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Review

Surface acoustic wave sensors in the bioanalytical field: Recent trends and challenges

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ABSTRACT

This is a comparison of the latest developments in the emerging field of surface acoustic wave (SAW) sensors. Progress has been made particularly with regard to (sub-) microstructure technology and material sciences. Improvements are displayed based on the impact on a new generation of SAW sensors working efficiently in liquid media, from modeling to the fabrication steps of the individual components. It is explained, which obstacles have to be overcome for applications to the bioanalytical field. SAW sensors are shown to be extremely useful for the analysis of both small and large molecules as well as whole cells interacting with an immobilized binding partner. The output signal gives information about the pure mass loading, intrinsic properties of bound materials, or viscoelastic effects like structural rearrangements. Different setups are shown that minimize the influence of physical bulk effects on the sensor signal, e.g. salt content and viscosity. The choice of materials which can be used for sensible surfaces are presented, enabling the development of completely new coupling chemistries. Finally, the advantages compared to other biosensor technologies are pointed out.

Contents

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1. Sensor technologies

1.1. *Basic principle of SAW sensor technology*

SAW devices use piezoelectric materials to generate an acoustic wave. Basic discoveries were made in the late 19th century. Initially, the piezoelectric effect was described by Pierre and Paul-Jacques Curie and later on the properties of the surface acoustic wave mode of propagation by John William Strutt. A surface acoustic wave (SAW) is an acoustic, mechanical wave that propagates confined to the surface of a cut piezoelectric crystal. Coupling to any medium contacting the surface strongly affects the velocity and/or amplitude of the wave. Further development of photolithographic techniques for computer chips and telecommunication devices to optically transfer micro- and nanostructure patterns onto a substrate, allowed fabrication of micro- and nanostructures implemented in modern biosensors. In a typical approach (compare Fig. 1a and [1]), an electrical signal is converted at interdigital transducers (IDT's) into polarized transversal waves travelling parallel to the sensing surface, utilizing the piezoelectric properties of the substrate material. This approach is very sensitive to specific biological interactions with the sensor surface. Typically, the wave is transmitted confined to an independent guiding layer and not the substrate. Thus, the acoustic energy is concentrated within the guiding layer rather than in the bulk of the piezoelectric material. The sensitivity of the sensor for surface modifications is increased, by the choice of material, and the design of the guiding layer [2,3] as well as by the structure of the sensor and the transducers [4]. The waves are travelling across the sensitive area, altered by biochemical events at its surface. Afterwards, the wave is converted back at another IDT into an electrical signal. Input and output signals are transformed, for example into a resulting signal of frequency or phase changes, which can then be correlated to the corresponding mass and mechanical properties in the fluid contacting the sensitive surface. The components necessary for the measurement of aqueous or other fluid components are displayed in Fig. 1b. For construction or judgement of such devices it is important that most SAW sensors are highly sensitive for altering properties of the liquid medium, i.e. the temperature, pressure, viscosity or salt content of the contacting liquid. The application of the sensor is defined by the coating of the sensor surface, e.g. with antibodies. In vapor sensors, the coating absorbs only certain chemicals. A biosensor is created, when the coating binds specific biological components of liquids. In principle, SAW sensors are operated on frequencies between 25 and 500 MHz. Based on the frequency, the penetration depth adjusts. With increasing frequency, the penetration depth decreases. Therefore, the sensitivity of SAW sensors increases by the square of the frequency, yielding a sensor highly sensitive for surface interactions. Most binding events monitored occur in close proximity to the biosensor surface.

1.2. *SAW versus SPR technology*

For time resolved, on-line, marker-free detection of binding events and *in situ* measurements in the liquid phase, SAW sensors are still in the shadow of the widespread optical methods, especially surface plasmon resonance (SPR) technology (Fig. 2). The reason being the development and subsequent availability of several highly developed SPR biosensors from different companies during the last more than 15 years. The geometrical setup of these SPR sensors is mostly in the easy-to-build *Kretschmann* configuration. The developers of SAW sensors have to catch up to this head start, and also have to compete with the attention of the scientific community and of the potential customers, which are focused on SPR sensors. But SPR sensors are still problematic regarding certain measurements: (i) the detection of changes in the refractive index brought into proportion to the mass changes as the only signal, while the SAW sensors are sensitive to changes in mass, density, viscosity and acoustic coupling phenomena, (ii) surface chemistry is largely limited by the obligatory noble (mostly gold) surface, (iii) the refractive index as the SPR signal is greatly influenced by physical side effects, which means that instruments have to be calibrated for changes in the buffer. Such changes my for example result from common buffer contents like glycerol or solvents like DMSO.

