

## Acoustic-Based Biosensors

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## Synonyms

[Acoustic waves](#); [CMUTs](#); [Medical imaging](#)

## Definitions

A biosensor is defined as an analytical device that uses a biological recognition system to target molecules or macromolecules. Biosensors use a physiochemical transducer to convert the signal from the bio-recognition system into a detectable signal [1]. Biosensors consist of three components: (1) the detector, which identifies the stimulus; (2) the transducer, which converts this stimulus to an output; and (3) the output system, which involves amplification and display of the output in an appropriate format [1].

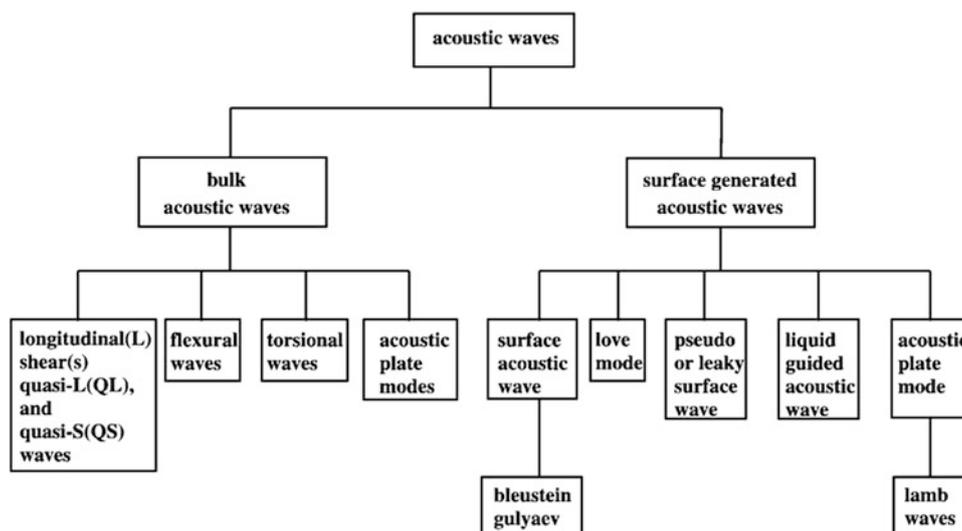
Piezoelectricity is a phenomenon displayed in certain crystals, such as quartz and Rochelle salt, where mechanical stress induces voltage generation and vice versa.

## Overview

There is an increasing demand for small, reliable, disposable, and inexpensive sensors in industrial, medical, and a variety of other science and engineering fields. Sensors are one of the fastest growing markets, with annual growth of about 18 %. In particular, the market for biosensors is increasingly promising due to their application in progressing areas of health care, biotechnology, and medicine. For instance, the uses of biosensors in personal glucose testing, HIV, and early cancer detection are areas with great medical relevance [1]. In addition, the ability to detect pathogenic and physiologically relevant molecules in the body with high sensitivity and selectivity offers a powerful tool in early diagnosis and treatment of diseases [1].

An acoustic wave biosensor utilizes acoustic or mechanical waves as a detection mechanism to obtain medical, biochemical, and biophysical information about the analyte of interest [1, 2]. It detects changes in mass, elasticity, conductivity, and dielectric properties from mechanical or electrical variations. These devices also employ the piezoelectric effect to excite acoustic waves electrically at an input transducer and to receive the waves at the output transducer [2].

The first scientific experiment of piezoelectricity was conducted in 1880 by Pierre and Paul Jacques Curie, who found that compression of various crystals leads to voltage production on their surface. They showed the converse effect the following year by demonstrating the elongation of



**Fig. 1** Classification of acoustic waves [1]

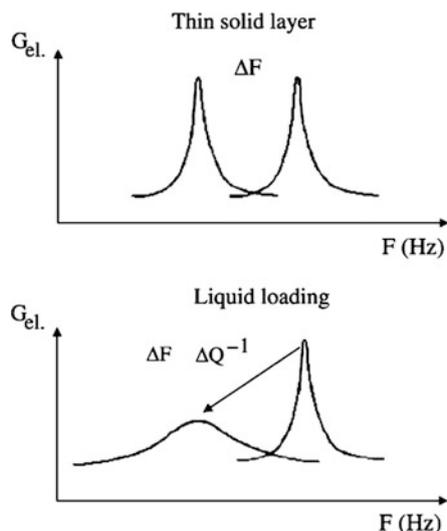
certain crystals when injected with electric current. Although these observations intrigued the scientific community, piezoelectricity remained much of a laboratory technology until Paul Langevin used piezoelectric transducers to construct sonar for submarine detection in 1915 [3]. Acoustic biosensors can be made with piezoelectric crystals such as quartz, lithium niobate, or lithium tantalate since they are robust and environmentally stable. In addition, such sensors are versatile and can detect, in principle, various biomolecules [1]. Acoustic wave sensors can be categorized according to the waves they generate, such as bulk or surface acoustic waves (Fig. 1). Each of these wave mechanisms have various advantages and disadvantages depending on their specific applications [1].

