local temperature within an organism. The heat generated by a planar ultrasonic wave with an intensity of I (W cm^{-3}) in a unit volume of biological tissue is: $Q = 2\alpha It$ ($\text{J} \cdot \text{cm}^{-3}$) [41], where α is the sound pressure absorption coefficient of the tissue, and t (s) is the action time. Considering the contact between the ultrasonic probe and the human tissue through the coupling

agent, when the ultrasonic radiation to the human tissue, its acoustic absorption coefficient is related to the ultrasonic frequency, which can be approximately expressed as: $\alpha = 0.026f^{1.1}$ (cm^{-1}). Assuming that the density of human tissue is $\rho = 1.00 \text{ g} \cdot \text{cm}^{-3}$, and the specific heat is $C_m = 4.14 \text{ J} \cdot \text{cm}^{-3} \cdot ^\circ\text{C}^{-1}$, the temperature of the tissue after ultrasonic irradiation at t time is as follows [42]:

$$\Delta T = \frac{2 \times 0.026}{\rho C_m} I t f^{1.1} = 0.012 I t f^{1.1} (^\circ\text{C}).$$

The above formula shows that when the ultrasonic wave with a frequency of 1 MHz and a sound intensity of 1 W cm^{-2} is irradiated into human tissue, the temperature will rise at a rate of $0.012 \text{ }^\circ\text{C} \cdot \text{s}^{-1}$. Therefore, in ultrasonic tumor ablation, the ablation temperature can be controlled according to ultrasonic frequency, sound intensity and irradiation time.

Mechanical mechanism. When the heat generated by ultrasound is not enough to significantly raise the temperature of the tissue, the mechanical parameters of the sound field will play a major role, and this biological effect is the mechanical mechanism. A typical mechanical action is a radiant force, which means that when ultrasound acts on an organism through a fluid with a sound speed of c , it is equivalent to thinking that a steady-state force acts on the object [43].

Cavitation effect. In a broad sense, cavitation effect refers to the various forms of movement of bubbles caused by ultrasound [44]. According to the different dynamic behavior of bubbles, it can be divided into stable cavitation and transient cavitation [45]. When there are bubbles in the liquid, the action of ultrasound will cause the bubbles to enter a resonance state, and the stable movement of the bubbles caused by ultrasound is called stable cavitation. When the sound intensity is high, the movement of the bubble becomes complex and violent, and the empty core existing in the liquid rapidly expands, contracts and collapses, which is called transient cavitation. Both types of cavitation require bubbles, which, when the bubble size is right, can produce stable cavitation at low pressure. When the bubble is too small, it can only act as a cavitation core, which is a higher sound intensity that can produce transient cavitation [46].

The above biological effects are summarized in figure 3. When the sound intensity is lower than $10^{-3} \text{ W cm}^{-2}$, no biological effect of ultrasound occurs. When the sound intensity is lower than 1 W cm^{-2} , the steady-state cavitation effect is dominant. Until the sound is stronger than 1 W cm^{-2} , the ultrasound will cause tissue damage. In the range of low intensity and long irradiation time, the damage of issue is mainly caused by thermal mechanism. In the range of extremely loud intensity and short irradiation time, the damage mechanism is mainly the transient cavitation mechanism. When the sound intensity is in the middle range of $700\text{--}1500 \text{ W cm}^{-2}$, the damage mainly comes from the mechanical mechanism.

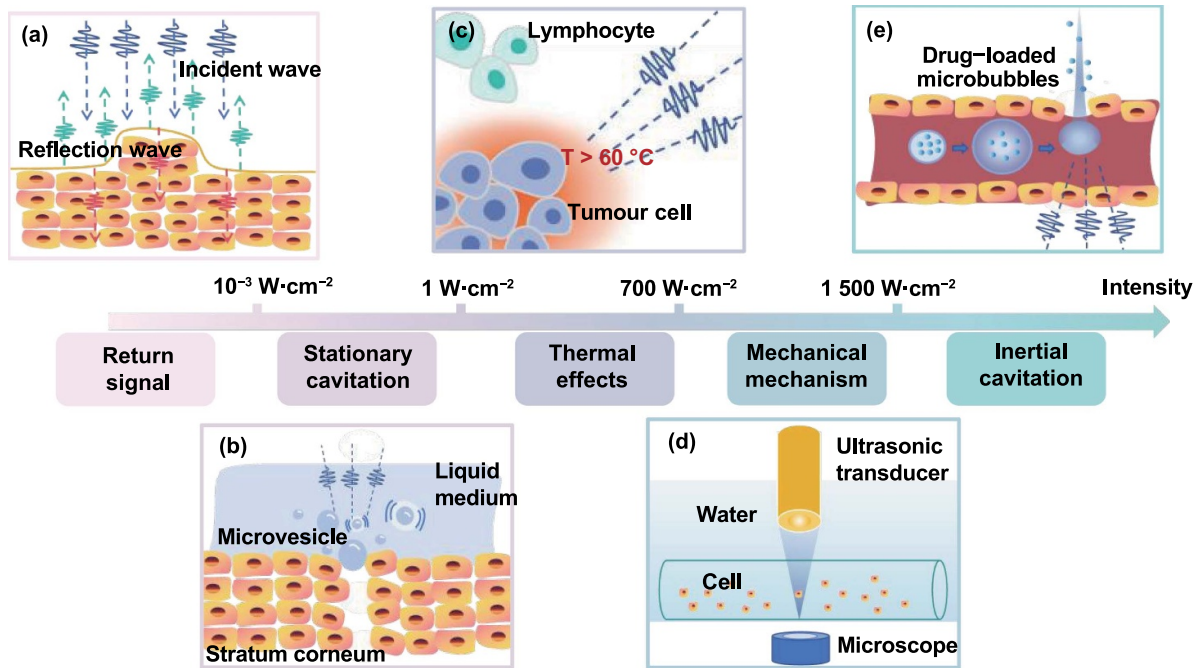


Figure 3. Biological effects of ultrasound at different intensity ranges. (a) ultrasonic echo. (b) stationary cavitation. (c) thermal effects. (d) mechanical mechanism. (e) inertial cavitation.

3. Functional materials

Piezoelectric transducers are generally composed of three parts: piezoelectric layer, backing layer and matching layer. The piezoelectric layer is located in the middle, which plays the role of electromechanical conversion. The backing layer is located behind the piezoelectric layer, which mainly absorbs ultrasonic waves and prevents the ringing effect caused by excessive vibration of the piezoelectric material. The matching layer is located in the front, which is used to achieve acoustic impedance matching and reduce the reflection of ultrasonic waves at the interface [47]. Among them, piezoelectric materials are indispensable [48]. In this section, we describe in detail the materials used in the focused ultrasonic transducer.

3.1. Piezoelectric materials

Piezoelectric materials are a key part of piezoelectric transducers, and piezoelectric transducers are the core of most focused ultrasound systems, the selection of suitable piezoelectric materials is very important for focused ultrasonic transducers. As shown in figure 4, we present the comparison of different piezoelectric materials in terms of electromechanical coupling coefficient, density, longitudinal piezoelectric coefficient, Young's modulus, acoustic impedance and complex shape and matching capability. This section focuses on the advantages and disadvantages of five common piezoelectric materials for focused ultrasound applications.

Piezoelectric ceramics. Piezoelectric ceramics are types of polycrystalline materials that play a crucial role in the field of ultrasonic application [49, 50]. Common piezoelectric ceramics include PZT, potassium sodium niobate (KNN), BT among others [51–54]. Zhen *et al* prepared a piezoelectric transducer with resonance frequency of 2 MHz using PZT-4 and assembled it with ultrasonic lens into a focused ultrasonic system. Su *et al* [55] used PZT to prepare a focusing system for intravascular ultrasound imaging. Although the piezoelectric properties of piezoelectric ceramics are very good, their mechanical strength is low. This limitation becomes particularly evident when the material is ground to thicknesses comparable to the grain size, complicating the design of focused ultrasound systems [56]. This limitation has posed challenges to their broader application in the development of focused ultrasound systems.

Piezoelectric single crystal. Quartz single crystal is the earliest piezoelectric single crystal discovered by human beings. It has good mechanical properties and is easy to cut, grind and polish. The single crystal commonly used in focused ultrasonic transducers is lithium niobate (LiNbO_3). Its piezoelectric properties are very excellent, which has a great relationship with the cutting orientation and cutting orientation. Typically, the LiNbO_3 for piezoelectric transducers is a 36° Y cut. Tiefensee *et al* [57] prepared a focused ultrasonic probe with a piezoelectric layer thickness of only $7.1 \mu\text{m}$ s using LiNbO_3 . Through the focusing design, it is possible to emit narrow beam sound waves that can be used to capture

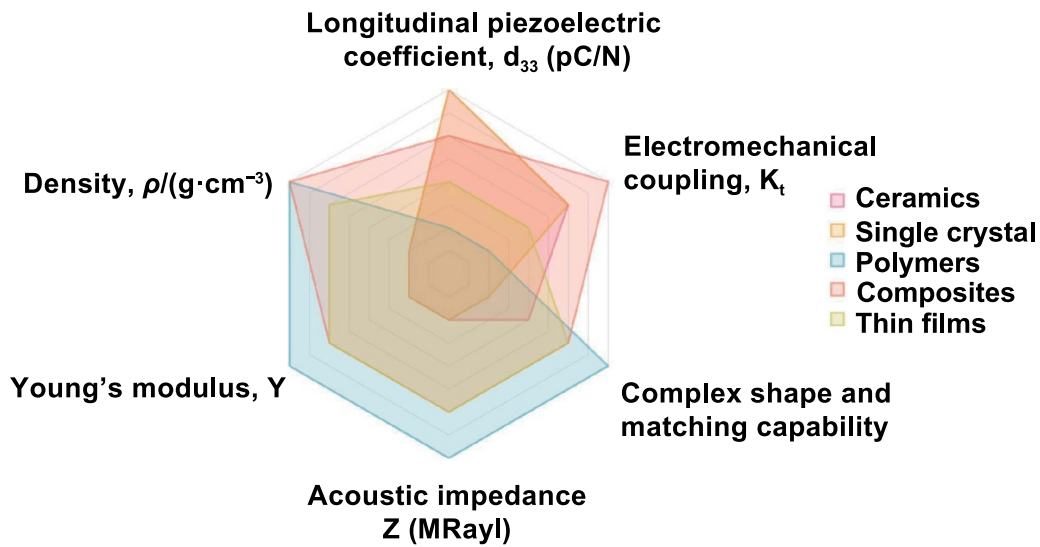


Figure 4. Comparison of the advantages and disadvantages of piezoelectric and physical properties of piezoelectric materials for focused ultrasound applications.

individual tiny cells. Currently, fabricating LiNbO₃ layers of several microns thick remains a challenging and complex task.

