Anal Bioanal Chem (2008) 391:1509–1519
DOI 10.1007/s00216-008-1911-5

REVIEW

Surface acoustic wave biosensors: a review

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Received: 22 November 2007 / Revised: 18 January 2008 / Accepted: 22 January 2008 / Published online: 12 February 2008

Abstract This review presents an overview of 20 years of worldwide development in the field of biosensors based on special types of surface acoustic wave (SAW) devices that permit the highly sensitive detection of biorelevant molecules in liquid media (such as water or aqueous buffer solutions). 1987 saw the first approaches, which used either horizontally polarized shear waves (HPSW) in a delay line configuration on lithium tantalate ($LiTaO_3$) substrates or SAW resonator structures on quartz or $LiTaO_3$ with periodic mass gratings. The latter are termed "surface transverse waves" (STW), and they have comparatively low attenuation values when operated in liquids. Later Love wave devices were developed, which used a film resonance effect to significantly reduce attenuation. All of these sensor approaches were accompanied by the development of appropriate sensing films. First attempts used simple layers of adsorbed antibodies. Later approaches used various types of covalently bound layers, for example those utilizing intermediate hydrogel layers. Recent approaches involve SAW biosensor devices inserted into compact systems with integrated fluidics for sample handling. To achieve this, the SAW biosensors can be embedded into micromachined polymer housings. Combining these two features will extend the system to create versatile biosensor arrays for generic lab use or for diagnostic purposes.

Keywords Surface acoustic wave · Biosensors · Interaction analysis · Chip

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Introduction

By the early 1980s, electro-acoustic devices had shown themselves to be suitable for many technical applications, especially in electronics, electronic data processing and high-frequency technology. In particular, the increasing demands of commercial products in the telecommunication area provided the basis for mass-produced surface acoustic wave (SAW) devices for high-frequency applications in the range of 100 MHz to a few GHz. In general, SAW devices generate and detect acoustic waves using interdigital transducers (IDT) on the surface of a piezoelectric crystal [1]. In this way, the acoustic energy is strongly confined at the surface of the device in the range of the acoustic wavelength, regardless of the thickness of the complete substrate [2]. For this reason, the wave is potentially very sensitive towards any change on the surface, such as mass loading, viscosity and conductivity changes. Wohltjen and Dessy first presented a sensor based on such a SAW device that supported "Rayleigh-type" surface acoustic waves (RSAW). After coating the device with a sensitive polymer layer, it was used as a chemical sensor for organic gas detection [3–5]. Since then numerous SAW sensor approaches for a variety of applications in gas sensing have been suggested [6, 7].

However, early attempts to transfer this promising new technology into a biosensor in order to detect proteins were less successful [8–10]. The reason for this is that to achieve this aim the device usually has to be operated in buffer solutions. When immersed in aqueous liquids, the RSAW devices commonly used for gas sensing suffer from immense attenuation due to displacement components perpendicular to the surface. The latter generate compression waves which radiate into the liquid and cause high attenuation of the device [9]. Therefore, research activity was initially largely focused on alternative acoustic wave types such as bulk

acoustic waves (BAW) that mostly use thickness shear modes (TSM); the devices commonly known as quartz crystal microbalances (QCM) [11–15]. The resonance frequencies of these devices are usually in the range of 10–50 MHz. At higher frequencies the devices become too thin and thus too fragile for practical use. However, higher frequencies are most desirable, because the mass sensitivity increases with increasing frequency [16].

On the other hand, when substrate thickness decreases the generation of different types of surface waves with an additional shear mode becomes possible [17]. Such a device could be based on acoustic plate modes (APM). In this case the acoustic energy is trapped by multiple reflections between the two surfaces of the substrate. Therefore, these devices have the advantage that the IDTs which generate the acoustic waves are located on the back side of the device and are thus away from the sensing front side, which must be immersed in the liquid. The devices are driven with horizontal shear waves to reduce their attenuation in water. However, a major drawback of using APM devices is the fact that it is difficult to operate these devices in a standard oscillator circuit, which is the easiest electronic setup and the one that is most commonly used to determine the resonance frequency of a device (see the "Electronic periphery" section). The reason for this is that several APMs are usually excited simultaneously, but the frequency separation between these modes is often limited. In this case the use of an oscillator circuit would result in a risk of mode hopping, i.e., the jumping of the frequency of oscillation from one mode to another. Consequently, APM devices were mostly evaluated using expensive electronic systems such as network analyzers [18, 19]. One way to overcome this problem is to use much thinner Lamb wave devices using symmetric acoustic modes. These devices typically have thicknesses in the range of the acoustic wavelength. The devices will then operate on their main resonance frequency only, which is sensitive to mass loading on the surface. Like QCMs, Lamb wave devices tend to be very fragile due to the reduced device thickness with increasing frequency [20, 21]. This is especially problematic if such a device needs to be tightened against the liquid to be sensed.