The goal of this entry is to categorize and describe the mainstream acoustic wave biosensors. We will begin by discussing biosensors that utilize bulk acoustic waves and subsequently analyze devices that employ surface acoustic waves. We will also examine sensors that employ capacitive micromachined ultrasound transducers, a novel technology that does not require piezoelectric substrates. For each type of these sensors, we will present an overview of their scientific mechanisms and fabrication techniques in the “[Basic Methodology](#)” section. We will then go on to discuss the advantages and applications in biology and medicine in the “[Key Research Findings](#)” and “[Future Direction for Research](#)” sections.

## Basic Methodology

### Bulk Acoustic Wave (BAW) Devices

Bulk acoustic wave (BAW) biosensors employ either longitudinal or shear waves, although the latter is often preferred to reduce acoustic radiation in the medium of interest. They are the oldest and the simplest acoustic wave devices. BAW devices consist of a parallel electrode placed on both sides of the thin piece of crystal. BAW sensor can technically employ any piezoelectric element, and typically quartz is used, as it is an inexpensive material readily available in nature and easily synthesizable in abundant quantities. In addition, thin disks of quartz are more stable at high temperatures than other piezoelectric elements. When an alternating electric field is applied, it results in a potential difference between the two electrodes and the shear deformation of the crystal.



**Fig. 2** Changes to the resonance peaks due to a thin solid layer (*top*) and liquid (*bottom*). Note the decrease in  $Q$  for TSM resonator in liquid [18]

As a result, there is mechanical oscillation of a standing wave across the bulk of the quartz. The frequency of the vibrations is dependent on quartz properties such as density, size, and phase in contact with the crystal surface [4]. Currently, thickness shear mode (TSM) resonator and shear horizontal acoustic plate mode (SH-APM) sensors remain the most widespread BAW sensors. The other two common BAW sensors that lie beyond the scope of this entry are the thin rod acoustic wave sensors and the flexural plate wave devices [4].

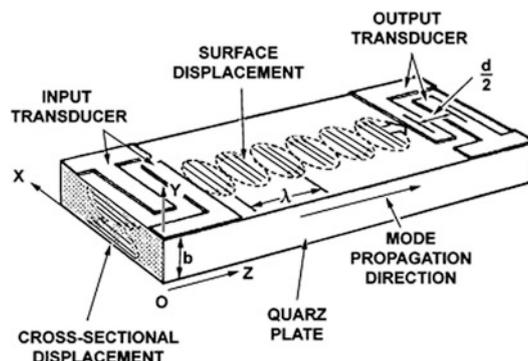
### BAW Device: Thickness Shear Mode (TSM) Resonator

TSM resonator, also known as quartz crystal microbalance (QCM), is the simplest and most widespread acoustic wave device today. TSM typically composes of a quartz plate sandwiched by electrodes on opposite faces. Electric field crosses through this plate when voltage is applied to the electrodes, resulting in a shear mechanical strain or displacement in the quartz. By oscillating the voltage frequency, a mechanical resonance can be generated, where the maximum displacement of crystal occurs at the surfaces. The resonant frequency,  $F_r$ , and the quality factor,  $Q$ , are the two resonance parameters. While  $F_r$  is the mechanical thickness shear resonance as mentioned before, it is also defined as the frequency of the maximum value of the electrical conductance,  $G_{el}$ .  $Q$  is approximated mathematically from the electrical conductance resonance spectrum as  $Q = F_r/\Delta F_{BW}$ , or the ratio of resonant frequency to the half bandwidth [5].

Coupling of molecules in solid, liquid, or gas phase to the TSM resonator changes the resonance parameters. When mass attaches onto the crystal face, it raises the quartz's overall weight and reduces  $F_r$ . Sauerbrey first derived the mathematical relationship between loading mass and  $F_r$  to be

$$\Delta f = - \frac{2f_0^2 \Delta m}{A_{piezo} (u_q p_q)^{1/2}} \quad (1)$$

The variables  $\Delta f$ ,  $f_0$ ,  $\Delta m$ ,  $A_{piezo}$ ,  $u_q$ , and  $p_q$  represent, respectively, the crystal's measured frequency shift, initial resonant frequency, mass change, surface area, shear modulus, and density [6]. TSM resonators immersed in liquid present a special case because acoustic energy dissipation



**Fig. 3** SH-APM can sense on either side of the device because waves travel between the upper and lower surfaces of the plate [2]

through the fluid lowers  $Q$  as well. Additional formulas need to be applied to account for the liquid's viscosity and loading [6]. Figure 2 shows a comparison between shifts induced by solid and liquid loading on resonators.