Piezoelectric polymer. Piezoelectric polymers represent a relatively newer class of materials in the field of piezoelectricity. The earliest discovered piezoelectric polymer is polyvinylidene fluoride (PVDF) [58], which has the advantages of stretchability, thermoplasticity and easy fabrication. Although PVDF's performance is notably influenced by temperature variations and its electromechanical coupling coefficient is relatively low, the outstanding mechanical properties make it very suitable for making narrow-pulse ultrasonic transducers with high resolution [59, 60]. Furthermore, PVDF offers potential applications in the development of wearable focused ultrasound devices [61].

Piezoelectric composites. Piezoelectric composites are engineered materials made by embedding piezoelectric ceramic phases in a polymer matrix to enhance certain properties beneficial for specific applications. Common piezoelectric composites refer to ferroelectric ceramics and polymer matrix composites, which can have high electromechanical coupling coefficient and low acoustic impedance at the same time [62]. This combination allows for efficient conversion of electrical energy into mechanical energy (and vice versa), making them highly effective for use in ultrasound imaging where clear, high-resolution images are required. Xu *et al* [63–68] used piezoelectric composites with a 1–3 connectivity pattern (one-dimensional ceramic rods embedded in a three-dimensional polymer matrix) in wearable ultrasound devices, enhancing acoustic matching due to their lower impedance compared to traditional materials. Although the flexibility of piezoelectric composites is better than that of piezoelectric ceramics and single crystals, making them more suitable for integration into wearable devices that conform to the human body, achieving

consistent material properties and performance across production batches remains a challenge due to variability in the embedding process [69].

Piezoelectric film. The development of Microelectromechanical Systems (MEMS) technology has spurred advancements in piezoelectric materials, leading to innovations in thinness, miniaturization, and complexity of structures. In 1997, Barrow *et al* [70] prepared 60 μm PZT films by the sol-gel method. One team fabricated MEMS acoustic sensors and ultrasonic transducers by sputtering PZT on silicon substrates using thin film deposition technology [71, 72]. This work significantly enhances the sensors' sensitivity and resolution. In addition to conventional ferroelectric thin films, ZnO [73] and AlN [74], which are commonly used in semiconductors, can also be used as active materials for focused ultrasound transducers. While ZnO and AlN offer superior consistency and reliability for semiconductor applications, their piezoelectric performance is not as strong as that of traditional PZT-based films. However, they remain valuable for focused ultrasound transducers where material properties can be optimized for specific applications.

3.2. Backing layer

There are two main roles of the backing layer in the focused ultrasound transducer. The first function is to suppress the excessive vibration of the piezoelectric material and achieve short pulse waves. This process is vital for improving the axial resolution of the transducer, enabling more precise imaging by producing clearer images of structures along the beam's axis. The second role is to absorb ultrasonic waves to stop the continued backward propagation of sound waves from the piezoelectric material. According to the above principle, the acoustic impedance of the backing layer needs to be significantly

different from that of the piezoelectric material to facilitate the desired attenuation and reflection characteristics. Ideally, the acoustic impedance of the backing material should be carefully chosen to be either significantly lower than the 35 MRayl typical of piezoelectric ceramics [69], aiming for an impedance mismatch that optimizes sound wave attenuation and minimizes backward propagation. Typically, a material with an acoustic impedance of $3 \sim 5$ MRayl is chosen to fabricate the backing layer. Traditionally, the material commonly used as a backing layer is a conductive silver epoxy resin [75]. If you want to obtain a backing layer with adjustable impedance, you can choose epoxy resin doped tungsten powder to obtain different acoustic impedance by changing the content of tungsten [76]. With the development of transducers in the direction of high frequency and high resolution, many other materials have emerged. Nicolaidis *et al* [77] studied the effect of using materials such as aluminum, brass, and polyvinyl chloride as backing layers on the performance of underwater acoustic transducers. Finding different materials will result in different resolutions.

3.3. Matching layer

Acoustic matching greatly increases the coupling between the focusing transducer and the propagating medium and reduces the energy loss. There are many theories on how to design acoustic matching layers. The most widely used design principle for acoustic matching layers is the $1/4$ wavelength theory. According to this theory, the optimal thickness of the matching layer is one quarter of the ultrasound wavelength in the material, allowing for maximal energy transmission into the target medium by minimizing the reflection at the interface. For the focused ultrasound transducer, the matching layer needs to be extremely thin and the acoustic impedance of the matching layer needs to be well matched with the medium in order to make the ultrasonic wave form a very narrow beam. Therefore, a variety of active and passive materials have been developed, such as nanocomposites [78–80], metamaterials [81] and metasurfaces [82]. Fang *et al* [83] used anodized aluminum oxide doped with epoxy resin for acoustic matching. The composite was able to establish a link between PZT with an acoustic impedance of 35 MRayl and human skin with an acoustic impedance of 1.5 MRayl. To obtain better performance, they fabricated the matching layer using a deep reactive ion etching method. Tiefensee *et al* [57] fabricated a matching layer with an acoustic impedance of 7 MRayl using a composite material containing cerium oxide nanoparticles. This choice was guided by the nanoparticles' ability to fine-tune the acoustic impedance of the layer, optimizing it for specific medical ultrasound applications.

4. Manufacturing approaches for PFUT

In the focused ultrasonic system, the piezoelectric transducer is the most important part. Unlike non-focusing transducers, which emit waves that naturally spread out, focusing transducers employ physical or electronic methods to concentrate

the sound field, thereby forming an extremely narrow beam for enhanced precision and depth control. Single-element transducers, in contrast to array system, can only use physical focusing. Both linear and planar arrays utilize electronic focusing, which adjusts the phase of the signals emitted by each element in the array to precisely shape and direct the sound beam. Physical focusing methods include: surface focusing and additional acoustic lens. In this section, the content and development status of these focusing methods are introduced in detail.

4.1. Curved surface focusing

Surface focusing involves the surface of a piezoelectric material forming a curved shape, with the aim of directing ultrasonic waves to a focal point, thereby enhancing the intensity and precision of the ultrasound beam. Common bending methods for piezoelectric materials are summarized below.

One of the most commonly used methods is the ball compression method, in which pressure is applied to the surface of the piezoelectric material through a steel ball to create a depression on the surface of the material. Figure 5(a) shows the process of preparing the LiNbO_3 single crystal transducer by ball pressing [84]. First, the piezoelectric single crystal or ceramic is mechanically thinned to an ideal thickness. A layer of Cr/Au electrodes is then sputtered on the surface, and the backing material is cast on one side of the piezoelectric material. Finally, the ball pressing process is pressed and focused at 90°C using highly polished chromium/steel ball bearings. A special clamp is usually used to achieve pressure focusing. This method is generally used for piezoelectric ceramics and piezoelectric single crystals, especially after mechanical thinning to tens of micrometres. The advantage of the ball pressing method is that the process is simple, but due to the brittle nature of ceramic and single crystal materials [85], it often leads to the fragmentation of piezoelectric materials. To address limitations of the ball pressing method, the mechanical grinding technique was developed, utilizing a high-strength object to gradually wearing down the piezoelectric material until the desired curved shape is achieved. That is, a high-strength object is used to grind the surface of the piezoelectric material until a curved shape is formed [86, 87]. For piezoelectric ceramics and piezoelectric single crystals of tens of micrometers, this method has absolute advantages, but for ultra-thin piezoelectric ceramics with thickness less than 10 micrometers, this method will not be applicable.

Both of the above methods directly transform the surface of the flat piezoelectric material into a curved surface, and since most of the piezoelectric materials are brittle and hard materials, the preparation process faces great risks, which may lead to a significant decline in the performance of the piezoelectric material or even failure. A better scheme is to prepare a backing layer with a curved surface structure [92]. Some studies have used aluminum (Al) [93] as a bending backing layer because it is soft and easy to process into a focused structure. In addition, aluminum has good electrical conductivity and suitable acoustic impedance. Zhang *et al* [94] loaded P(VDF-TrFE) films on the surface of an ellipsoidal backing layer for photoacoustic microscopy.