Current research mainly focuses on two types of acoustic devices for biosensing applications: BAW-based biosensors using QCMs and SAW-based biosensors. However, only the latter allow the use of high frequencies in the range of several 100 MHz to GHz, implying higher mass sensitivities compared to QCMs [16, 22]. This review deals with SAW-based biosensors, beginning with an overview of 20 years of SAW biosensor development. It focuses on papers which have presented significant milestones in technological progress in this field. It presents different approaches to the realization of sensor devices and surface modifications for various biochemical applications. The review ends with recent SAW-based biosensor system developments which are close to yielding commercial products for lab instruments or point-of-care diagnosis.

History of pure horizontal surface shear wave devices

As mentioned above, early studies in the 1980s that attempted to transfer the simple method of SAW gas sensing into a biosensor were not successful, since RSAW devices suffer from immense attenuation when immersed in liquids [9]. Early successful approaches using horizontally polarized shear wave (HPSW) devices in a delay line configuration could only be obtained if the liquid to be investigated was an oil or another nonpolar liquid. Even then, the attenuation of the these devices was relatively high. When immersed in water, such devices suffered from even higher attenuation [23, 24]. This made it very difficult to operate these devices with simple electronic setups. The main cause of this high attenuation was the significant dielectric mismatch between the liquid and the substrate. The dielectric constant (DC) of water is about 78 [25], which is much higher than the DC of quartz (DC ~ 4 [25]), a common substrate material in SAW devices at that time. At the high frequencies applied, the periodic electric fields generated in the IDTs were simply shorted out when these devices were immersed completely in water.

First successful approaches

Two approaches published in 1987 can claim to be the first to overcome this problem [26, 27]. Flory and Baer used a new acoustic wave type called surface transverse waves (STW) [26, 28]. This type of wave is also a HPSW, but as it propagates it is kept on the device's surface by a periodic mass grating with a periodicity of $\lambda/2$, where λ is the wavelength of the SAW. This approach overcame the lack of energy confinement of a pure HPSW to the crystal surface that happens when traveling along the open surface of a crystal. Although this type of surface wave was more suited to applications in liquids, the substrate material was still quartz and therefore the previously described problem of high dielectric mismatch still applied. In order to solve this problem Flory and Baer used a thick shielding layer to reduce the high DC influence of water on the transducers. Using this approach they achieved lower attenuation values that potentially allowed easy device operation with a simple oscillator circuit in a biosensing experiment [29].

The second approach was presented by Shiokawa and Moriizumi [27]. They used substrate materials with considerably higher DC values than that of quartz: lithium niobate ($LiNbO_3$) and lithium tantalate ($LiTaO_3$) at different crystal cuts. Typical DC values are 30 for $LiNbO_3$ and 43

for $LiTaO_3$ [25]. Because of its considerably higher DC value, $LiTaO_3$ was found to be best suited to operation in water, even when the device was completely immersed in water and not covered with an additional shielding layer on the IDTs. The authors called this type of wave "shear horizontal (SH) SAW." This is comparable to a HPSW, but on this special substrate it can be defined as a "leaky wave," since the SH SAW loses slight amounts of acoustic energy into the bulk of the crystal. The authors proposed to use a "dual delay line configuration" with two devices on one chip. They discussed SAW interactions with water as well as the sensitivity of the SAW to viscosity changes and mass loading on the bare sensor surface. Their aim was to evaluate the potential use of the sensor as a biosensor. However, this first work did not describe any biospecific layers. SAW devices based on 36°YX $LiTaO_3$ were first used as biosensors in the early 1990s [30–32].

Developments based on Love waves

Five years after the first successful approaches on SAW biosensors were published, another type of SH SAW device was found to be even more suitable: those that benefit from the so-called Love wave effect. This is an acoustic resonance of a deposited layer with the HPSW traveling along the substrate. Originally the related physical effect was discovered by Love [33] after observing the damage caused far from the epicentre of an earthquake by earthquake waves that are guided through geological stratigraphic layers. Here, as well as on SAW devices, this effect is due to the lower acoustic wave velocity in the layer, which results in the acoustic wave being guided through the layer. Therefore, acoustic losses into the bulk of the substrate or into the liquid above the sensor surface can be minimized on SAW devices. Also, a reduction in attenuation can be obtained if the layer is adjusted to an optimum thickness. In this case, an acoustic film resonance occurs which increases the sensitivity of the device towards changes in physical properties at its surface, including mass loading. Early works in this field were presented in 1992 by two independent groups.

Gizeli et al. reported an enhancement in sensitivity that was obtained by applying a resonating polymer film [34]. The device was a quartz substrate supporting a HPSW-type of SAW termed a "surface skimming bulk wave" (SSBW). This is because this type of wave tends to irradiate into the bulk of the substrate, even when immersed in water. Therefore, such devices generally feature high attenuation and are thus unsuitable for use in an oscillator circuit. In order to reduce this attenuation, a Love wave-based layer resonance was excited. To achieve this, polymer layers consisting of poly (methyl methacrylate) (PMMA) of various thicknesses were deposited onto the SAW device. The authors showed that the attenuation decreases drastically with increasing layer thickness, implying that the SSBW is converted to a Love wave. However, the theoretically derived optimal layer thickness for the actual PMMA film resonance could not be observed, as the intrinsic attenuation of the polymer turned out to be too high. An applicable layer thickness with minimal losses was found to be significantly below the theoretical value of the optimum [35, 36]. Biosensors based on Love wave devices developed by Gizeli and coworkers are described in the section "Applications of SAW biosensors."