TSM resonators possess lower mass sensitivity than most acoustic wave sensors that employ other mechanisms since they typically operate between only 5 and 30 MHz. Thinner devices can be used to increase frequencies that result in increased mass sensitivity, and they are more fragile and harder to manufacture and handle [5]. Recent research on this topic has been on creating high-frequency TSM resonators with piezoelectric films and bulk silicon micromachining techniques.

### TSM Fabrication

TSM resonator fabrication usually utilizes photolithography [2]. The resonance frequency of the quartz crystal depends on the shear modulus, density, and material thickness [1]. After polishing the quartz, photoresist is deposited, and the device is exposed to UV light through a mask, which determines the active areas that have to be metalized on the devices. On a TSM resonator, they represent the location of the electrode plates. A chemical interface is then added to the remaining crystal surface, where molecules in the liquid can bond to and be detected [2].

### BAW Device: Shear Horizontal Acoustic Plate Mode (SH-APM) Sensor

First introduced in the 1980s, SH-APM sensors use a thin piezoelectric substrate, or a plate, to guide the acoustic wave and to confine its energy within the plate's top and bottom surfaces. Most of the production and analysis principles employed in SH-APM sensors are used in a TSM resonator. Their most striking difference is that SH-APM sensors employ interdigital transducers (IDT) rather than electrode plates. IDTs are deposited on opposite ends of a surface, where one IDT generates displacement waves through application of an oscillating voltage and the other receives it (Fig. 3) [2]. The surface without IDT is immersed in the targeted liquid and acts as the sensor, so the device will not suffer from corrosion problems as electrode plates do in biological solutions [7].

Like TSM resonators, SH-APM sensors prevent the acoustic waves from gaining a shear vertical component and thus lessening energy radiation in the form of compression waves into the liquid. They achieve this by restraining particle displacement within the plate plane. However, given a SH-APM and a TSM device of similar plate thickness, the former usually attains higher mass sensitivity than the latter because IDT is much smaller and precise than the electrode plates on TSM. In general, SH-APM devices generate waves with a frequency ranging from 100 to 150 MHz, but they are also more complex and expensive than their TSM relatives [2].

### **SH-APM Fabrication**

Although the crystals and substrates may be different, SH-APM sensors are fabricated in a similar fashion as TSM resonators. One difference that must be noted is the use of IDTs in SH-APM fabrication, which is not present in TSM resonators. Depending on the application, the optimization of sensor performance can be achieved through adjustments of the length, width, position, and thickness of the IDTs. These parameters can be altered by varying the design of the masks, amount of photoresist, and other chemicals used in the fabrication process [2, 7].

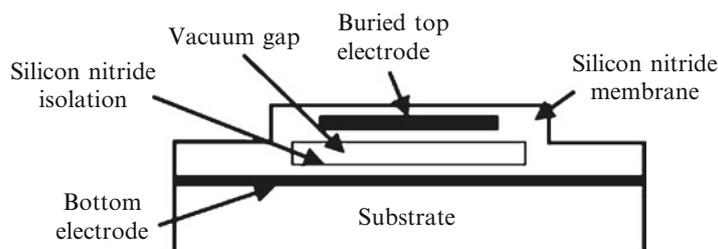
Moreover, SH-APM devices require additional processing during their fabrication of the thin plates with respect to the IDT periodicity. Thin slices of piezoelectric materials such as quartz are often used. The whole procedure permits researchers to choose the correct crystallographic orientation for generating the desired shear waves. Despite this improvement, SH-APM devices remain less sensitive than SAW devices for two reasons. First, energy of the wave does not reach a maximum at the surface. Second, similar to TSM, SH-APM is restrained by a minimum thickness of piezoelectric plate [2, 7].