1.3. *SAW versus QCM technology*

Generally, acoustic wave devices use similar technologies, and are best described by their mode of wave propagation. The first such devices manufactured are the relatively simple thickness shear mode resonators, also known as quartz crystal microbalances (QCM). QCM's are bulk wave sensors, where the waves propagate in the complete piezoelectric substrate. QCMs use a thickness shear mode vibration, with the vibration of the complete substrate. The displacement is maximized at the upper and lower surfaces of the crystal, making the device sensitive to surface interactions. Thus, various QCM's

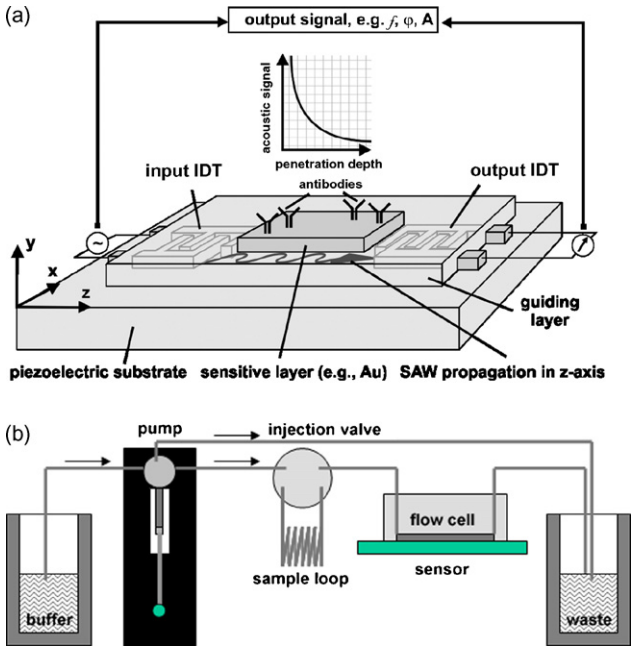

Fig. 1 – Components required for a SAW biosensor. (a) Schematic drawing of a SAW device design (provided by Corinna Bernsdorff; not to scale). At the input or transmitting IDT, an oscillating electric field is applied to create a substrate-deforming mechanical wave, which propagates along the z-axis through the substrate and is then reconverted into an electric field for measurement at the receiving output IDT. The associated distribution of potential energy is indicated by the arrow to indicate that this configuration limits the loss of energy into the medium above the sensor surface (bulk). The penetration depth of the signal into the medium varies, e.g. depending on the type of sensor and the frequency, but the signal declines exponentially (inset). In the example, the fingers of the IDT's aligned parallel to the x-axis. The displacement of the wave is following that direction, parallel to the surface ("shear horizontal" or SH-SAW). This reduces the loss of energy due to damping of the signal from a liquid medium. Thus, the use of the device as a biosensor is enabled. (b) Constituents of a biosensor. To run liquids over the surface of a sensor chip, a sealed flow cell is required. The liquid usually is moved forward at a defined flow rate by a peristaltic or syringe pump. The sample is injected into the buffer stream using either an injection valve for single injections, or an autosampler for rapid, standardized injections, enabling high throughput analyses. To read out the sensor chip, a network analyzer can be used, or a reader unit is constructed for the electronic contacting of the chips to generate and detect the harmonic oscillations of the sensor chip by high-frequency electronics, comprising a frequency generator and an I/Q demodulator. A microcontroller processes the resulting signals and allows controlling the system via a computer provided with a corresponding software as the user interface (not shown).

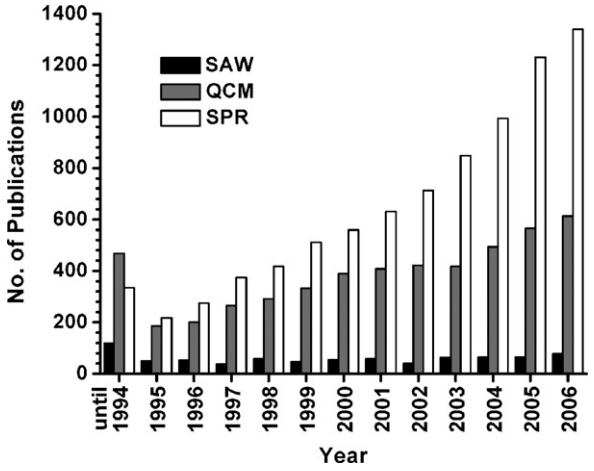

Fig. 2 – A summary of the number of articles per year referencing either "surface acoustic wave sensor", "quartz crystal microbalance" or "surface plasmon resonance" based on citation index databases. Note that until the late 1990s, SAW sensors mostly were used as chemical sensors.