The second approach was initiated by Kovacs et al. [37, 38]. The authors developed the first Love wave devices based on sputtered SiO_2 layers for (bio)chemical sensing in liquids. Admittedly, a real biosensor was not described and the theoretically derived layer thickness of several μm could not be obtained at this stage [38, 39]. Later approaches by other groups revealed that thick SiO_2 layers are difficult to deposit using standard sputtering technology without inducing high mechanical stress within the layer. A Love wave device based on sputtered SiO_2 with an optimal layer thickness was first presented in 1996 by Du et al. [40]. They used a special sputtering technique for the deposition of stress-free SiO_2 layers, even at thicknesses of up to several μm. Such a device was applied for biosensing experiments by Harding et al. in 1997 [41].

Developments based on the combination of STW and Love waves

Meanwhile, Rapp and coworkers suggested the use of a commercially available SAW device with a design closely resembling the STW approach published by Flory and Baer, as described in the section "First successful approaches," but based on $LiTaO_3$ substrate. This device was presented as an immunosensor in 1993 [32]. A second approach with a similar device was published in 1995 [42]. However, a major drawback of commercially available SAW devices is the fact that the IDTs mostly consist of low-cost aluminum. Therefore, the lifetimes of such devices in aqueous media are limited to a few hours due to corrosion effects. For this reason, additional protection layers are required. Polyimide [43] and parylene C [poly-(2-chloro-*p*-xylylene)] [44] were found to be appropriate layer materials for this purpose. Additionally, these protection layers provide a chemically homogeneous surface for further (bio)chemical modifications [44–48].

A second drawback of commercially available SAW devices is the common use of bond wires to connect the device with the driving electronics. Bond wires restrict the use of sample cells with small volumes. Furthermore, they tend to collect air bubbles in the sample stream. Therefore, a new device using capacitive coupling instead of bond wires was developed. The resulting device was a SAW resonator on $LiTaO_3$ substrate with gold as IDT material. In order to enable capacitive coupling, large contact pads were integrat-

ed into the sensor design. This coupling concept enabled the design of considerably smaller sample cells with volumes of only a few μl [49, 50]. The choice of gold as substrate material made the device inherently resistant to corrosion in aqueous buffer solutions. A very important aspect of the design is the fact that the device is realized as a resonator. Similar to the design suggested by Flory and Baer (see section "First successful approaches"), a resonator produces STW-like surface waves because the reflective fingers act as a mass grating, which keeps the SAW on the substrate surface [51]. Compared to a classical delay line setup, resonators feature much smaller attenuation values and very distinct and sharp resonances, which makes them extremely suitable for use in simple electronic setups, especially oscillators [52]. With this device, various types of biosensing applications were performed [49, 53, 54]. For all these measurements, the devices were coated with parylene C for surface homogenization prior to applying a biospecific layer. Apart from providing a homogeneous surface, parylene C was also deposited in layers with specifically higher thicknesses in order to excite Love waves. The main advantage of using parylene C as wave-guiding layer is a significantly lower intrinsic attenuation than for other polymers, such as PMMA. As parylene C is deposited in a chemical vapor deposition (CVD) process at room temperature, the generation of even very thick layers with almost no intrinsic mechanical stress can be performed. Furthermore, Rapp and coworkers were able to demonstrate the occurrence of Love mode resonances online during the deposition process. With this experimental setup, more than one Love mode could even be observed using the resonator device [55]. Consequently, Rapp and coworkers were able to combine the advantages of STW and Love waves. It was suggested that Love waves could be excited with much thinner wave guiding layers using STW devices. The reason for this is the significant amount of pre-existing wave guiding characteristics for the STW grating structure on the device. Therefore, STW-based Love wave devices should feature significantly lower attenuations than Love wave devices based on SH SAW.

Applications of SAW biosensors

Surface modification and principal sensor setup

In principle, a biosensor comprises a biochemical recognition system and a transducer which transforms the biochemical (biological) response into an measurable output signal [56]. Thus, to pemit the use of a SAW device as a biosensor, the device has to be coated with a biospecific layer corresponding to the analyte. The immobilization chemistry strongly depends upon the underlying SAW substrate with or without a guiding layer and hence on the chemical environment available. Gold surfaces, for example, allow the use of functionalized thiols, whereas quartz or SiO_2 surfaces enable the use of various silanes. Both methods provide monolayers of active groups for the subsequent coupling of analyte-specific molecules or, if required, underlying mediator layers like hydrogels. Thus the surface modification method of SAW biosensors is highly independent of the detection principle and can often be derived from other label-free detection methods [57].

The basic setup of a SAW-based biosensor is shown in Fig. 1. The SAW device is operated by the driving electronics and integrated in a sample flow carrying the analyte. As mentioned before, SAW devices generate and detect the acoustic wave by means of IDTs on the surface of a piezoelectric substrate. Analyte-specific molecules (e.g., antibodies) are immobilized on the SAW device to catch analyte molecules (e.g., antigens) from the sample stream. Analytes binding to the immobilized capture molecules will influence the velocity of the SAW and hence the output signal generated by the driving electronics.