### **Surface Acoustic Wave Sensors (SAW)**

Surface acoustic wave (SAW) sensors have been used for years in measuring temperature, pressure, viscosity, acceleration, concentration, and chemical/biological entities [3]. They are also used to perform signal-processing operations and are sensitive to their environment [8]. This type of acoustic wave sensors consists of basic components such as piezoelectric substrate (crystals such as quartz, GaAs, or LiNbO<sub>3</sub>), micrometallization patterns (electrodes), interdigital transducers (IDT), and active thin films. Unlike BAW, which only interacts with the environment at the opposite surface of the material by traversing through it, SAW travels along or near the surface of the piezoelectric material [3]. The piezoelectric device detects small mass changes at the surface of the sensor as a frequency response, as the electrodes on the surface of the piezoelectric substrate transmit and receive acoustic waves [8]. The acoustic wave is confined to the surface of the piezoelectric substrate, and the excited wave is propagated along the crystal surface. The surface wave velocity changes due to the mass, or the viscosity changes due to the binding reactions on the sensor surface. The range that SAW device operates depends on the acoustic velocity of the crystal substrate and IDT wavelength, and it usually lies between lower MHz range to the GHz range [8]. These devices are commonly used because of their ability to directly sense the changes in mechanical and mass properties, and they have a broad range of applications such as pressure, temperature, viscosity, mass, and chemical and biological sensing [8]. SAW sensors coated with organic and/or inorganic materials can be used to analyze absorption on the surface of a device [9]. For chemical sensing, the chemoselective material must be tailored to the analyte of interest. During its operation, SAW sensor responds to a gas or vapor exposure in air by a shift in resonant signal frequency and then recovers to the original signal frequency, when the sensor is exposed to ambient air free of the responding analyte [8]. The SAW velocity changes according to the absorbed chemical substance, and it results in the alternation of the mass load, the elastic stress, and the conductivity of the polymer coating on the SAW device.

SAW devices are also considered as “electronic noses.” An electronic nose is a device that is composed of a chemical-sensing system and a pattern-recognition system. Electronic noses mostly have the ability to detect very low vapor concentrations [8]. If there is vapor on the piezoelectric surface of the SAW device, the chemical substances in the vapor and in the acoustic wave interact and the properties of the wave changes. Sensitivity of the SAW detector is dependent on the temperature of the piezoelectric crystal and the vapor-pressure of the analyte. Chemical concentration of analyte of interest can be tested by monitoring the frequency. The SAW chemical sensor





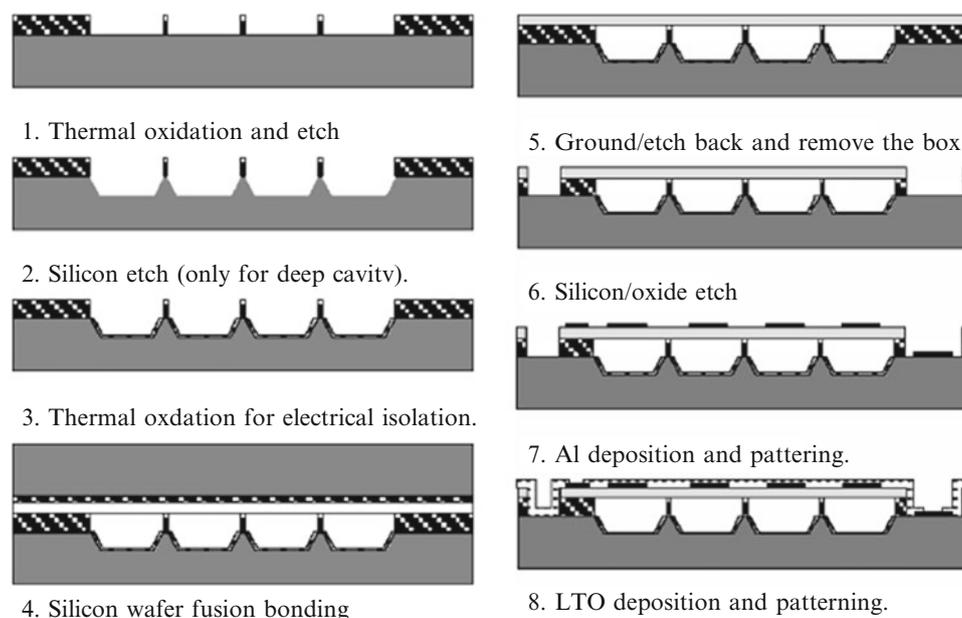
**Fig. 5** Schematic cross section of a CMUT transducer membrane [28]

acoustic velocity and a zero-temperature coefficient of frequency. Extremely high velocity SAW modes with moderate coupling coefficient in AlN and GaN thin films are deposited on SiC, diamond, or sapphire substrates [12]. In addition, imprint lithography is a commercial method to fabricate SAW devices, especially for simple pattern, one-mask-level applications, where large areas can be patterned with nanometer-scale critical dimensions and high fidelity. Moreover, nanoimprint lithography is becoming a popular lithographic method. SAW filters and SAW correlators present ideal structures to be fabricated using this method.