are manufactured as biosensors. An increase in the frequency and, thus, the sensitivity, is limited by manufacturing, as this would require thinner, more fragile substrates. Typically, frequencies between 5 and 30 MHz are used. In SAW sensors, the waves only propagate in a guiding layer at the surface of the substrate (Fig. 1a). Thereby, the thickness of the substrate does not influence detection behaviour of the SAW sensors. SAW sensors in Love mode have a solid overlayer deposited on top of the substrate material (compare Fig. 1a). The loading of SAW sensors can be analyzed using perturbation theory [5–7], or Christoffel's equation [8]. The propagating wave is affected by the nature of the medium, especially liquids, in contact with the guiding layer. When shear acoustic energy material with a lower acoustic velocity than the piezoelectric substrate, e.g. SiO_2, is used as the guiding layer, the sensitivity is expressed as a function of the layer thickness. Currently, Love-wave sensors are the most sensitive acoustic sensors. The acoustic energy of these sensors is coupled to the liquid layer perturbing the wave, while energy loss into the medium is minimized. The waveguide also protects and insulates the electrodes from liquid media. In comparison to QCM's, where the energy is distributed throughout the substrate, thus reducing the energy and sensitivity at the sensing surface, in SAW sensors the energy propagation path is highly localized inside the guiding layer.

1.4. *SAW sensors*

Three types of frequently used SAW sensors are considered: (a) Rayleigh-SAW sensors, (b) Lamb-wave sensors, and (c) Love-wave sensors. All three SAW sensor types have several advantages compared to QCM sensors, especially regarding the damping of fluids [9]. In Rayleigh wave sensors and in Lamb-wave sensors, the material waves are displaced in the y-axis (Fig. 1a) in the direction of the medium. In Rayleigh or bulk acoustic wave sensors, waves can be excited at the opposite surface from the detection surface. However, the energy is dis-

tributed across the complete substrate material and not at the detection surface. Thus, both Rayleigh wave sensors are only and Lamb-wave sensors are mostly used as gas sensors, since the waves are damped in liquids. Lamb-wave sensors are also known as flexural plate wave sensors. The waves are propagated in a thin membrane, mainly consisting of SiO_2 deposited on the piezoelectric substrate. In contrast to Rayleigh waves, the propagation velocity in the membrane is slower than in the fluid contacting the surface. In Lamb-wave sensors, energy is not dissipated and they can be used in gaseous and fluid environments. Lamb-wave sensors are highly mass sensitive, but to achieve such high sensitivities, the membranes have to be very thin (a few micrometers) [10], making them fragile and adding difficulty in fabrication and handling. Additionally, the acoustic energy is distributed between both surfaces of the device, leading to a concentration of the acoustic energy at the sensing surface only in very thin plates. Love-wave sensors are currently the most sensitive acoustic sensors (see Section 1.3).

From 1996 to 2006, the number of articles referencing "surface acoustic wave sensors" increased by a factor of 1.5–78, while the articles referring to "quartz crystal microbalance" tripled to 613 and the articles referring to "surface plasmon resonance" increased by a factor of 5–1340 (Fig. 2). This shows that the big potential of the SAW technology has not yet been recognized in the Scientific community, or that the technological obstacles are too high for applying this sensor technology to fluid biological samples. SAW sensors are often self-constructed and are applied to measure the frequency shift of the surface acoustic wave resonance mode (Table 1) [11,12]. Comparable to the traditional QCMs, a linear dependency of the resonance frequency on the mass deposition can be expressed in the so-called *Sauerbrey* equation [13]. SAW sensors were shown to be more sensitive than QCM sensors for surface mass change, density, viscosity, and electrical conductivity [14]. Product and methods reviews [15–17] have shown that several commercial, SAW-based sensors are available for air analysis, especially to monitor levels of known hazardous contaminants. Best known is Microsensor Systems Inc. (MSI), Bowling Green, Ky., USA (now a subsidiary of Mine Safety Appliances, MSA), for chemical vapor detection hazardous to humans and explosives. Detectors are installed for example in infrastructural systems.