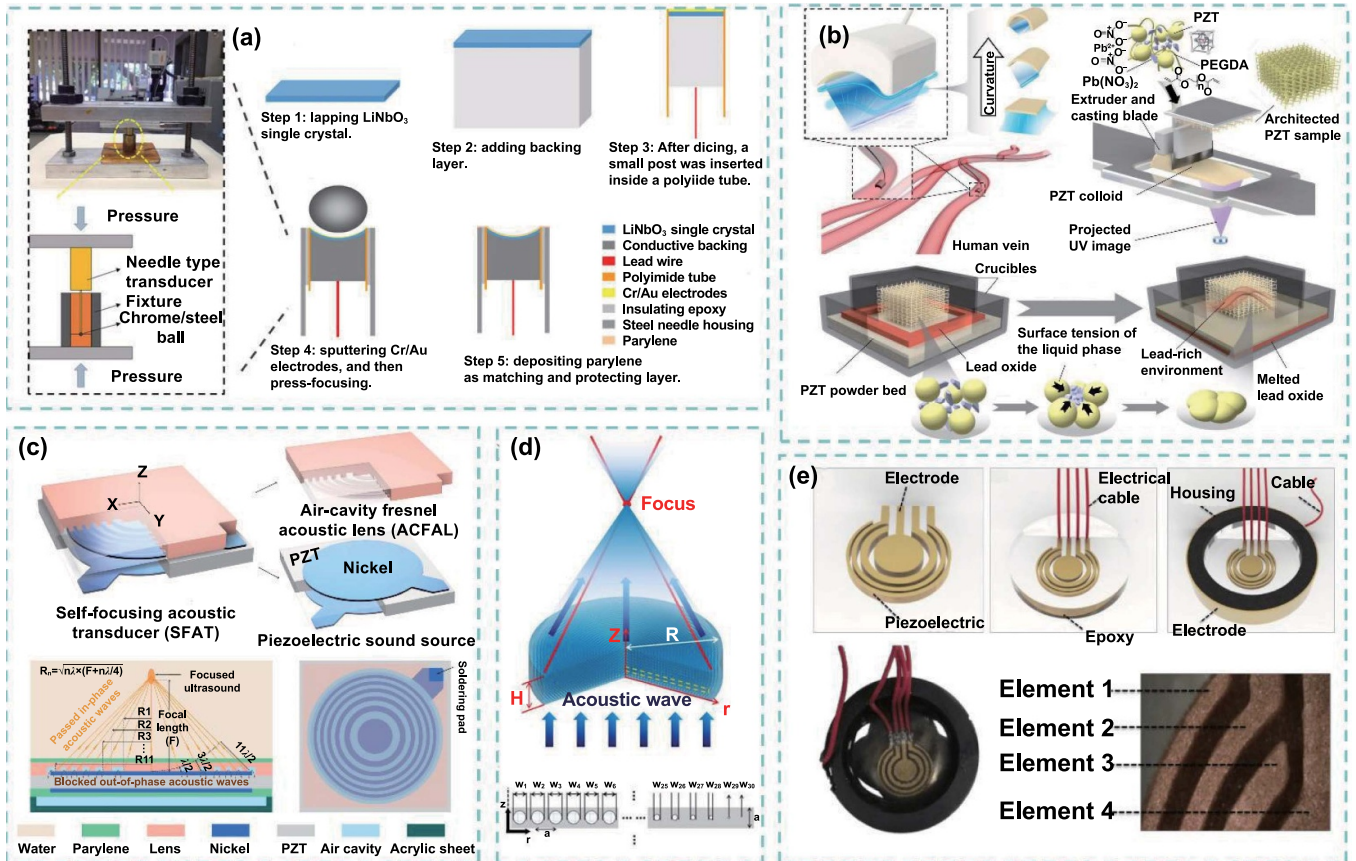


Figure 5. Different focusing techniques for ultrasonic transducers. (a) The actual picture and concrete steps of surface PFUT preparation by ball pressing method [84]. Reproduced from [84]. [CC BY 4.0](#). (b) 3D printing curved piezoelectric ceramics [88]. Reproduced from [88]. [CC BY 4.0](#). (c) Acoustic lens based on Fresnel principle [89]. Reproduced from [89]. [CC BY 4.0](#). (d) Acoustic lens based on acoustic metamaterials [90]. Reprinted from [90], with the permission of AIP Publishing. (e) 3D printed annular piezoelectric transducer [91]. Reproduced from [91]. [CC BY 4.0](#).

Advances in additive manufacturing technology have promoted the fabrication of curved piezoelectric ceramics [95]. The use of 3D printing technology to fabricate various geometries of piezoelectric ceramics has attracted more and more attention. Due to the problems of poor compactness and low piezoelectric coefficient of ceramics produced by this technology, many studies are making efforts to improve the processing process [96]. As shown in figure 5(b), Lu *et al* [88] proposed a new additive manufacturing technology with an excellent sintering process. They fabricated PZT elements with good performance and corresponding matching layers and backing layers.

4.2. Acoustic lens

Acoustic lenses are a form of passive focusing that can change the spatiotemporal distribution of ultrasonic waves. Compared with curved surface transducers, more complex sound fields can be formed by means of acoustic lenses. When designing acoustic lenses, various equivalent parameters of each lens are usually determined according to the desired sound field. Common acoustic lenses include: curved lens [97], Fresnel lens [89, 98], metamaterial [99] and phonon crystal [90], etc.

Curved lens uses materials of different thicknesses to focus sound waves [100] and is the simplest type of acoustic lens. The Fresnel lens is characterized by concentric circular sections, each designed to phase-shift the sound waves in a manner that they constructively interfered at the focal point. As shown in figure 5(c), Tang and Kim [89] used the MEMS process to fabricate three kinds of Fresnel acoustic lenses with air cavities, which are not only very thin, but also able to reduce impedance mismatch and achieve good acoustic focusing. Acoustic metamaterials are materials with sub-wavelength periodic artificial structures, including local resonant structures [101], gradient index planes [102], Helmholtz cavities [103], and others. Li *et al* [90] proposed a metasurface lens for underwater focusing, but its integration with an ultrasonic transducer is difficult. Phononic crystals can also be used for sound field modulation. An example is the gradient index phononic crystal, as shown in figure 5(d), adept at acoustic focusing by manipulating wave paths through spatially varying material properties.

In fact, the role of acoustic lenses is not limited to ultrasound focusing, it can achieve more complex sound field modulation. However, because the lens is often located between the external medium and the piezoelectric material, it will lead to impedance mismatch and cause problems such as

low energy transmission efficiency. Recently, the development of 3D printing technology has promoted the application of various shapes of acoustic lenses in focused ultrasound transducers.

4.3. Phased array focusing

With the development of electronic technology and micro and nano machining technology, phased array based focusing transducer has appeared. Unlike single-element transducers, which require mechanical scanning, phased array probes can control the size and position of the focus using electronic techniques [104, 105]. In a phased array transducer, the size of each array element is no larger than half of the wavelength in the target medium, and several small elements are arranged according to certain rules. By controlling the time at which each element emits a spherical wave, a dynamically focused sound field is formed.

A common phased array is based on a ring array that is capable of generating a focus that moves axially by applying an electrical signal to each ring piezoelectric element. The earliest use of concentric ring arrays was in 1989 [106], and Foster *et al* used 12 ring chips for focused ultrasound imaging. Chen *et al* [107] used laser cutting to process $66\ \mu\text{m}$ lead magnesium niobate (PMN-PT) single crystals to form a ring array with a radius of 8 mm. Each element of the transducer was connected to the pad by a lead bonding process. Snook *et al* [108] developed ring arrays based on fine-grained lead titanate ceramics for the crosstalk problem. In the above studies, laser cutting technology is used to process piezoelectric materials. Compared with traditional cutting technology, laser technology has less influence on the properties of piezoelectric materials [109]. Femtosecond laser and picosecond laser technology, as ultra-short pulse technology, are widely used in micro and nano processing technology [29, 110]. In 2004, Brown *et al* [111] proposed an alternative to mechanically cutting by fabricating arrays by deposition of ring electrode patterns onto the surface of piezoelectric materials. In this work, the PZT sample is first bonded to a glass plate and then mechanically thinned. The electrodes were then sputtered on the PZT and patterned using a lithography process to form eight separate elements. Finally, the copper-covered printed circuit board is bonded to the PZT. Sammoura *et al* [112] designed a multi-electrode ring PMUT with a PZT thickness of $2\ \mu\text{m}$ and a radius of $135\ \mu\text{m}$. The resulting device has an excellent electromechanical coupling factor. Not only piezoelectric ceramics and single crystals, but also piezoelectric polymers have been used to fabricate ring arrays. Ketterling *et al* [113] bonded annular PVDF on a polyimide film covering a copper electrode and filled the gap using epoxy resin. Gottlieb *et al* [114] fabricated a high-frequency ring transducer using P(VDF-TrFE) and a double-sided polyimide circuit. Since the acoustic impedance of the polymer itself is low, no matching layer is required. In recent reports [91], attempts have been made to fabricate annular arrays using 3D printing and progress has been made (figure 5(e)).

A more complex array is a two-dimensional (2D) planar array. It not only needs to consider the structure design of

the transducer, but also needs to consider the electronic control technology. Here only the device fabrication is discussed, excluding the electronics. Conventional 2D arrays use cutting techniques to determine the number of elements by varying numbers of cuts. MEMS process-based arrays directly utilize patterning processes, such as dry etching, wet etching, etc, to form small components. Due to the complexity of 2D phased array technology, it has not been widely used in the field of ultrasound therapy.

In recent years, flexible ultrasonic transducers have received extensive attention. The wearable ultrasonic transducer array can be worn directly on the skin, enabling real-time and continuous blood pressure monitoring [66]. Due to the use of elastic electrodes, the array is conformal with the skin. In order to be widely used in medical applications, more research needs to be done in electronic control, signal processing and phased array algorithms. In addition, researchers have used flexible ultrasound arrays for neural regulation [115], and even use it for brain stimulation in conjunction with brain-computer interface (BCI) technology [116].

4.4. Multiple self-focusing

The multi-element self-focusing transducer makes a special structure on the surface of the piezoelectric material, so that each region of the piezoelectric material emits different phases of ultrasonic waves, so as to realize the regulation of sound waves [117]. This method is very similar to acoustic lenses, especially through the special structural design of the material to achieve focusing [118]. The difference is that the acoustic lens is a passive material and does not change the structure of the piezoelectric material itself, while the multivariate self-focusing directly changes the piezoelectric material. Therefore, although the multivariate self-focusing method does not produce complex acoustic fields like acoustic lenses, it can greatly reduce the energy loss caused by impedance mismatch for focused ultrasound transducers.

The first common self-focusing method is based on the Fresnel half-band. Spaced rings are formed on the surface of the piezoelectric material by micromachining techniques, and the sound waves generated by each sound source are delayed by an integer multiple of the wavelength, then interference occurs at the focal point [119]. The specific preparation process mainly includes: laser cutting, filling epoxy resin, and sputtering electrode, making matching layer and backing layer. Compared with the ring phased array, this method requires only one wire to be connected to each ring separately, reducing the difficulty caused by electron focusing. An alternative approach to self-focusing is to fabricate piezoelectric materials with acoustic metas faces. Acoustic metamaterial can be designed to modulate the phase and amplitude of the acoustic wave by designing the structure of different units to enable acoustic focusing. For example, Li *et al* [120] fabricated an active gradient metamaterial that achieves broadband self-focusing of ultrasonic waves under water.

Another self-focusing method is to use type 1–3 piezoelectric composites. In the type 1–3 piezoelectric composite material, the piezoelectric material is connected in 1 dimension and

the polymer is connected in 3 dimensions. With the help of the curved surface forming process, each piezoelectric column can be located in different planes and emit different phase sound waves. The first type of focusing transducer is made of 1–3 type piezoelectric composite material with uneven thickness [121]. The traditional 1–3 piezoelectric composites can form many longitudinal vibrating piezoelectric columns by cutting and filling process. Further, through mechanical grinding, a surface of uneven thickness can be formed to improve focusing performance. The second type of focused transducers made of type 1–3 piezoelectric composites is based on flexible electronic technology [122]. The composite structure of elastic material and piezoelectric ceramics is prepared to make the whole device flexible.

5. Applications of PFUT

The biomedical applications of focused ultrasonic transducers can be divided into two broad categories. The first type is used in ultrasonic medical diagnosis, ultrasonic solid detection and other fields. In this kind of focused ultrasound system, the intensity of the ultrasonic wave is not large, and the focusing technology is mainly used to improve the sensitivity and resolution. The second type of application is to focus ultrasound energy to a sufficient intensity to produce corresponding biological effects, such as ultrasonic tumor ablation, ultrasonic nerve stimulation, ultrasonic acoustic tweezers, etc. Table 1 summarizes several properties of the focused ultrasound transducers in biomedical applications. This section mainly introduces the development status of focused ultrasound in these fields, including process progress and application direction.