### Capacitive Micromachined Ultrasonic Transducers (CMUTs)

Electrostatic transducers have been used for sound wave excitation and detection as an alternative to piezoelectric devices that are used widely for nondestructive evaluation and medical-related applications. The vibration of a thin plate under electrostatic forces is the main acoustic actuation and sensing mechanism of these devices. These devices are based on the electrostatic attraction force between the backplate and the metallized membrane. The simplest forms of this device consist of a thin metal membrane that is stretched above a back electrode forming a small gap [13]. Upon exposure to sound waves, the gap height is modulated at the frequency of the incoming pressure field that induces a change in the device capacitance, which generates an output voltage proportional to the amplitude of the field. The capacitor is also used to generate sound waves. The advantage of the electrostatic devices compared to the other types of transducers is the impedance matching between the transducer and the surrounding medium. Advances in the silicon micromachining techniques enabled the fabrication of microelectromechanical system (MEMS)-based electrostatic transducers. These devices use the ultrasonic waves due to the miniaturization capacity of the silicon machining techniques and are called capacitive micromachined ultrasonic transducers (CMUTs) [13].

CMUTs are made of small and thin transducer membranes that are suspended over a conductive silicon substrate (Fig. 5). The two plates of the capacitor, the substrate and the membrane, are separated by a vacuum-sealed cavity. Two-dimensional (2D) arrays of miniaturized electrostatic cells are microscale cells that operate in parallel and driven in phase. Surface silicon micromachining is used for their microfabrication [13]. The operation principle of these devices is based on the capacitance modulation of a microcondenser. Between the metallized membrane and the substrate, a direct current voltage is applied. The membrane is attracted toward the bulk by the electrostatic force, and induced stress within the membrane resists the attraction. If the membrane is exposed to ultrasound, a current output is generated as the capacitance changes under constant bias voltage. The amplitude of the current output is a function of the frequency of the incident wave, the bias voltage, and the capacitance of the device. CMUTs perform operation in the megahertz range. The lateral dimensions of each cell are in the order of tens of microns [13]. The gap between the membrane and the substrate vacuum sealed or unsealed can be as small as 500 Å. The membranes may be conductive or coated with a conductive electrode. This structure results in very efficient transducers that can compete with their piezoelectric counterparts in terms of efficiency and bandwidth. The



**Fig. 6** Major steps of CMUT fabrication with wafer-bonding method (Reprinted with permission from Ergun et al. [14])

small and thin membranes that constitute the CMUT transducer are micromachined onto a silicon substrate [13].

### CMUT Fabrication

There are two conventional methods to fabricate CMUT: sacrificial release process and wafer-bonding method. The first CMUT was created by using a sacrificial release process, and this method has become the standard CMUT fabrication for many years. In the sacrificial release process, a cavity underneath the membrane is created by depositing or growing a sacrificial layer on the carrier substrate. The sacrificial layer is removed with an etchant after the membrane deposition. However, there are some problems associated with this technology. The surface micromachining process causes limitation on the cavity and membrane size of a CMUT device. In addition, it is hard to batch produce surface micromachined CMUTs to tight quality specifications [14]. On the other hand, wafer-bonding method is a new fabrication technique that combines bulk and surface micromachining techniques. The transducer membrane and cavity are defined on a SOI wafer and on a prime wafer, respectively. Two wafers are then bonded by using silicon direct bonding in a vacuum environment, together forming the transducer (Fig. 6) [14]. This new method improves CMUT performance since it decreases the number of process steps and device turn-around time and increases the overall uniformity, reliability, repeatability.

## Key Research Findings

### Advantages of BAW Devices over SAW Devices

Acoustic biosensors generally employ BAW rather than SAW because BAW devices generate waves that mainly propagate in the shear horizontal motion. Since shear horizontal wave does not radiate significant amount of energy into liquids, it minimizes damping in the liquid operation. Besides few exceptions, the SAW sensor induces considerable surface-normal displacement that radiates

compression waves into the liquid and causes excessive damping. Since biosensors detect chemicals in liquid solutions, BAW is often preferred over SAW for many biosensing applications [2].

### **Biological Applications of SH-APM Sensors**

SH-APM sensors have been utilized in various biological applications. For example, Liren et al. [15] presented a urease biosensor in which a 0.5 mm thick ZX-LiNbO<sub>3</sub> substrate was used and a resonant frequency approximately centered at 50 MHz. APM was generated and detected by IDTs, with a period of 88 μm and a center distance of 10 mm, on the same PZ crystal. The group also fabricated two pairs of IDTs on the substrate so that one would conduct biochemical reactions while the other acted as a reference. Using this device, they successfully measured urea concentrations by detecting variations in the resonant frequency [15].