Only few systems are available for handling liquid samples. The first layered devices used in biosensing and in liquid media were developed in the mid-1990s [18–20]. Typically, Love-wave sensors are used for liquids at a frequency of about 120–200 MHz [21]. Commercially available is the S-sens® K5 (Nanofilm, Germany) with five sensor elements on one sensor chip operated in Love-wave geometry. Instead of measuring the frequency shift, they measure in delay-line geometry. The S-sens® K5 is working at two fixed frequencies differing by about 0.3 MHz, with $\varphi(f1) - \varphi(f2) \approx 180^\circ$ at a frequency range between 130 and 170 MHz [22]. The mass sensitivity of this sensor depends on changes in the phase velocity inside the guiding layer [22–24]. The mass can be discriminated from viscoelastic effects by using both the phase shift and the amplitude shift of the surface acoustic wave [22]. The advantages of measuring at two fixed frequencies are exemplified in Fig. 3 at the unprocessed phase signal of the injection of 5% glycerol and 100 mM sodium hydroxide. The influence of many physical parameters on the sensor signal, e.g. by temperature [25], salts and viscosity, is largely reduced as well as sensitivity deviations between different sensor elements [22]. The ViSmart™ (BiODE) sensors (Vectron, Hudson, USA) with single sensor elements are used to detect the viscosity of fluids, especially oils, by shifts in the amplitude signal resulting from the power loss into the fluid. Other groups only use the phase shift as the output signal [26]. Both approaches result in a decrease in signals that may be evaluated and, thus, the depth

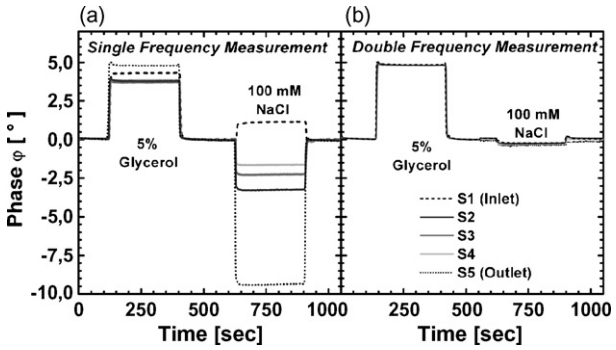

Fig. 3 – Comparison of (a) one and (b) two frequency measurements with a S-sens® K5 sensor array. Phase shifts for five sensor elements during the injection of 5% (w/v) glycerol/water and 100 mM NaCl solution with respect to water as running buffer.

Table 1 – Presented are the sensitivities of surface acoustic wave sensors in resonance mode with comparable output signals

Sensitivity ($cm^2\,g^{-1}$)	Reference and sensor type	Sensitivity ($ng\,cm^{-3}\,Hz^{-1}$)	Reference and sensor type
519	Love [45]	360	Love [7]
430	Love [20]	130	Love [21]
380	Love [114]	7.1	SH-SAW [107]
274	Love [62]	3.3	SH-SAW [113]
142–155	Love [63]	1.55	SH-SAW [110]
70	SH-SAW [35]	1.05	Love [40]
		0.8	SH-SAW [107]
		0.64	SH-SAW [81]

Two out of various sensitivity specifications presented in the papers are selected. The values were grouped, if possible, by making the following assumptions: $cm^3 = mL$, $(\mu g\,kHz^{-1}) = (ng\,Hz^{-1})$, or the reciprocal value is presented.