5.1. Ultrasonic imaging

With the development of piezoelectric materials and preparation technology, piezoelectric ultrasonic transducers have been widely used in medical diagnostic imaging. Generally speaking, the image quality of ultrasonic imaging is mainly affected by the spatial resolution and sensitivity of the transducer [48]. Spatial resolution determines the degree of differentiation between the imaging target and other objects, and the higher the center frequency and bandwidth of the transducer are, the better the axial resolution. The transverse resolution is determined by the focusing parameters of the transducer, which can be expressed as the ratio of the focal length of the transducer to the aperture size. Sensitivity is a physical quantity that represents the efficiency of electroacoustic energy conversion. High sensitivity means that the transducer can concentrate more emission energy at the focal point, thereby improving the contrast of the ultrasonic image and producing a brighter target image. When the frequency is higher than 20 MHz, focusing design is often required to improve imaging resolution and sensitivity due to energy attenuation. In addition, in photoacoustic imaging technology, the acoustic focusing technology of piezoelectric transducers can provide high reception sensitivity to the photoacoustic signals generated in the target region.

In medical imaging, intravascular ultrasound (IVUS) imaging is an important tool in the diagnosis of cardiovascular diseases. IVUS imaging is to obtain information such as vessel wall thickness and lesion location by forming high-resolution ultrasound images in arteries with the help of tiny ultrasonic transducers. Ultrasound plays a pivotal role in assessing blood flow and detecting abnormalities such as blockages, clots, and aneurysms within the vascular system. The center frequency of the general medical IVUS imaging transducer is between 20 and 60 MHz. Further extending its application, endoscopic ultrasound combines the advantages of endoscopy and ultrasound, allowing for high-resolution images of the digestive tract and its adjacent structures. This technique is particularly useful in evaluating submucosal lesions, staging cancer, and guiding biopsies, offering a level of detail that surpasses traditional imaging methods. Additionally, ultrasound imaging is integral in obstetrics for monitoring fetal development, in musculoskeletal assessments to visualize ligaments and tendons, and in guiding needle placement during biopsies or injections. Advances in ultrasound technology, such as 3D imaging and focused ultrasound for therapeutic purposes, continue to expand its applications, underscoring its vital role in the diagnosis, treatment, and management of various medical conditions. The following introduces some specific work in recent years.

Unit transducers usually use a curved surface structure to focus. Yoon *et al* [128] proposed an angle-focused single crystal probe to address the problem of small lumen area during intravascular obstruction (figure 6(a)). The transducer consists of a curved single crystal material combined with an aperture with a 60° inclination angle, a center frequency of 45 MHz, and an axial and transverse resolution of 25 and 120 μm , respectively. It can achieve high resolution imaging of intravascular narrow areas. Fei *et al* [129] prepared an IVUS transducer with a single-sided concave structure by ball pressure method. Compared to planar transducers, half-concave transducer has a higher center frequency (35 MHz), wider bandwidth (54%), and higher resolution (34.5 μm axial resolution, 392 μm transverse resolution). The above studies have all used piezoelectric single crystal PMN-PT due to its outstanding piezoelectric properties and mature preparation process. However, considering its brittleness, other piezoelectric materials are also used, such as PZT [123], KNN [84], LiNbO₃ [130], PVDF [131], ZnO [132] and so on. Lee *et al* [130] developed a dual-frequency ultrasonic transducer prepared by a 50 μm thick PZT and 28 μm thick LiNbO₃, operating at 35 MHz and 105 MHz, respectively, as shown in figure 6(b). The simulation results show that the geometric focal length produced by the spherical pressure method is shorter than the natural focal depth, and the DOF regions of the two transducers overlap to work together. As an important supplement to ultrasound imaging, photoacoustic imaging has attracted much attention due to its combination of high sensitivity of optical imaging and low attenuation of acoustic imaging [16]. Focusing technique plays an important role in photoacoustic transducers because it can improve the receiving sensitivity of piezoelectric transducers at the focal point. Nguyen *et al* [133] fabricated a photoacoustic imaging system based on a

Table 1. Summary of several properties of focused ultrasound transducers in biomedical applications.

| Application | Focusing technique | Piezoelectric materials | Center frequency/MHz | Spatial Res./mm | | |
|---|--|-------------------------|----------------------|-----------------|-------|-------|
| | | | | Lateral | Axial | |
| Intravascular ultrasound imaging | Curved surface focusing Acoustic lens | PMN-PT | 35 | 2.3 | 5.5 | [123] |
| | | PZT-5H | 52.5 | 0.046 | 0.183 | [56] |
| Integration of ultrasound imaging and therapy | Phased array focusing | PZT-5H | 1 | 1.9 | 12.6 | [124] |
| Ultrasonic tumor ablation | Spherical transducer | — | 0.43 | 2.2 | 2.7 | [38] |
| Ultrasonic neuroregulation | Phased array focusing | PZT | 8.4 | 0.215 | 1.68 | [125] |
| | Phased array focusing | PZT | 0.215 | 0.215 | 1.68 | [126] |
| Cell manipulation | Curved surface focusing | LNO | 30 | 0.03 | 0.2 | [127] |

multifocal piezoelectric ultrasound transducer. The designed multi-spherical PVDF transducer has seven focal points, and the depth of field (from 0.4 to 10 mm) is extended by the superposition of focal fields (figure 6(c)). Fang *et al* [134] developed a transparent photoacoustic transducer for optical microscopy, made of PVDF laminated on a concave glass sheet. The experimental results show that the transducer has a center frequency of 24 MHz, a focal length of 1.3 mm, a focal depth of 1.6 mm, and 60% optical transmittance. Zhang *et al* [94] fabricated an ellipsoidal transducer using a piezoelectric polymer, which, in contrast to the spherical shape, has a continuous multifocal and is able to extend the depth of field. To fabricate the transducer, polyvinylidene difluoride trifluoroethylene P (VDF-TrFE) was pressed onto the surface of a bending die to achieve self-focusing.

Most high-frequency ultrasound transducers are too small and the lenses are not easy to fabricate, so improving the imaging resolution through acoustic lenses is not optimal. But efforts have been made. Su *et al* [55] stacked Fresnel band plates onto the surface of a single-plane transducer, and the sound waves were diffused and converged into the focal region, both increasing the intensity of the sound waves and reducing the focal size. Park *et al* [135] developed an integrated imaging system by fusing four techniques: ultrasound imaging, photoacoustic imaging, optical coherence tomography, and fluorescence imaging (figure 6(d)). The spherical acoustic lens is placed in the front to improve the lateral resolution and image contrast.

Currently, there is increasing interest in array transducers in the field of ultrasound imaging because they can improve imaging performance using electronic focusing. The development of semiconductor processes has promoted the application of MEMS technology in piezoelectric transducers. But limited by cost and yield, there is still a long way to go.

5.2. Focused ultrasound ablation

Unlike ultrasonic diagnosis, which uses transducers to receive ultrasonic signals reflected by human tissues for imaging, ultrasonic therapy uses various biological effects of ultrasound on human tissues to treat focal areas. Therefore, the

transducers used for ultrasound therapy need to focus the sound waves in a small area, so that the energy can be applied to the body's lesions with the least possible damage to the surrounding tissue. HIFU was first proposed in 1932, when Ter Haar and Coussios found that focused ultrasound could heat tissue [136]. In 1942, Lynn *et al* [137] pointed out that focused ultrasound could cause drastic changes in energy at the focal point without damaging the tissue in the beam path. So far, HIFU transducers have been successfully used in the treatment of various tumors, such as liver tumors [138], breast cancer [139], brain cancer [140], uterine fibroids [141] and bone cancer [142].

In tumor ablation, ultrasonic waves emitted by the transducer pass through the skin and human tissues, accompanied by energy attenuation, and eventually reach the lesions in the human body. Through the focusing design of the transducer, the acoustic beam can form a high-energy focus at the lesion and use the biological effect with the tissue to achieve the destruction of the disease cells. Generally speaking, the maximum diameter of the lesion area is 3 ~ 4 cm, and the boundary width cannot exceed 50 μm to ensure that the surrounding tissue is not destroyed. In order to control the focused sound beam accurately, efforts have been made in theoretical simulation and structural design [143–147]. Choi and Roh [36] designed a novel toroidal concave transducer through theoretical simulation (figure 7(a)). The transducer can effectively focus the ultrasound beam while suppressing the sidelobe and avoiding damage to the surrounding tissue. Zhang *et al* [148] numerically investigated the phased array algorithm of a ring array transducer to create a more precise focus for the treatment of breast cancer (figure 7(b)). Li *et al* [38] designed a spherical cavity transducer with two ends open. 64 concave piezoelectric ceramics emit 430 kHz ultrasonic waves and form a focused sound field after many reflections. Figure 7(c) shows the regular sound field generated by the spherical cavity transducer. Liu and Ren [37] designed an acoustic focusing lens with a periodic groove structure. Using this corrugated lens can reduce the relative sidelobe amplitude by about 3 dB.

Due to the small scope of each ultrasound examination, ultrasound tumor ablation still faces the problem of long