SH-APM sensors have also been applied in immunochemical reactions. In order to observe antigen-antibody reactions through mass loading on the crystal surface, Dahint et al. [7] constructed an immunosensor using a 150 MHz APM device on a ZX-LiNbO<sub>3</sub> plate with a thickness of 0.5 mm. These sensors, which could detect mass as small as to 200 pg/mm<sup>2</sup> of crystal surface, marked a shift in resonant frequency of around 1 kHz upon antigen adsorption [7].

### **Biological Applications of TSM Resonators**

Many biosensors that employ TSM resonators are available on the market today. Depending on their design, they can detect biological entities such as nucleic acids, viruses, bacteria, and cells. An example of TSM-based biosensor was presented by Davis et al. [16]. They used a coating of human IgG and subsequently used a TSM resonator to detect the presence of sheep antihuman IgG as marked by the decrease in the resonant frequency, signifying an increase in the mass loading from the attachment of the antibodies [16].

TSM sensors can also be used as DNA-based sensors. Okahata et al. [17] studied the use of oscillatory-driven 9 or 27 MHz quartz to quantify DNA-DNA and DNA-protein interactions. They used quartz with one side specifically coated and the other side rubber cased, which was dipped into a stirred and thermostated solution of the target. Binding amounts were evaluated quantitatively as mass per unit area. Effects of probe immobilization techniques, chain lengths, ionic strengths, temperatures and mismatches on hybridization, regulatory protein binding, and electrostatic effects in DNA-binding properties of lysine-containing oligopeptides were evaluated quantitatively. In addition, Tessier et al. [18] used a TSM sensor, or specifically an antibody functionalized quartz sensor, to detect human erythrocytes. Adsorption and desorption studies of antibody-conjugated phages at antigen-immobilized TSM resonator surfaces in a high-throughput setup were also performed [4].

### **Biological Applications of SAW**

SAW devices are useful in industrial and commercial applications of chemical and biological sensing. In biological applications, these devices can be used to detect molecules by mass. A potential application of SAW devices in biology is in building immunosensors. In a study, immunosensor SAW devices were first coated with a parylene thin film to create a chemically homogeneous layer. Then, photoactive and functional groups containing dextran were immobilized, and antibodies were bonded. This sensor consisted of lithium tantalate substrate with gold transducers and used to monitor urease binding [10]. This sensor was applied to monitor the amount of the urea in human urine to diagnose the onset of liver and kidney diseases [10]. In addition, another study immobilized polysaccharides to a silicon oxide surface intended for SAW. The pneumococcal polysaccharide (PPS) vaccine can immobilize via protein A after pretreatment of the surface with

hydrochloric acid. The results show that the immobilization of PPS via protein A increased the sensitivity of *Streptococcus pneumoniae* antibodies detection in human serum when compared with ELISA [19]. This study shows that SAW sensors can be used in detection of microbial contaminants in the environment.

### **Advantages of CMUT Devices**

Piezoelectric ultrasonic transducers are used to generate and detect ultrasound over the last 30 years. This technology gives a bandwidth as high as 60–80 % and a high sensitivity [20]. Nevertheless, the piezoelectric transducers have disadvantages in air or fluid-coupled applications due to the impedance mismatch between the medium and the piezoceramic material. Moreover, it is an expensive technique and shows some restrictions for the 2D arrays. On the other hand, CMUT devices became an attractive alternative to piezoelectric transducers as they have inherently low mechanical impedance associated with a thin vibrating membrane. Thin membranes that are fully supported with insulating posts on all sides and these devices have the advantage of the good mechanical properties of silicone and silicon nitride [21]. As the mechanical impedance of such thin membranes is much closer to those of fluids in a wide frequency range, CMUTs are better in immersion applications than piezoelectric devices. Moreover, CMUTs are fabricated using standard micromachining processes and provide ease of fabrication, batch production, and very high level of integration and repeatability. Taking advantage of the microfabrication techniques, these devices can provide the broad bandwidth and coupling efficiency required for high performance. Furthermore, this kind of ultrasonic transducers have the ability to make complex array designs using standard photolithographic techniques that makes them usable for imaging applications [21]. A transducer with a wider band increases the resolution as well as enabling the design of the image processed. In addition, CMUTs are an alternative for intravascular imaging systems as they can be microfabricated as small 2D imaging arrays and maintain electroacoustic performance [21].

### **Biological Applications of CMUTS**

Today's ultrasound technology has a wide range of applications in industrial and medical field, from distance measurement to medical diagnostic imaging. The fields such as dermatology, ophthalmology, and cardiovascular medicine require ultrasonic imaging systems. CMUTs enable in vivo medical imaging at high frequencies. They are also used in the microfluidics and acoustic sensing, which have applications in the biomedical engineering.