Detection of proteins

Direct immobilization of analyte-specific molecules on the sensor surface

The first feasibility studies with SAW devices usually did not aim at highly sophisticated surface modification methods. Instead, simple affinity systems with one binding partner immobilized directly on the sensor surface with or without a guiding layer were preferred to demonstrate the performance of the particular SAW system.

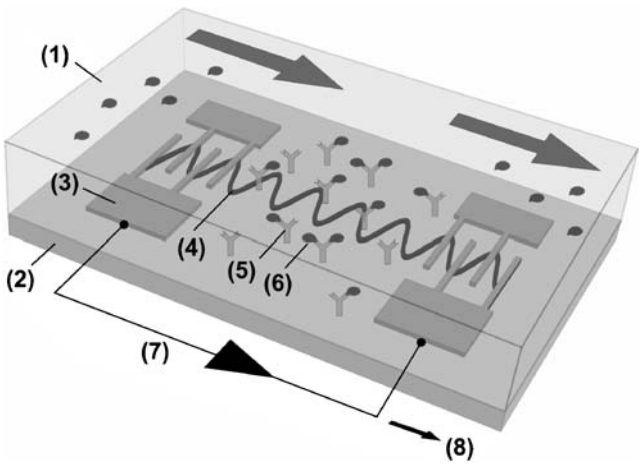

Fig. 1 Basic SAW biosensor setup exemplified by a SAW immunosensor. The *arrows at the top* indicate the flow of the liquid sample (*1*) in which the sensor is immersed. The elements of the SAW biosensor are a piezoelectric crystal (*2*), IDTs (*3*), the surface acoustic wave (*4*), and immobilized antibodies (*5*) corresponding to the analyte molecules (*6*) in the sample. The driving electronics (*7*) operate the SAW biosensor and generate changes in the output signal (*8*) as the analyte binds to the sensor surface

The first STW immunosensor was described in 1992 by Baer et al. The sensor was based on the device previously developed in the same group (see the section "First successful approaches"). Anti-IgG was immobilized on the surface of the quartz via silanization, and IgG was used as analyte [29]. Later the same device was applied in an inhibition assay for the detection of atrazine (see the section "Detection of small molecules").

Rapp et al. presented the first SH SAW immunosensor based on $LiTaO_3$ in 1993 (see the section "Developments based on the combination of STW and Love waves"). Anti-glucose oxidase was immobilized on the commercially available SAW device to detect glucose oxidase in the sample [32]. Later, similar devices were coated with layers of polymers, polyimide or parylene C, in order to protect the aluminum IDTs from corrosion. Wessa et al. described two methods for the direct coupling of proteins to polyimide. With the cyano-transfer technique, anti-glucose oxidase was coupled to the polymer surface for the detection of glucose oxidase [46]. In a second approach, glucose oxidase was derivatized with photoreactive groups via 3-trifluoromethyl 3-(*m*-isothiocyanophenyl)-diazirine (TRIMID) and immobilized on the polyimide layer via photochemistry. The subsequent binding of the corresponding antibody was observed [47]. Further developments in this group aimed at the application of hydrogels as intermediate layers, and are described in the section "Immobilization analyte-specific molecules on the sensor surface via intermediate dextran layers."

The first Love wave device for biosensor measurements was presented in 1992 by Gizeli et al. (see the section "Developments based on Love waves"). The device was based on quartz with a PMMA wave-guiding layer. IgG was adsorbed at the sensor surface, and anti-IgG and protein A were used as analyte [34]. Measurements with the same device were performed by Rasmusson and Gizeli to investigate PMMA and novolac photoresist as wave-guiding layers. These layers were coated with an additional thin gold film. Protein A was adsorbed on the gold as the capture molecule, and IgG was used as the analyte [58]. Gizeli et al. and Saha et al. used Love wave devices with photoresist waveguides together with gold film. Gizeli et al. applied peptides with N-terminal cysteine groups which self assembled on the gold surface. Binding of the corresponding antibody was observed as well as antibody desorption, which was promoted by adding peptide to the bulk solution [59]. Saha et al. immobilized protein A or protein G on the gold surface. The binding of IgG to the proteins A and G was investigated, including the determination of kinetic and thermodynamic constants [60]. The same affinity system was used by Gizeli et al. to compare three different Love mode sensors based on quartz and $LiTaO_3$ with photoresist waveguides and thin gold layers [61]. Further developments included intermediate lipid bilayers and are described in the section "Immobilization of analyte-specific molecules on the sensor surface via intermediate layers based on lipide bilayers or fullerenes."

Leidl et al. and Hoummady et al. also used immobilized protein A for IgG detection to illustrate the performances of their SAW-based biosensors. Leidl et al. used a STW sensor based on quartz and a thin gold layer [24], whereas Hoummady et al. presented a sensor system that used SH SAW devices based on $LiTaO_3$ [62].

Harding et al. used Love wave SAW devices based on a quartz substrate with a SiO_2 guiding layer (see the section "Developments based on Love waves"). IgG was immobilized on the device surface via silanization as receptor layer for detecting anti-IgG and to study the kinetics of the binding reaction [41]. Josse et al. used a similar affinity system to investigate the wave-guiding effect of PMMA and cyanoethylcellulose on SH SAW devices based on $LiTaO_3$ [63].