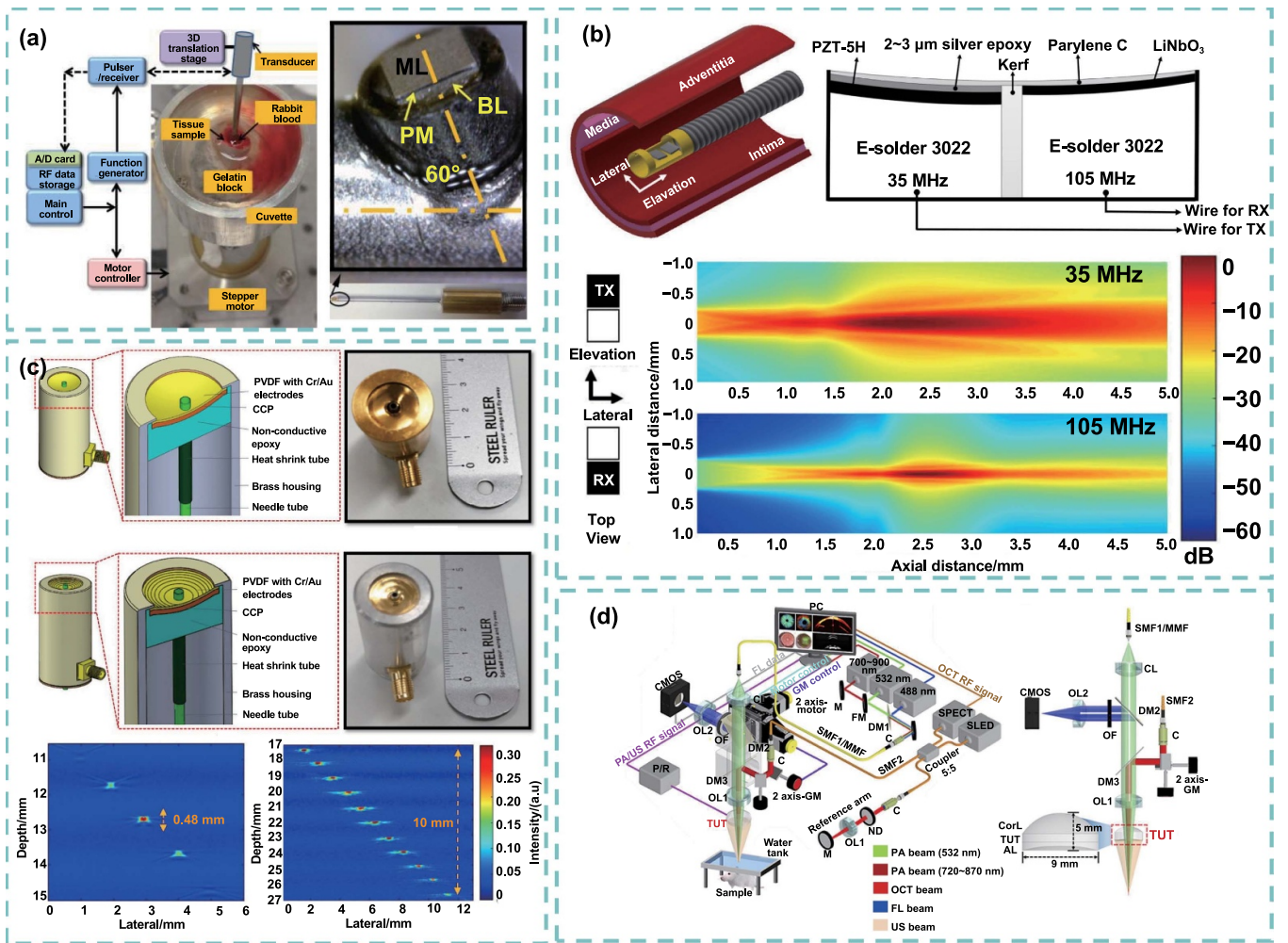


Figure 6. A focused transducer for ultrasound imaging. (a) Angle-focused single-crystal probe for intravascular imaging [128]. Reprinted from [128], Copyright © 2015 Elsevier B.V. All rights reserved. (b) Dual-frequency focused ultrasound transducer [130]. Reproduced from [130]. CC BY 4.0. (c) Multifocal piezoelectric ultrasonic transducer [133]. Reproduced from [133]. CC BY 4.0. (d) Four-mode ultrasound imaging system [135]. Reproduced from [135]. CC BY 4.0.

surgical time. In order to enlarge the ablation area, a common method is to increase the focus area with a dual-frequency focusing transducer. As shown in figure 7(d), Jeong *et al* [149] prepared an ultrasonic probe consisting of two frequencies of 4.1 and 2.7 MHz. Through sound field and temperature field tests, it was proved that the transducer could increase the range of axial ablation and greatly shorten the treatment time. Ma *et al* [150] designed and prepared a dual-frequency focused ultrasonic transducer with the same focal length of 15 mm at both 3 and 1.5 MHz operating frequencies. The tissue ablation experiment observed that dual-frequency ultrasound could produce higher ablation temperature. Park *et al* [151] combined two PZTS with opposite polarization directions and different thicknesses, and by filling epoxy resin, prepared focusing transducers with two frequencies, with a center frequency of 1.2 MHz and a second harmonic frequency of 2.4 MHz.

One of the key advantages of HIFU therapy is its non-invasive nature, significantly reducing the risk of complications associated with traditional surgical interventions, such as

infections and prolonged recovery times. Additionally, HIFU offers a therapeutic option for patients who may not be candidates for surgery due to various reasons, including the location of the tumor or underlying health conditions. As research and technology in the field of focused ultrasound continue to advance, the scope of HIFU therapy’s applications is expected to widen, further establishing its role as a vital tool in modern, minimally invasive medical treatments. In short, since HIFU transducers usually require higher sound intensity for use in biological tissues, it still needs to be improved considering the issue of safety.

5.3. Ultrasonic neuroregulation

Neuroregulation is a new technology that transfers energy into the body to regulate the nervous system, and it has a wide range of applications in human brain, ophthalmology and other diseases. LIFU is a non-invasive mode of nerve stimulation. Compared with transcranial magnetic stimulation, transcranial direct electrical stimulation, and transcranial alternating

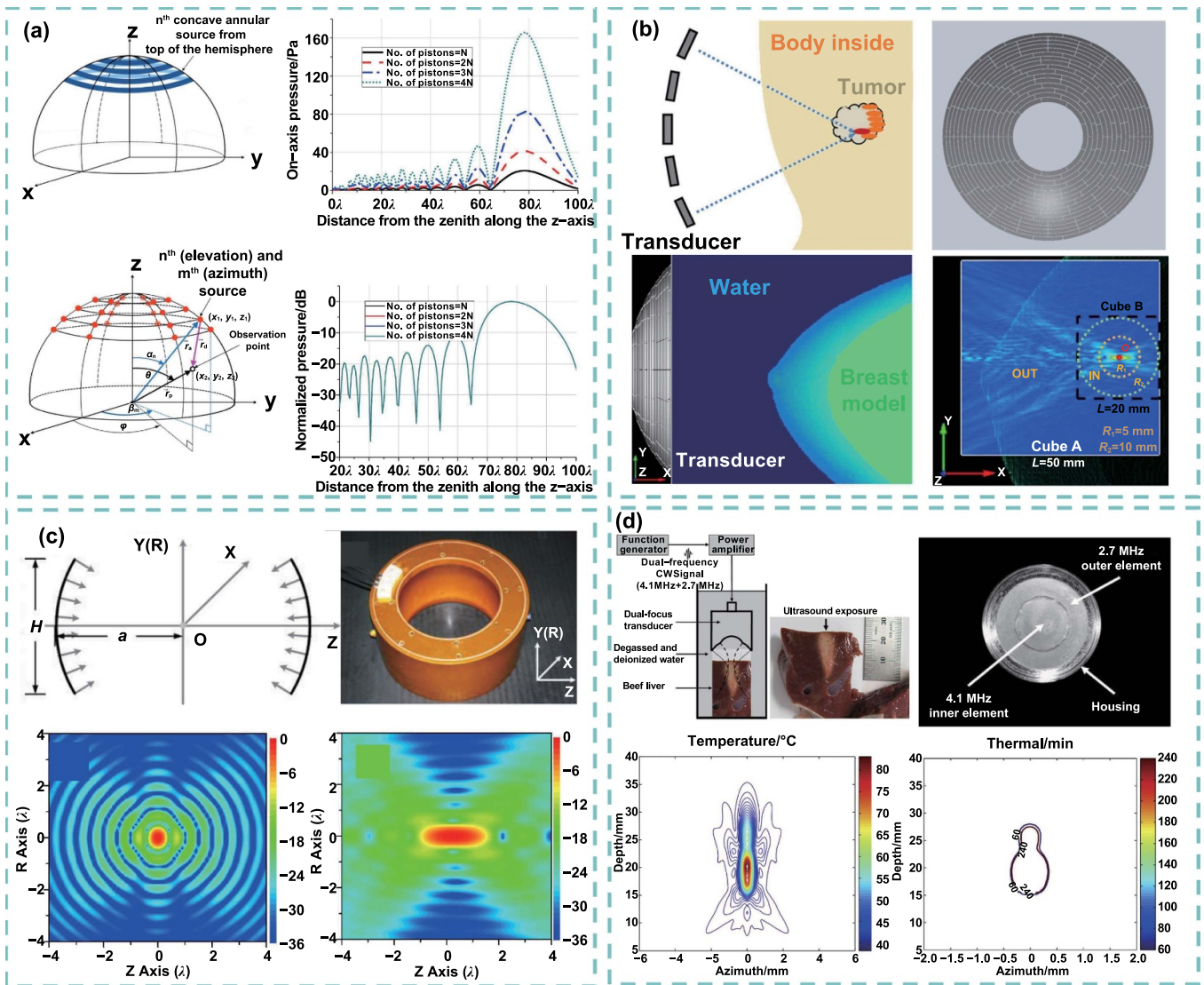


Figure 7. A focused transducer for ultrasound ablation. (a) Theoretical model of an annular focusing transducer [36]. Reprinted from [36], © 2017 Elsevier B.V. All rights reserved. (b) An annular ultrasound transducer for breast cancer treatment [148]. Reprinted from [148], © 2021 Elsevier B.V. All rights reserved. (c) A spherical cavity transducer with a periodic structure with reduced side lobe [38]. Reprinted from [38], with the permission of AIP Publishing. (d) A dual-frequency ultrasound transducer to extend the ablation range [149]. Reprinted from [149], © 2010 World Federation for Ultrasound in Medicine & Biology. Published by Elsevier Inc. All rights reserved.

current stimulation [152], LIFU has a higher spatial resolution at the millimetre scale, especially in the case of penetrating the skull and deep tissues, ultrasound has great application potential. LIFU has shown promise in preliminary studies for the treatment of conditions such as depression, obsessive-compulsive disorder, and chronic pain, as well as in enhancing cognitive functions and potentially treating neurodegenerative diseases like Alzheimer's. Moreover, the specificity of LIFU allows for targeting deep brain structures with minimal impact on overlying tissues, offering a level of precision that is difficult to achieve with other non-invasive modalities. Early LIFU transducers used geometric focusing. Fry *et al* [153] first demonstrated in 1950 that ultrasound modulated neural activity. They utilized a quartz crystal with a diameter of one inch (resonant frequency 980 kHz) and reported

a temporary suppression of spontaneous activity after ultrasound was transmitted through the ventral nerve cords of the crayfish. In 1958, they also presented results of *in vivo* ultrasound neuroregulation based on visual pathways [154]. This study reports that ultrasound stimulation of the lateral geniculate nucleus of cats for 20 ~ 120 s was able to significantly inhibit photo evoked potentials. This inhibition was fully restored after 30 min. In 2013, Deffieux *et al* [155] used a single crystal ultrasonic transducer with a diameter of 64 mm to modulate the visual motor behaviour of monkeys, as shown in figure 8(a), which was capable of generating a cigar-shaped focus of 5 mm × 5 mm × 33 mm. Legon *et al* [156] found in his study that 0.5 MHz focused ultrasound could pass through the human skull and produce a beam profile with a lateral resolution of 4.9 mm and an axial resolution of 18 mm.