Intravascular ultrasound (IVUS) is a medical imaging technique that uses ultrasound equipment with long, thin catheters and enables visualization of blood vessels through the blood column and inner wall of blood vessels. This gives information about cardiovascular diseases. In addition, a pulse-echo phased array B-scan sector, 1D linear CMUT array was produced by Demirci et al. [21] to demonstrate the viability of CMUTs for ultrasound imaging for medical applications. 64- and 128-element 1D CMUT arrays with 100 % yield and uniform element response were fabricated. For imaging experiments, resolution test phantom was used to mimic the attenuation properties of soft tissue. The image quality was found in order to show the practicality of using CMUT devices for ultrasound medical imaging due to its wide bandwidth and high sensitivity. Current 1-dimensional (1D) side-looking ultrasound imaging probes do not have the forward-viewing capability. Demirci et al. [21] showed forward-viewing annular CMUT arrays can be used for medical imaging applications. 64-element, forward-viewing annular arrays were fabricated and designed for imaging applications in the 20 MHz range. The devices operate in the 5–26 MHz range with a fractional bandwidth of 135 %. These forward-viewing annular CMUT arrays are promising tools for measuring blood flow and imaging upon being mounted on the front surface of

a cylindrical catheter probe [21]. Forward-viewing IVUS enables new procedures in cardiac medicine such as viewing blood vessels, guiding stent placement, and monitoring operations in the heart [22]. In addition, researchers focused on developing a forward-looking 2D imaging arrays that can be microfabricated and integrated with electronics. CMUTs are alternative tools for 2D medical imaging arrays. In a study, ring annular CMUT was used for forward-looking IVUS imaging at 16 MHz. This 1 mm diameter arrayed CMUT device was used for volumetric imaging, and they were found to have potential use in IVUS imaging catheters [22]. Another study by Knight et al. [23] modeled and designed the CMUT membranes for performance in forward-looking IVUS. They used finite element analysis to calculate the electromechanical coupling coefficient,  $k^2$ , and showed that the CMUT geometry can be optimized for maximum coupling coefficient, allowing CMUT IVUS array elements to be designed with more than 60 dB/V dynamic range with 10 MHz bandwidth around 20 MHz by fabricating a 1.02 mm diameter 64-element array [22]. A recent improvement in CMUT technology produces a three-dimensional ultrasound imaging system using a forward-looking ring array with a diameter of 2 mm and 64 elements each  $100\mu\text{m} \times 100\mu\text{m}$  in size. 3D images of several wire targets and Palmaz-Schatz stents indicate the potential of imaging with such a device. In addition, further improvements point to a promising future for forward-viewing CMUT ring arrays in intravascular imaging [24].

CMUT devices are used in the real-time in vivo imaging applications with an improved performance over the existing medical ultrasound transducers. A wafer-bonded CMUT probe showed a bandwidth of 130 % (3–13 MHz), which covers nearly the entire frequency range for medical ultrasound applications. The carotid artery and thyroid gland were imaged with surface and bulk micromachined CMUT arrays, and real-time in vivo images were compared with a PZT array. The bandwidth and resolution performance of the surface micromachined arrays were slightly better than PZT. However, depth of penetration was not as good as in PZT. Bulk micromachined CMUT arrays showed the first real-time in vivo images and had improved resolution and bandwidth but less depth of penetration. As a result, improved axial resolution and extremely broad bandwidth are achieved by CMUTs. Improved axial resolution will allow smaller targets to be resolved in tissue for such applications as imaging microcalcifications in the breast, small abnormalities in the thyroid, or better delineation of the intimal linings of blood vessels to search for plaque buildup [18].

## Future Directions for Research

Advancements made over the past decades have culminated in the initiation and development of acoustic wave biosensors. The ability to detect biological molecules by these sensors may contribute to treatment of many diseases such as HIV and cancer. In addition, these devices are promising in medical imaging given their ability to generate high-resolution pictures in real time. However, there are still limitations to some of these devices that can be surmounted through future research and though the potential of the application of these devices to biological situations has been recognized, more work is left to be done in order to employ them on a wider scale. Below are some limitations and potentials of the devices.