Schlensog et al. introduced a Love wave SAW device based on quartz with a SiO_2 guiding layer and a thin gold film. Thrombin DNA aptamers were coupled via an alkanethiol self-assembled monolayer (SAM) on the sensor surface for the detection of thrombin [64] and to investigate interactions in the blood-coagulation cascade [65]. A similar setup but with immobilized anti-thrombin antibodies was used for interaction analysis between thrombin and the immobilized antibody [66]. Jung et al. coupled thrombin-specific RNA aptamers via cellulosetosylate derivatives and compared the binding of elastase and thrombin to the aptamer [67].

Immobilization of analyte-specific antibodies on the sensor surface via protein A or protein G

Protein A and protein G enable the oriented immobilization of antibodies [68]. Welsch et al. used a SH SAW device fabricated on $LiTaO_3$ and covered with a thin gold layer. Protein A was immobilized on the sensor surface to couple anti-IgG for the detection of IgG. By labeling the antigen (IgG) with gold colloid, the signal was significantly enhanced. Furthermore, human serum albumin (HSA) was directly immobilized on the sensor surface for the detection of anti-HSA [69]. Freudenberg et al. optimized the setup by introducing a SiO_2 protective layer. They also developed a contactless method to connect the SAW device with the driving electronics that was based on inductive coupling, which is an alternative to capacitive coupling (see the section "Developments based on the combination of STW and Love waves"). The performance of the system was tested again with anti-IgG, which was coupled via protein A to the sensor surface, and IgG was used as analyte [70, 71].

Kwon and Roh also used SH SAW devices based on a $LiTaO_3$ substrate with a thin gold layer. They coupled

protein A via alkanethiol SAM on the gold surface. Afterwards IgG was immobilized on the protein A and anti-IgG could be detected [72].

Immobilization of analyte-specific molecules on the sensor surface via intermediate dextran layers

Intermediate hydrogel layers have been shown to be useful for preventing unspecific binding on sensor surfaces. This issue is important for all label-free detection methods. Furthermore, hydrogels enable mild reaction conditions so that capture molecules (e.g., antibodies) will retain their functionality in the subsequent modification step [73]. As depicted above, Rapp and coworkers used SH SAW devices based on $LiTaO_3$ which were coated with a polyimide or parylene C shielding layer (see the section "Developments based on the combination of STW and Love waves"). Intermediate functionalized dextran layers were favored to facilitate the subsequent binding of analyte-specific molecules. Dextrans can be bound covalently to the polymer layer by means of photoimmobilization [74]. This was first applied by Barié et al. to SAW biosensors coated with polyimide or parylene C. They used a single-step reaction of a copolymer consisting of carboxymethylated dextran and bovine serum albumin (BSA), whereas BSA was multiply derivatized via TRIMID with light-sensitive trifluoromethyl-aryldiazirine groups. Capture molecules were subsequently coupled by using carbodiimide chemistry on the hydrogel. The feasibility of this method was shown by immobilizing anti-urease for the detection of urease [43] and by immobilizing anti-IgG for the detection of IgG [45]. In a further approach, Länge et al. applied OptoDex, a dextran containing both photoactive and functional groups, as an intermediate layer on parylene C-coated SAW devices. Again the performance was tested via immobilized anti-urease and the detection of urease [49]. The surface modification was successfully applied for the interaction analysis of the binding of estrogen receptor on immobilized estradiol [53]. As the photoimmobilization procedure is restricted to compounds containing photoactive groups, Länge et al. developed a more versatile approach for hydrogel coupling on parylene C. For this, parylene C was activated via plasma oxidation and subsequent silanization, and then aminodextran was coupled covalently to the sensor surface. The feasibility of this procedure was shown by immobilizing folic acid and subsequently detecting anti-folic acid [54].

Immobilization of analyte-specific molecules on the sensor surface via intermediate layers based on lipide bilayers or fullerenes

As described above, Gizeli and coworkers presented Love wave biosensors based on quartz and different polymer waveguides (see the section "Direct immobilization of analyte-specific molecules on the sensor surface"). Aside from the direct adsorption of capture molecules, an immobilization strategy based on lipid bilayers was developed. An alkanethiol SAM was applied to a Love wave device based on quartz with a novolac photoresist used as the waveguide and a thin gold layer. After incubation with biotinylated phospholipid vesicles, a biotinylated lipid biolayer was formed. Biotinylated IgG was immobilized on the bilayer via streptavidin, and the binding of the corresponding antibody was detected [75]. Another Love wave SAW device consisted of a quartz substrate with a SiO_2 guiding layer. A lipid bilayer containing nitriloacetic acid was formed on this surface. After exposure of the bilayer to nickel (Ni^{2+}), the specific binding of histidine-tagged proteins was monitored [76].

Chang and Shih worked with SH SAW sensors based on $LiTaO_3$. The device was coated with polyvinyl chloride to support the immobilization of an intermediate layer consisting of fullerene molecules. Hemoglobin was adsorbed on the fullerene surface, and the binding of the corresponding antibody could be detected [77].