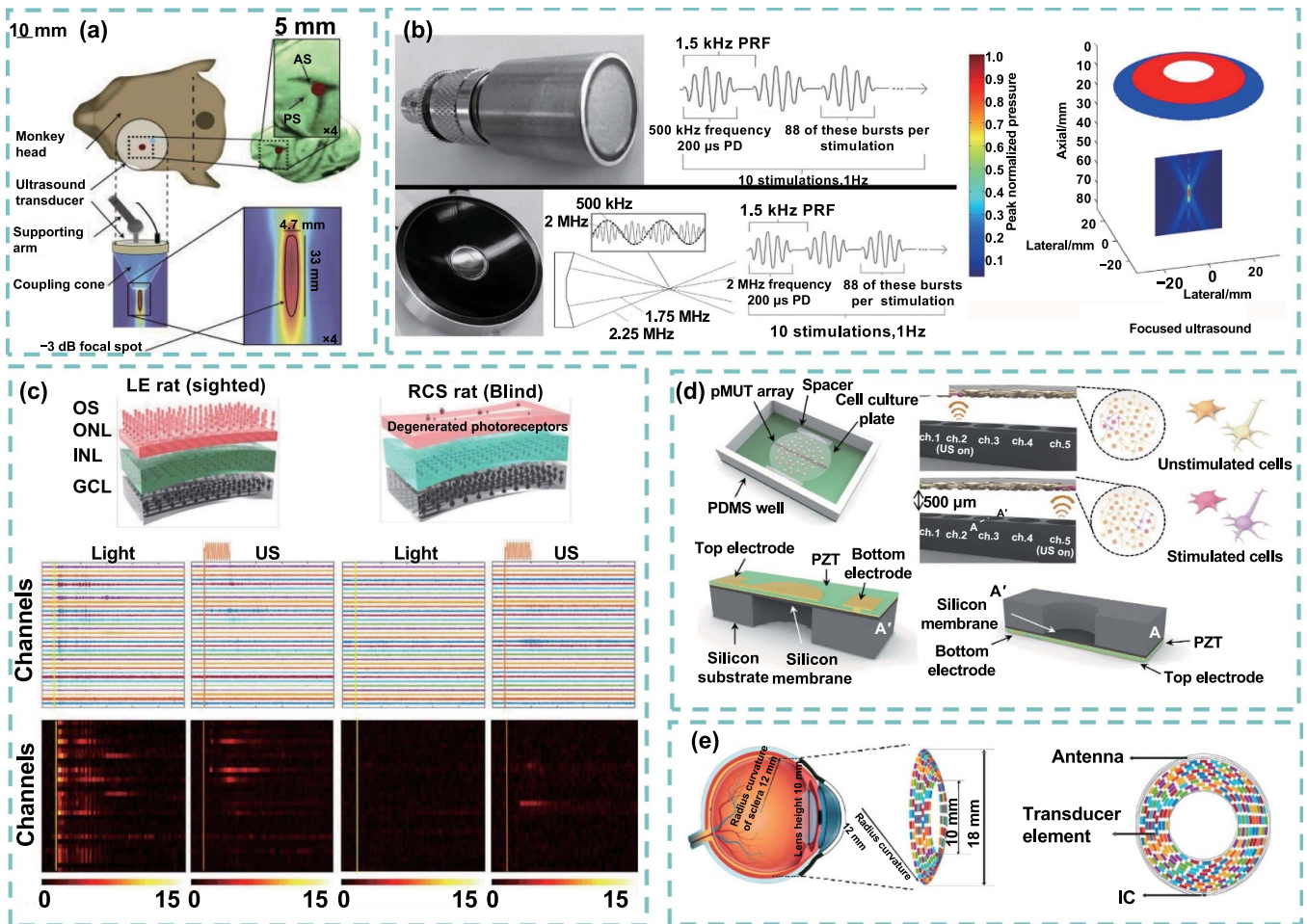


Figure 8. Focusing transducer for ultrasound neuromodulation. (a) A single-crystal focusing transducer for modulation of the visual nerve in a monkey [155]. Reprinted from [155]. © 2013 Elsevier Ltd. Published by Elsevier Inc. (b) Compare the sound field characteristics of the focused and unfocused transducers [157]. Reproduced from [157]. CC BY 4.0. (c) Proof of ultrasound stimulation of the retina [158]. Reproduced from [158]. CC BY 4.0. (d) MEMS ultrasonic stimulation system [159] Reproduced from [159]. CC BY 4.0. (e) Annular phased array for retinal prosthesis [160]. Reproduced from [160]. CC BY 4.0.

Mehić *et al* [157] studied the acoustic field distribution characteristics of single-crystal focused and non-focused transducers (figure 8(b)), and improved the anatomic specificity of neuroregulation by modulated focused ultrasound.

In order to realize the application of ultrasonic neuroregulation in broader neuroscience research, more experimental exploration has been carried out. Zheng and his team focused on transcranial wearable ultrasound stimulators. They prepared a bending transducer [161], heated PZT-5H/epoxy resin piezoelectric composite material in an oven to 65 °C, and focused the transducer through ball pressure. This wearable ultrasound device can improve the movement ability of Parkinson’s patients. Zheng and his team also developed a head-mounted ultrasonic transducer consisting of a disk piezoelectric ceramic and a focusing lens to induce neuroregulation in awake and freely moving mice [162]. Liu *et al* [163] connected rigid PZT islands with flexible Bridges to make them stretchable and more suitable for complex surfaces. Most studies have focused on single targets, and phased array transducers can be used when neural regulation of multiple targets is required [164, 165]. Tipsawat *et al* [126] fabricated a

32-element phased array PMUT using a MEMS process and demonstrated how to achieve ultrasonic focusing and steering. Costa [166] has prepared 26 × 26 2D phased array transducers with 2D arrays of PZT piezoelectric sensors micromachined directly on top of complementary metal oxide semiconductor (CMOS) integrated circuits. Lee *et al* [159] targeting the compatibility of PMUT ultrasonic transducers with cell experiments, proposed a new MEMS ultrasonic stimulation system for modulating neurons or brain slices at high resolution (figure 8(d)). In the future, ultrasonic neuroregulation will continue to develop into arrays to achieve more complex application needs. Although the acoustic lens will cause a certain amount of energy loss, with the help of the acoustic lens, a diversified ultrasonic field can be formed in the skull. Hu *et al* [167] developed a binary acoustic surface lens to achieve both the dual function of correcting cranial-induced beam aberrations and achieving dynamic focusing. Maimbourg *et al* [168, 169] for the first time coupled a single crystal transducer to a thick-controlled acoustic lens, enabling adaptive transcranial focusing by adjusting the thickness of the crystal. Jimenez–Gambin and his team reported

Table 2. Summary of typical low-intensity focused ultrasound transducers.

| Device type | Center freq. kHz ⁻¹ | Focal distance F mm ⁻¹ | Spatial res. mm ⁻¹ | | Peak pressure MPa ⁻¹ | References. |
|--|-----------------------------------|--------------------------------------|-------------------------------|-------|------------------------------------|-------------|
| | | | Lateral | Axial | | |
| Single crystal transducer (Dia = 10 cm) | 690 | 6 | 2.3 | 5.5 | 0.38 | [177] |
| Single crystal transducer (Dia = 6.4 cm) | 320 | 10 | 5 | 33 | 0.6 | [155] |
| Single crystal transducer (Dia = 3 cm) | 500 | 30 | 4.9 | 18 | 2.5 | [156] |
| Type 1–3 piezoelectric composites | 800 | 7 | 2.2 | — | 0.151 | [161] |
| Single crystal probe with acoustic lens | 2000 | 7 | — | — | 1.2 | [162] |
| 32 element PMUT phased array | 1400 | 20 | 1 | 9.2 | 0.44 | [165] |
| Integrated 2D phased array transmitter in CMOS | 8400 | 5 | 0.215 | 1.68 | 0.1 | [166] |

that 3D printed acoustic hololens can generate a wide variety of ultrasonic fields within the skull, such as bifocal beams, self-bending beams, volumetric focused beams, and ultrasonic vortices [170, 171].

In addition, LIFU has been widely used in retinal stimulation as an alternative to electrode stimulators. In 2012, Naor *et al* [172] first proposed an ultrasonic retinal prosthesis consisting of a multi-element phased array focusing transducer and a camera with an image processor that enables multifocal stimulation. In practical tests, acoustic coupling components are connected to the cornea to project complex acoustic images onto the retina. A year later, Menz *et al* [173] used a higher acoustic frequency (43 MHz) to demonstrate a stable response induced by ultrasonic stimulation in the retina of isolated salamanders. Interestingly, ultrasonic stimulation was found not to activate ganglion cells directly, but interneurons outside the photoreceptors. In a separate study [174], they further explored the physical mechanisms of ultrasonic retinal stimulation, which has three effects that can activate neurons: cavitation, acoustic radiant force, and thermal effects. They applied ultrasonic stimulation with a central frequency range of 0.5–43 MHz to the retinas of isolated salamanders, demonstrating that the principle of ultrasonic retinal stimulation is radiant force based on changes in neuronal strength thresholds. Zheng *et al* [160, 175, 176] carried out a series of studies on the design of the ring transducer, as shown in figure 8(e). By simulating the sound field and optimizing the number of chips, they determined 512 elements as the best design considering the feasibility of the process.

Table 2 summarizes some typical LIFU transducers and their associated characteristics, including center frequency, focal length, resolution and sound intensity. 2D phased array transducers integrated with CMOS have advantages in performance. In the future, LIFU transducers will be combined with BCI technology to play an important role in neural regulation. In addition, ultrasound stimulation of retina is also a worthy research direction [158].

5.4. Ultrasonic energy transfer

Wireless power transmission plays an important role in implantable devices and nerve electrical stimulation [178, 179]. Traditional inductive coupling technology cannot meet

the development needs of implantable devices because of serious energy attenuation and poor safety [180]. Ultrasonic-induced wireless energy transmission (UWET) is a new technology emerging in recent years. In UWET technology, mechanical energy carried by ultrasound is transmitted from the transmitting transducer to the receiving transducer to power other devices. The receiving transducer is generally placed at the focal point of the transmitting transducer to maximize the energy transfer efficiency. Because of its long transmission distance and safety for the human body, UWET is widely used in the implantable device [181]. Therefore, this section will introduce the latest progress of focusing ultrasonic transducers in wireless energy transmission systems.