### SAW Devices

There are a number of potential limitations with the SAW sensors as they are today. One limitation is that SAW sensors are sensitive to a variety of parameters [8]. In addition, the intensity of an acoustic wave can decrease in biological solution such that the sensing system may not work efficiently. Furthermore, many SAW devices that are used in the gas-sensing applications may not be used to

detect molecules in the liquid phase. When a fluid contacts the SAW surface, the longitudinal wave component pumps a compression wave into the fluid [2]. In air, the energy losses are not too effective. However, in many liquids, all the energy is pumped out of the acoustic wave before it reaches the device's receiving transducer. SAW devices can perform well in liquids when they rely on surface waves with no longitudinal components like horizontally polarized shear waves, surface transverse waves, and the guided acoustic waves called "love waves" [2]. Recent advances in liquid sensors and immunoassays improved the detection limits. In addition, surface technologies like functionalization with fluorescent probes, DNA, and enzymes increased the use of SAW devices in liquid samples [7]. There are also radar-type SAW sensors for high-voltage applications that detect at long distances. These sensors cannot be used scans of wider areas due to two main limitations. According to the radar equation, the radiofrequency signal changes with the fourth power of the distance between the radar unit and SAW sensor. As a result, high signal attenuation is governed by this equation. Second, only a few echo sounds can be distinguished because all sensors in the detection range respond immediately. Attaining this requires differentiated sensors that respond within different time slots, and multiple sensors can be used with a limited number of reflectors and limited identity-code capacity [25].

In addition, generation of acoustic waves in microstructures requires various processes and technologies, with compatibility as one of the main limitations in the development of smart sensors. Restrictions of manual handling and fabrication process limit minimum thickness of the devices to be about 100 microns. Adoption of silicon fabrication opens the possibility for the integration of the acoustic devices and electronic driving circuitry, leading to the development of smart sensors. This technique involves localization of specific fabrication steps to common areas to minimize the total number of process steps in the fabrication process as well as to maintain SAW and Lamb wave device integrity and quality [26].

Most of today's acoustic wave generation and focusing apparatus suffer from these further limitations: the piezoelectric arrays are expensive, and it is hard to get high-level, well-distributed intensities. In addition, shocks are generated at a rate of one or two shocks per second, whereas extracorporeal shockwave treatment (ESWT) typically requires thousands of shocks per treatment. Acoustic lenses are mostly fragile and noneffective for larger apertures. Moreover, electrohydraulic approach has disadvantages of nonuniform discharges, pain, and high noise level.

### **BAW Devices: TSM Resonator**

The limitations of TSM resonators are mostly related with the experimental setup, accuracy in modeling the sensor, and physical behavior of a viscoelastic polymer. Researchers should be careful in model approximations, parameter estimations, and measurement errors. For acoustically thin polymers, the thickness can be calculated with a small error, but the shear moduli can hardly be extracted from measurements due to negligible influence on the sensor behavior. On the other hand, the coating thickness should be known because of the existence of multiple identical solutions for acoustically thick polymers [27]. In addition, for detailed interpretation of sensor response in liquid requires more sophisticated experimental setup [4]. In addition, mechanical, optical, and electrochemical properties are helpful to characterize interactions at biological surfaces and interfaces. However, the needed equipment are expensive. While miniaturized quartz arrays seem to present a solution for low-cost sensor setups, miniaturization has its limitations because small electrode areas can load enough molecules to achieve measurable frequency shifts. As a solution, combination of automatized pipetting systems, microfluidics, integrated sensor arrays, and multicomponent data analysis may open the way toward high-throughput screening with acoustic wave sensors [4].

Two major challenges are present in the application of TSM resonator as a biosensor. First, cross-reactions such as unspecific protein adsorption affect the accuracy of the results. This limits the resonator's use to binding sites that specifically bond to the targeted biological molecules and poses a significant disadvantage in environments containing various compounds. Second, since the resonator only responds to mass loadings, the analysis cannot differentiate this signal from other factors that can affect the resonant frequency such as viscoelasticity and acoustic coupling effect. This leads to a disagreement between the experimental and theoretical values of mass uptake, an error that needs to be accounted for by researchers [4]. Immunochemical analyses or nucleic acid hybridization results of TSM resonators should always be coupled with a reference analysis method. In addition, dry- and wet-coated TSM resonators may not give the same results due to changes in viscoelasticity, so calibration should be done in the sensing medium during nucleic acid analyses. Complexation of DNA may limit the flexibility of the molecule strands and ionic strength changes or interaction with the surface might vary extension and shape of the molecule. These may change viscoelastic behavior and produce erroneous results from TSM resonators [4].

### CMUTs

CMUTs have the potential to make ultrasound a far more versatile and important imaging modality. This technology has made advances in acoustic matching and the microminiaturization of electronics. It enables higher-frequency imaging, allows clinicians to view small features in the body, and is useful for ultrasound imaging especially in the area of volumetric in vivo imaging, intravascular, and intracardiac research.

### Cross-References

- ▶ [Biosensor](#)
- ▶ [Biosensors Using Atomic Force Microscopes](#)
- ▶ [Biosensors Using Lasers](#)
- ▶ [Biosensors Using Magnetics](#)
- ▶ [Biosensors Using Surface-Enhanced Raman Scattering](#)
- ▶ [Piezoelectric](#)

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