Detection of DNA

DNA was detected by means of complementary hybridization between DNA probe and target. Roh and coworkers used a SH SAW device based on $LiTaO_3$, which was coated with a thin gold layer. The probe DNA was immobilized directly on the gold surface, and a 15-mer oligonucleotide DNA was detected. This target DNA mutant is known to cause Hunter syndrome [78, 79]. Gronewold et al. used a Love wave device based on quartz with a SiO_2 guiding layer and a thin gold coating. The probe oligonucleotides were immobilized via an intermediate dextran layer. The p53 gene fragment was investigated. Cancer-associated single-nucleotide exchanges or deletions in comparison with the wild-type sequences could be identified via differences in the dissociation rates of the mutants [80].

Detection of bacteria

SAW immunosensors were successfully applied to detect *Escherichia coli* (*E. coli*), *Legionella*, the anthracis simulant B8 *Bacillus thuringiensis* (B8) and M13 bacteriophage (M13) acting as model analyte for bacteria or viruses. Tamarin et al. used Love wave sensors based on quartz substrate with a SiO_2 wave-guiding layer. Antibodies against M13 were immobilized on the sensor surface to detect the bacteriophage directly [81]. Howe and Harding [82] and Moll et al. [83] used similar devices to detect *E. coli* and *Legionella*. Both found that the sensitivities obtained by the direct detection of the bacteria via immobilized antibodies were not sufficient. They identified

the roughness of the SiO_2 guiding layer as main reason for this, so they developed other surface modifications. Howe and Harding first adsorbed the bacteria to be detected (*E. coli* or *Legionella*) on the SAW device and then detected the adsorbed amount via binding of the corresponding antibody [82]. Moll. et al. added the corresponding antibodies to the *E. coli* samples and coupled anti-species antibodies to the SAW device. Then the *E. coli* could be detected by the binding of the *E. coli*–anti-*E. coli* complex on the sensor [83].

Branch and Brozik used Love wave devices based on $LiTaO_3$ with either polyimide or polystyrene waveguides. Protein G was adsorbed on the surface to couple antibodies against B8, and the antracic simulant was detected directly [84]. Berkenpas et al. used a novel substrate supporting SH SAW, langasite ($La_3Ga_5SiO_{14}$), which was coated with a thin gold layer. Antibodies against *E. coli* were immobilized via an intermediate polyethylene glycol hydrogel layer for the direct detection of the bacteria [85].

Detection of small molecules

The direct detection of low molecular weight compounds (M_r<1000) with label-free detection methods may be a challenge due to the reduced effect of small molecules on the parameters influencing the signal response [57].

The first SAW enzyme sensors were developed in 1992/1993 using SH SAW devices based on $LiTaO_3$ substrate (see the section "First successful approaches"). They used the pH change associated with an enzyme substrate reaction. Inoue et al. coupled glucose oxidase for the detection of glucose [30], while Kondoh et al. coupled urease for the detection of urea on the SAW device [31]. Furthermore, Kondoh et al. coupled cholinesterase to the sensor surface and investigated the reaction with butyrylcholine. This enzyme reaction could be inhibited by adding fenitrothion, an organophosphorus pesticide [86].

Tom-Moy et al. used the STW device developed by Flory and Baer (see the section "First successful approaches") to detect the pesticide atrazine. Due to the limitations of the mass sensitivity of the STW device, they preferred the indirect detection of atrazine via an inhibition assay. To achieve this, biotinylated atrazine was immobilized on the sensor surface via avidin–biotin coupling, and anti-atrazine was added to the atrazine samples. After equilibration the antibody which was not occupied completely by atrazine was able to bind to the STW sensor and hence enabled the atrazine concentration in the sample to be determined. Atrazine concentrations in the range 0.06–10 ppm were detected [51]. In contrast to this, Gizeli presented the direct detection of 400 ppb atrazine. A Love wave sensor based on quartz with a novolac photoresist waveguide and a thin gold layer was used, and anti-atrazine was coupled to the surface via adsorbed protein A [87].

Dickert et al. coated SAW devices based on $LiTaO_3$ with molecular imprinted polymers for the detection of polycyclic aromatic compounds. One could argue that these were not biosensors due to the polymeric character of the coating, but still these experiments are an example of the detection of small molecules in aqueous media with SAW devices [88].

Stubbs et al. developed a SAW immunoassay for the detection of analytes in the gas phase, e.g., cocaine plumes. For this purpose, RSAW devices based on quartz were used. Antibodies were coupled to the RSAW device via adsorbed protein A and coated with a hydrogel layer to overcome the problem of hydration of the biomolecule [89]. Benzoylecgonine, the major metabolite of cocaine, could be detected in vapor [90].

Recent trends and future developments

Laboratory setups versus commercial sensor systems

Even though SAW-based (bio)sensor systems have been the focus of academic and industrial research for a number of years, most of these approaches only feature laboratory setups that are suitable for proof-of-principle evaluation and first experimental tests. For real commercial success, two crucial issues need to be solved: an appropriate production process is required, as is an applicable handling process for future SAW-based biosensors. Collings and Caruso point out that disposable, simple and cheap biosensors will most likely be suitable for mass market applications [57]. These requirements fit perfectly to the market strategy and technology that already exist for SAW devices as a low-price mass-produced item in the electronic industry. Since SAW devices used as filter elements for high-frequency electronics are already mass-produced, a market-compatible biosensor based on the same technology should be affordable, including costs of production and implementation. In this context, only the adaptation to create a SAW biosensor as a next-generation mass-produced article is missing. Furthermore, SAW devices allow simple high-frequency remote control techniques. Thus, another important feature of SAW technology is their use in remote sensing applications. Tanguay and Sawan describe an application of a SAW sensor designed for implants that is completely remote controlled and monitored [91]. Leonte et al. suggest a SAW sensor for liquid applications that can be remotely interrogated [92].