In the past 20 years, ultrasonic wireless energy transmission technology has developed rapidly. Back in 2007, Maleki *et al* proposed an energy collector based on ZnO nanowire, in which they connected multiple collectors in parallel and series to increase the output current and voltage [181]. Subsequently, researchers have proposed ultrasonic energy transfer devices based on other piezoelectric materials, such as PZT, PMN-PT, PVDF, and 1–3 piezoelectric composites [182–184]. In order to improve energy transmission efficiency, focused ultrasonic transducers are generally used as the energy emission part. Feng *et al* developed an ultrasonic transmission and communication system based on flexible electronics technology. For the energy emission transducer, they specially designed a focusing ultrasonic transducer with a plum structure, as shown in figure 9(a), which can change the longitudinal position of the focus by adjusting the curvature of the base [185]. Compared with conventional planar transducers, the transducer developed by the team has better flexibility and lower energy attenuation [186]. Jiang *et al* made use of circular PZT to prepare a curved structure piezoelectric ultrasonic transducer with self-focusing function, as shown in figure 9(b). In this work, they combined acousto-optic converters with piezoelectric transducers to establish a two-mode ultrasonic energy transmission system. The test results show that the system can produce milliwatt energy and is capable of high resolution signal communication (SNR to 22.5 dB) under 12 mm thick pig tissue [187].

In theory, the focusing transducer can improve the energy output by enhancing the sound intensity at the focal point, but considering the safety of ultrasound in the human body, the sound intensity must be less than the threshold. Another way

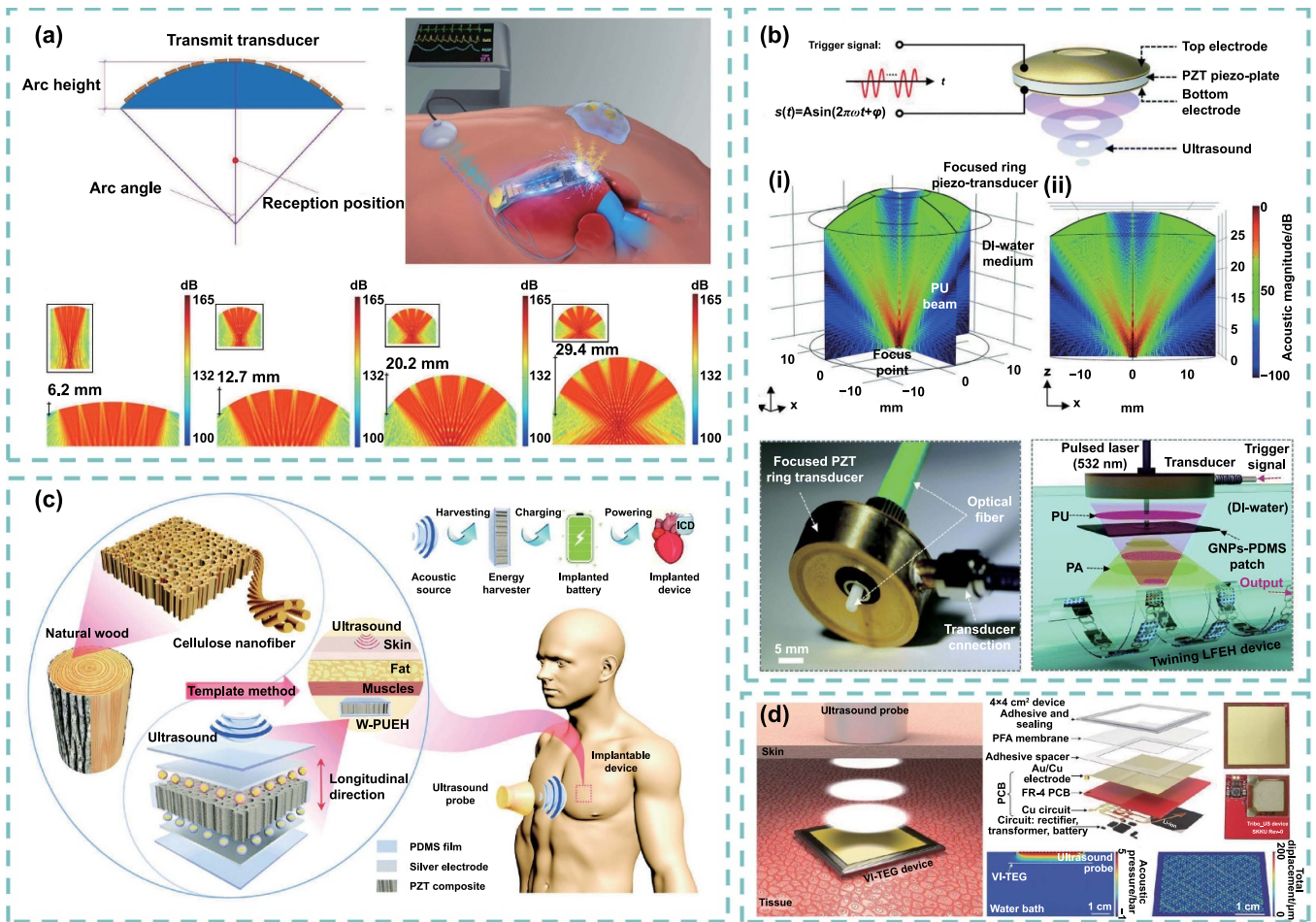


Figure 9. Focusing transducers for ultrasonic wireless energy transfer systems. (a) Ultrasonic transmitter with plum structure [185]. Reproduced from [185]. CC BY 4.0. (b) Photoacoustic and piezoelectric dual-modal ultrasonic energy delivery system [187]. Reproduced from [187] with permission from the Royal Society of Chemistry. (c) Piezoelectric transducer based on bionic wood structure [188]. Reproduced from [188] with permission from the Royal Society of Chemistry. (d) The first use of triboelectric sensors to receive ultrasonic energy [189]. From [189]. Reprinted with permission from AAAS.

to boost output is to improve the performance of the receiving transducer. For example, Hong *et al* focused on improving the acoustic impedance and electromechanical coupling coefficient of the ultrasonic transducer, as shown in figure 9(c). Inspired by the bionic wood structure, they prepared a new type 1–3 piezoelectric composite material, which was successfully used in the wireless energy transmission system across muscles [188]. In fact, most of the research work on wireless ultrasonic energy transfer is based on piezoelectric materials [190–193]. It was not until 2019 that Kim *et al* first proposed the use of triboelectric sensors for ultrasonic energy harvesting. As figure 9(d) shows, They built an ultrasonic wireless transmission system that emits ultrasonic waves from piezoelectric ultrasonic probes located outside the body, while implantable triboelectric sensors integrated with flexible printed circuits collect the energy [189]. In 2022, Liu *et al* further improved the energy transfer efficiency by improving the structure of the triboelectric sensor [194].

In recent years, the research interest in combining wireless ultrasonic energy transmission systems with electrodes has been growing rapidly [195, 196]. The electrical signal output

of the ultrasonic transducer is applied to the electrode by the rectifier to achieve retinal nerve stimulation and deep brain stimulation. Zhang *et al* [195] developed an energy harvesting device that connects a single piezoelectric crystal with a thickness of 350 μm s to a stretchable electrode to form a 6 \times 6 microarray. Using a focused transducer probe to apply 1 MHz ultrasound, the electrodes will output electrical signals to stimulate the brain and achieve analgesic management [195]. Jiang *et al* used a wireless ultrasonic energy delivery system for retinal electrical stimulation. Powering the electrodes through external ultrasonic stimulation could facilitate the treatment of retinal degenerative diseases [197, 198]. This work develops a new path for the future application of focused ultrasound transducers in eye diseases. In the future, with the rapid development of transparent piezoelectric materials, emission-type transducers located outside the eyeball can be made into glasses to provide continuous energy for implanted electrodes. In summary, the focusing performance of transmitter transducers will affect the application of wireless energy transmission systems in implantable devices. Especially in some tiny human organs, the location of the focal point must be

small enough to guarantee the safety of the surrounding tissue, which is often not satisfied by traditional non-focusing transducers.

5.5. Ultrasonic tweezers

Sound waves can generate a large acoustic radiation force and be used to manipulate small substances such as particles and cells [199]. It has many applications in biomechanics, chemistry, medicine and other fields. Compared with optical and magnetic tweezers, acoustic tweezers have the advantages of non-invasive and wide application. A common acoustic tweezer is the single-beam acoustic tweezer, which is generally made of curved piezoelectric material. The particles are located at the focus of the transducer and are affected by acoustic radiation force to change their shape or movement.

Ultrasonic acoustic tweezers can play a role in cell mechanics, such as assessing the mechanical properties of cells. Shung *et al* [200, 201] fabricated two acoustic tweezers with a center frequency of 50 and 30 MHz, respectively, using LNO of different thicknesses (figure 10(a)). The transverse and axial resolution of the transducer are increased to 84 and 49 μm , respectively, by the hot pressing process. As shown in the mechanical properties of the cell can be obtained by studying the relationship between the sound pressure and the deformability of the cell when it is trapped at the focal point. Another application is to capture the cell and make it move following the moving trajectory of the transducer [202, 203]. Jiang *et al* [127] fabricated a high-performance curved surface type 1–3 piezoelectric composite with a center frequency of 23.4 MHz. And as seen in figure 10(b), when the acoustic tweezers move at a lower speed, the trapped particles also follow the focus of the acoustic tweezers.

In order to achieve higher frequencies, piezoelectric thin film technology has been valued. Chen *et al* [204] used a mechanical thinning process to polish LNO crystals, which can achieve thicknesses as low as 6 μm s and center frequencies as high as 300 MHz (figure 10(c)). The relationship between excitation frequency and control particle size is investigated. It is found that particles of different sizes can be captured by changing the wavelength of incident wave. Fei *et al* [205] used lithography and etching techniques to prepare silicon-based acoustic lenses that can focus UHF acoustic beams emitted by ZnO transducers (figure 10(d)). In cell manipulation experiments, the system can stably clamp 5-micron microspheres. Fei *et al* [205] fabricated ultrasonic tweezers with ultra-high center frequency (230 MHz) and ultra-narrow acoustic microbeam (8.2 μm) by sputtering 10 μm $\text{Al}_{0.82}\text{Sc}_{0.18}$ onto a pre-focused metal substrate, as shown in figure 10(e). The results of acoustic capture experiments showed that the device was able to capture polystyrene microspheres and epidermoid cancer cells under non-contact conditions.

Ultrasonic tweezers represent a groundbreaking advancement in the field of biomedical engineering. Unlike traditional mechanical tweezers, ultrasonic tweezers can handle delicate biological structures without direct physical contact, thus minimizing the risk of damage and contamination. This feature is particularly advantageous for applications requiring

sterile conditions and gentle handling, such as in the sorting and assembly of cellular constructs, tissue engineering, and regenerative medicine. Furthermore, in the realm of targeted drug delivery, ultrasonic tweezers can guide microcarriers loaded with therapeutic agents directly to specific sites within the body, enhancing the efficacy and reducing the side effects of treatments. Ultrasonic tweezers also find applications in the precise manipulation and study of single cells, enabling researchers to investigate cellular responses and interactions under controlled conditions. This contributes to a deeper understanding of cellular mechanics, embryonic development, and disease progression at the cellular level. As research progresses, the potential medical applications of ultrasonic tweezers continue to expand, promising revolutionary advancements in cell therapy, regenerative medicine, and drug delivery. Their ability to manipulate matter at the micro-scale with high precision and minimal invasiveness positions ultrasonic tweezers as a key tool in the future of biomedical research and therapeutic interventions.