The main benefit of SAW technology is the fact that SAW devices can be operated with simple and cheap electronic components. As SAW devices do not require expensive setups (such as optical setups), the cost per additional sample channel is very low. This allows the creation of cost-effective sensor arrays of an arbitrary number of single sensors, which can be read out in real time and in parallel. However, in order

to transform a laboratory setup into a market-compatible sensor system, simply designing the sensor—if necessary in combination with a biospecific coating—is not sufficient. Most contributions to the scientific community relating to SAW-based sensor technology do not suggest overall system designs but rather basic approaches limited to the sensor element itself. Apart from the sensor, there are a number of additional issues which must be addressed when considering a market-compatible overall system.

Integration within peripheral fluidics

The fluidic embedding of a sensor device is a key element in the design of a market-compatible sensor system. Cass and Toumazou state that no system can move from laboratory use to personal or commercial care systems without solving this issue [93]. Besides supplying the sensor with the desired analyte and fluids, a proper fluidic setup would enable features such as sample pretreatment, purification and concentration while providing an easy interface for the user to interact with the sensor. To create such a fluidic system, basic issues such as the generation of pumping speed, the switching and distribution of fluids, and so on, would need to be solved. Furthermore, easy interconnectivity to pre-existing laboratory equipment, such as automated fluidic handling systems, spotters and comparable products must be provided.

Sensor production and package design

Being typical MEMS components, SAW devices are normally produced using lithography and subsequent metal deposition onto a desired substrate. Several processes have been described recently that produce SAW components via standard CMOS technology, which reduces the cost of production [94]. No matter which process is used, however, the resulting SAW devices are brittle and fragile components which are not suitable for the end user to handle. Furthermore, compromises in terms of suitable device operation characteristics must be accepted when suboptimal piezoelectric materials are used (see the section "First successful approaches"). Therefore, an ideal approach includes not only the use of piezoelectric crystals that are most suited to SAW biosensors—even if they are not standard CMOS materials—but also an appropriate user friendly interface that shields the sensor elements and provides fluidic contact. This means that the first step of system integration must result in suitable sensor packaging. It has been stated by Lec that an applicable sensor enclosure that provides mechanical, electrical and biological integrity and protection is often neglected. Designing such a sensor periphery is a challenging task [95]. It is difficult to separate the biological environment, most likely a water-based fluidic environment, from the sensor and the sensor's electronics; indeed, it is very often impossible in the sensor principles that have been suggested so far. However, a robust sensor package would greatly simplify the handling of the SAW device itself.

Electronic periphery

Another important issue is the electronic periphery of the sensor system. Coté et al. point out that laboratory sensor setups often require extensive electronic peripheries and components, such as network analyzers [96]. Among the electronic setups that have been proposed for reading out the resonance frequency or phase of a SAW device, Lec states that the resonator principle is extremely well suited to portable and highly integrated devices [95]. The latter is important, because setups targeted at the end-user market should not exceed the size of a shoe box. In general, the detection of a resonance frequency is easily achievable with a high precision in real time even with standard electronics and does not require extensive peripheral components.

However, most SAW devices presented to the scientific community are delay line devices for which easy resonance frequency detection is not possible in most cases, since the devices do not feature a single defined resonance frequency. Additionally, delay line devices suffer from high insertion losses since the acoustic wave has to travel a long distance on the device surface, which is usually equipped with sealing elements to keep the transducers separated from the fluidic channel. Hence, these devices are often coated with a layer of a defined thickness in order to obtain wave-guiding characteristics, i.e., Love mode devices, in order to attempt to partially compensate for the higher insertion loss. These devices are usually evaluated by the detection of phase shifts due to mass loading, since phase detection can be performed even if the insertion loss of a single device is very high [97]. In contrast, SAW resonator devices feature much lower insertion losses and are therefore more suited to the detection of resonance frequency shifts via an oscillator circuit. This sensor design requires complete immersion in the liquid channel, including the transducers. Thus, the choice of the substrate material (see the section "First successful approaches") and the production of SAW resonators are more difficult tasks than they are for delay line devices. Additionally, resonator-based SAW devices are much more sensitive to tolerances within the manufacturing process. Hence, such SAW biosensor approaches are not very common within the scientific community [49, 53, 54, 88]. Nevertheless, once these obstacles are solved, SAW resonators offer a higher potential to yield highly integrated and applicable biosensor systems.

Recent developments

Recent contributions to the scientific community have focused on overall system design for SAW-based biosensors.

Sakong et al. suggest a SAW biosensor that is supplied with a fluidic system consisting of a microfluidic polyimide tubing system [79]. The system is designed for the detection of DNA. Cole et al. suggest an approach that goes even further, integrating passive fluidic components directly next to the sensor system itself [98]. The authors describe a microfluidic sensor periphery manufactured by standard microstructure technology in a photoresist layer (SU-8) used as the surrounding material for the fluidic channels, which are located directly on the substrate of the SAW device beside the transducer structure. The generated SU-8 structure is then coated with a thin layer of parylene for SU-8 and device passivation. As a result, all passive microfluidic components such as reservoirs and filter columns are integrated directly beside the SAW device. The overall system is enclosed in a plastic cover manufactured by micro stereo lithography methods. This cover also provides the connection to the fluidic periphery, which consists of a pump and a valve system. Since this approach covers the whole structure at an early stage, the SAW-based sensing device is not accessible for subsequent surface modification. However, this might be a very important feature for an application as a biosensor, since a future user might tend to apply individual biospecific coatings just before measurement. A similar approach was suggested by Francis et al. [99]. The authors describe a SAW biosensor on lithium tantalate which is embedded in a fluidic surround; this system is also manufactured by microfabrication technologies in SU-8. The last process step is the closure of the SAW cell by gluing a glass substrate to the top of the cell. However, before this, the surface of the SAW device remains accessible throughout the manufacturing process. A further successful application of a packaged SAW resonator in a liquid environment is described by Länge et al. [100]. The authors suggest an approach where a single SAW device is embedded in a polymer housing with integrated microfluidic channels. These channels can be interfaced to surrounding fluidics. This approach is suitable for forming sensor arrays of variable sizes through the interconnection of single housed sensors, resulting in very flexible biosensor arrays. When provided with a polymer layer of adequate thickness, the sensor can be operated as a Love wave device, thus multiplying the sensitivity [55]. Recent developments have resulted in housings produced by injection molding, thus yielding mass-market-compatible sensor systems which are suitable for a wide range of applications [101]. Each housing features an effective sample volume of only 250 nl, which allows fast sensor responses and minimization of sample consumption. In the near future a system will be available which allows individual surface modification at any time, since the active part of the sensor will remain open. Reversible closure of the single devices is performed mechanically by assembling several biosensor chips into an array in the biosensor setup. Hence, the closure takes place immediately before the biosensing measurements and does not require any additional interfering materials such as adhesives and sealing elements.

Commercial systems

Although SAW-based sensor technology has been the focus of academic and industrial research for some time, SAW-based biosensor systems are not yet established in the market. Among the most notable of the close-to-commercial SAW biosensor systems is the "S-Sens" system [102]. It features a flow cell comprising an internal volume of 6 μl and uses a sensor chip with five integrated SAW delay line devices. The SAW devices consist of gold IDTs on quartz substrate material, and this can be sputtered with a SiO_2 layer in order to obtain wave-guiding characteristics and thus a Love-mode device [64]. Consequently, as stated in the section "Electronic periphery," this type of device must be evaluated by the phase shift due to mass loading and not by evaluating the resonance frequency shift. Since such devices are comparatively large, the single sensors will probably need to be used several times to save costs. The system is offered with a variety of possible surfaces (such as gold or SiO_2) to allow various surface modification protocols to be used. Experimental results with this system have been described [65–67, 80, 103, 104].

Summary and conclusion

In this review, a brief overview of the 20-year history of SAW-based biosensor technology has been given. Important approaches and devices that have been introduced to the scientific community over those 20 years have been described, as well as very recent developments. We think that an important feature for successful device operation in liquid is the use of STW or SH SAW—or a combination of both—excited on appropriate substrate materials. However, the most important aspect of turning a SAW device into a biosensor is suitable surface modification, for which different examples and applications have been presented. It was shown by the published literature that SAW biosensors allow the detection of various analytes over relevant concentration ranges, even if the best possible sensitivity data or limit of detection values were not determined for each SAW biosensor setup. In order to get a fair comparison of all measurement setups presented, it would have been necessary to test them with the same analytical parameters. So far such comparative data have been unavailable.

SAW resonators are particularly well suited to use in simple electronic setups, as they feature low insertion losses and sharp resonance frequencies. The latter is of great importance for the insertion of such devices into oscillator

circuits, which have been described as being highly suitable for use in end-user market systems or point-of-care diagnostics. As the SAW component itself and the electronic setup can be realized using cheap components and standard industrial processes, a SAW-based biosensor system could easily feature a high number of single sensor devices integrated into a cost-effective sensor array which can be read out in real time and in parallel.

The importance of a the proper embedding of the SAW device into the sensor housing as well as suitable fluidic and electronic surroundings has been pointed out, and recent approaches to developing such sensor systems have been described. One sensor system which has already reached a level of development that is very close to a complete commercial sensor system has been presented. Another promising and very versatile biosensor system approach based on an array of disposable single housed SAW devices has been described. The performance of the latter in biosensing applications is currently being investigated by the authors of this review.

Considering all of these aspects, it can be stated that SAW-based biosensors offer the possibility of observing real-time binding events of proteins at relevant sensitivity levels and at low cost. Therefore SAW-based biosensor technology is a promising approach which may eventually be able to compete against established but much more complex optical-based biosensing techniques, like surface plasmon resonance (SPR).

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