Indeed, a predominant trend in the development of ultrasonic tweezers involves the utilization of single crystal materials for their construction. Within the realm of biomedical applications, these advanced tweezers have emerged as indispensable assets for the manipulation and sorting of cells with unparalleled precision. Leveraging focused ultrasonic transducers, these tweezers offer a refined control scheme, enhancing their efficacy in various biomedical contexts. Looking ahead, the ongoing optimization of acoustic parameters stands as a key challenge, essential for expanding the scope of applications while concurrently minimizing the risk of tissue damage. This concerted effort toward refinement promises to unlock the full potential of ultrasonic tweezers, enabling their widespread adoption and transformative impact across diverse biomedical domains.

6. Conclusions and outlook

In the past few decades, advances in piezoelectric materials and their processing and manufacturing techniques have promoted the development of focused piezoelectric transducers [206]. Ultrasound transducers with focusing technology have made great breakthroughs in the fields of medical imaging, wireless energy transfer, and neuromodulation. Figure 11 gives a summary of the development of focused ultrasound since 1930. The focused transducer has a higher resolution in the high-frequency range than the unfocused ultrasound transducer, and is able to focus the energy over a small range. This advance has given focused ultrasound an important place in the field of medical imaging and therapy. However, many problems need to be solved to realize the clinical application of focusing transducers. In the following, prospects are presented from the aspects of materials, preparation, and application safety.

- (1) Material innovation: the selection of piezoelectric materials plays an important role in the performance and design of focused ultrasound systems, and new piezoelectric

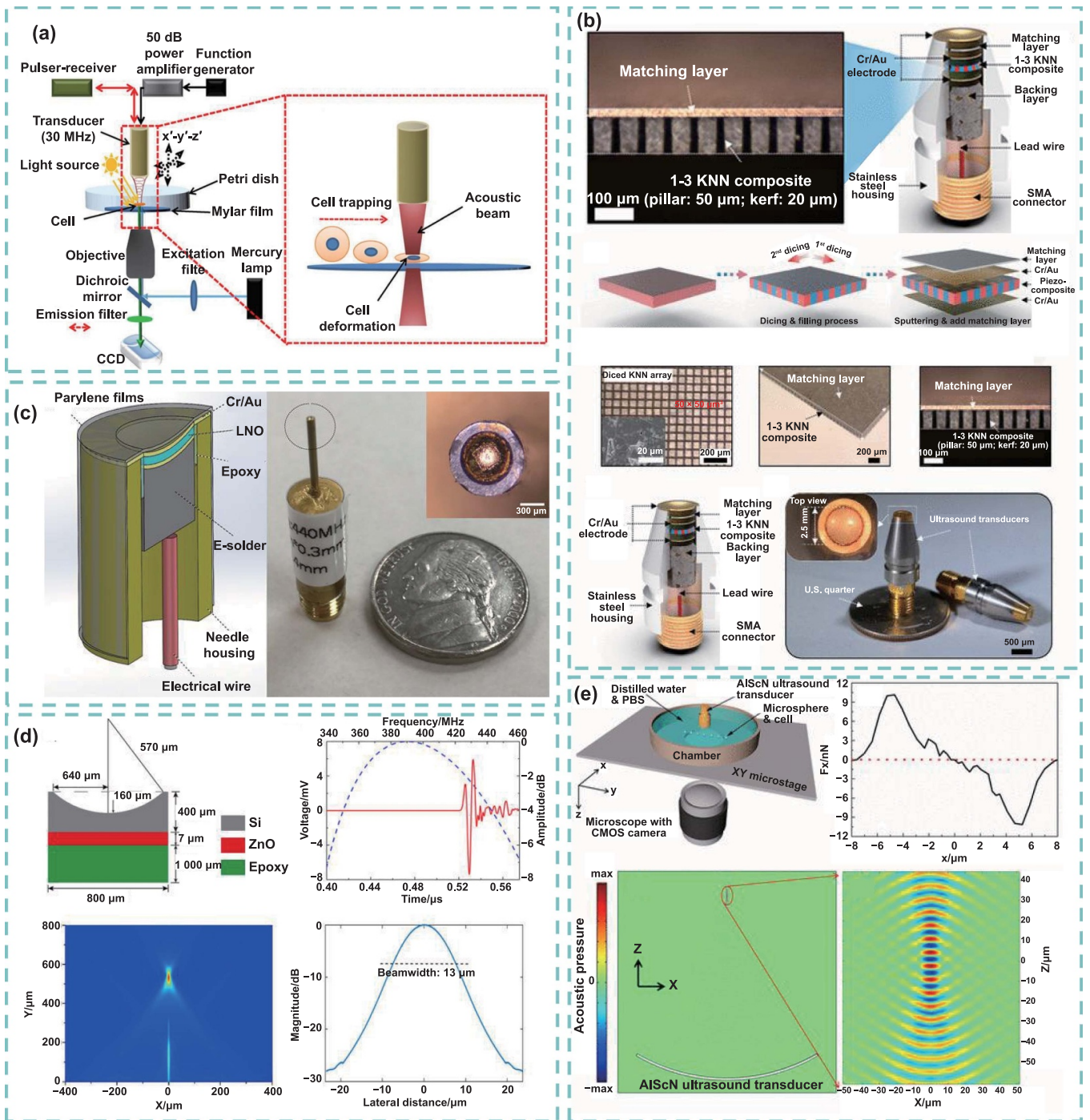


Figure 10. Focusing transducers for ultrasonic wireless energy transfer systems. (a) Dual-frequency ultrasonic tweezers [201]. Reproduced from [201]. CC BY 4.0. (b) Acoustic tweezers based on type 1–3 piezoelectric composite materials [127]. Reprinted with permission from [127]. Copyright (2022) American Chemical Society. (c) 300 MHz acoustic tweezers based on LNO single crystal [204] [204] John Wiley & Sons. © 2017 Wiley Periodicals, Inc. (d) Pulse echo test and acoustic field distribution diagram of silicon-based acoustic lens [205]. Reprinted from [205], © 2017 Published by Elsevier B.V. (e) Sound field diagram of scandium doped aluminum nitride focused ultrasound transducer [93]. Reprinted with permission from [93]. Copyright (2017) American Chemical Society.

materials will have higher piezoelectric coefficients and electromechanical conversion efficiency, better mechanical properties and thermal stability. One trend is the development of high-performance piezoelectric composites that can provide compatibility with advanced manufacturing processes and improve the durability of piezoelectric

transducers. In addition, the development of nanotechnology has promoted the application of nano-scale piezoelectric ultrasonic transducers.

(2) Fabrication techniques: the design and fabrication of focused piezoelectric ultrasonic transducers still face many challenges. The development of physical focusing

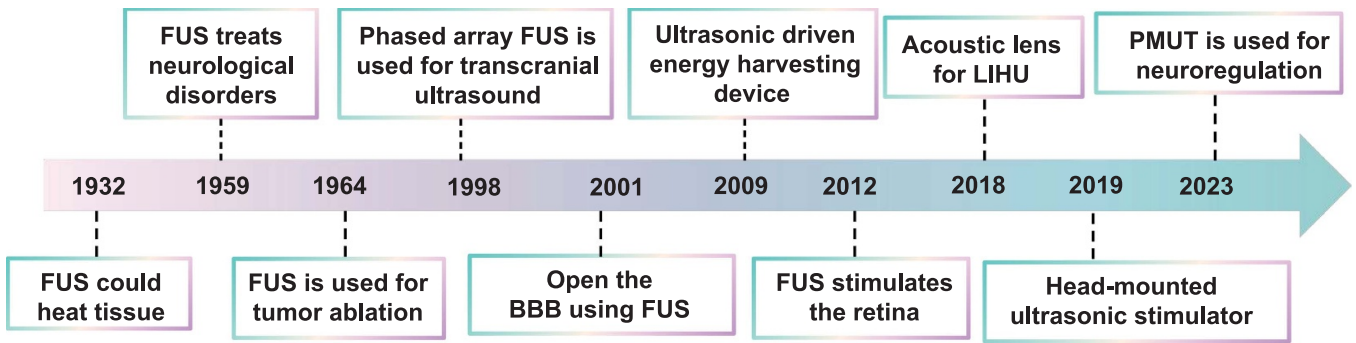


Figure 11. Development of focused ultrasound since 1930.

such as surface self-focusing and multicomponent self-focusing is limited by the properties of materials and processing techniques. The emergence of 3D printing technology opens up new ways to design and fabricate ultrasonic transducers with complex geometry and centralized functions. For acoustic lens focusing, the development of various new materials promotes the integration of tunable acoustic lenses while reducing impedance mismatches. Although electronic focusing technology enables more precise focusing, it also presents a series of challenges, requiring complex electronic control systems and algorithms to achieve sonic manipulation. Despite these challenges, electronic focusing offers significant advantages in terms of flexibility, precision, and the ability to achieve complex focusing patterns.

- (3) Integration with other technologies: the combination of focused ultrasonic transducers with other advanced technologies holds great promise for advances in medicine, industry and consumer electronics. The combination of ultrasound imaging technology and MRI technology for ultrasound therapy can improve the accuracy of treatment. In the future, the integration of diagnosis and treatment is an important trend in the medical field. In addition to this, focusing technology is combined with nanotechnology for targeted drug delivery. In consumer electronics, focused ultrasonic transducers are integrated with wearable technology and can be used for non-invasive monitoring of vital signs and internal conditions. Focused ultrasonic transducers can be integrated into combining BCI systems to deliver non-invasive brain stimulation with high spatial resolution. This could enable precise targeting of specific brain regions associated with neurological disorders, cognitive enhancement, or mood regulation. At the same time, with virtual reality and augmented reality systems, haptic feedback can be provided without direct contact. In conclusion, the application prospects of focused ultrasonic transducers are huge, and future research will focus on the combination with other technologies to achieve more intelligent adaptive systems.

Acknowledgments

This work was supported by National Natural Science Foundation of China (12072189, 82171011), Shanghai Jiao Tong University ‘Deep Blue Program’ Fund (Grant No. SL2103), the Project of Biobank (No. YBKB202117) from Shanghai Ninth People’s Hospital, Shanghai Jiao Tong University School of Medicine and Science Foundation of National Key Laboratory of Science and Technology on Advanced Composites in Special Environments (No.6142905223704). The authors are also grateful to the Center for Advanced Electronic Materials and Devices (AEMD) of Shanghai Jiao Tong University.

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