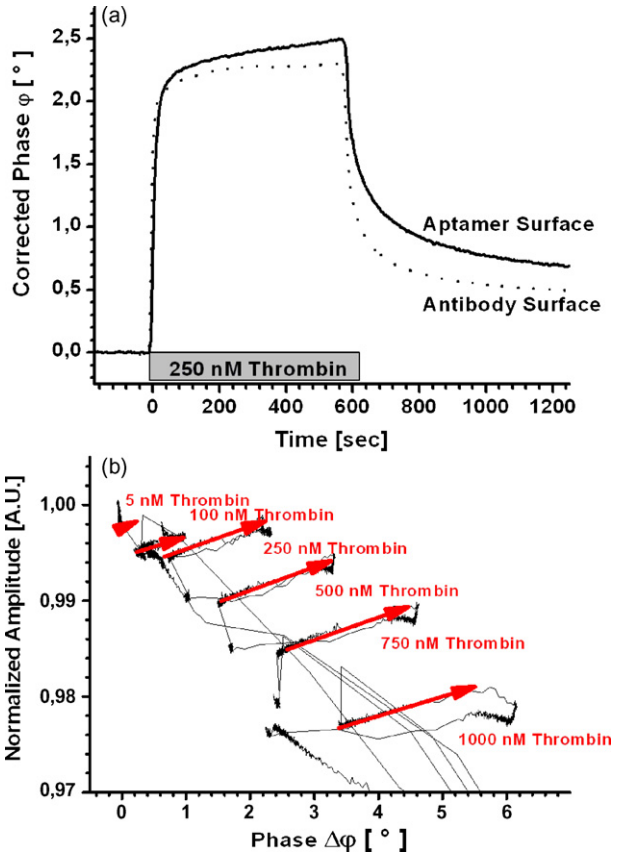

Fig. 4 – Thrombin binding to a S-sens® K5 biosensor quartz chip surface with an 11-mercapto undecanoic acid self-assembled monolayer. The biochip was introduced into the biosensor and measurements were performed at a constant flow of 40 μL min^{-1}. The carboxyl head groups were modified via carbodiimide chemistry by 2 μM RNA anti-thrombin aptamer [86,119] and 200 nM anti-thrombin antibody [22], respectively. Three out of five sensor elements of the sensor array were modified by the ligand. The remaining two were modified by non-binding antibodies and aptamers, respectively, and binding events were corrected for unspecific binding. Standard deviations for the binding events were <8%. (a) Comparison of injections of 250 nM thrombin to the respective ligand surfaces. The aptamer surface (solid line) was regenerated under flow conditions to baseline with 0.1 nM NaOH solution and the antibody surface (dotted line) with 10 mM glycine, pH 3.0. Kinetic evaluation of the binding events resulted in a $K_D = 181 \pm 20$ nM for the aptamers [119] and $K_D = 116 \pm 9$ nM for the antibodies [22]. (b) Phase-amplitude diagram for consecutive injections of thrombin to sensor cells containing the aptamer-modified surface. The arrows indicate the association of thrombin with the aptamer surface at different concentrations. The angle between those arrows (association) and the phase-axis is small. For thrombin binding events, the mass increase dominates over the negligible viscoelastic effects.

of analysis. The advantage of applying both the phase and the amplitude signal are illustrated in scattering plots to create a sensor which discriminates tastes by principles comparable to the tongue, i.e. by differences in unspecific interaction with a surface [27].

Another necessary feature is the addition of sensor elements, preferably on the same sensor chip, which are then addressed simultaneously. This enables the use of parallel analysis and, thus, application of one sensor element as a reference. From a biological point of view, a reference is necessary to differentiate specific interaction and binding events on the sensor element from unspecific binding events. From a physical perspective, parameters like temperature instability and buffer contents can be detected by one or more reference elements and can then be subtracted. Improvement in sensing technology as seen in the two frequency measurement with a reduced influence of physical parameters on the sensor signal (Figs. 3 and 4) results in an increasing independence of the analysis from the, in this respect unnecessary, reference elements.

2. Modeling and developments

Originally, the SAW sensor-based technology was developed for gas and vapor detection. Water has the negative property of damping the sensor signal. Further development started with modeling the influence of viscous liquids and other non-gravimetric effects on the mass sensitivity [6,8,28–31]. An example of such developments is the investigation of fluids damping the signal of flexural plate wave devices [32]. Mathematical modeling and simulations of these systems is essential for the development of new sensors, especially with respect to the usage of new materials and the wave propagation therein [33–35]. This can be applied to improve the signal-to-noise ratio or to remove triple transit echoes. This may additionally be applied for realization of new forms of SAW sensors like the surface transverse waves family of sensors [36]. The practical studies resulting from theoretical considerations are essential for the development [37]. One example are investigations regarding modifications with an impact on wave propagation across the substrate ([37–42], compare pioneering works from [43–45]), on the production process [46], or new forms of sensors, e.g. in a wireless mode [47–49]. Certain factors are important for the creation of transportable devices, the size of the system components [50,51], packaging [52] and the power consumption for long lasting of the power source [53]. This facilitates the development of new transportable or “lab-on-a-chip” devices.

3. Combination of methods

3.1. *SAW sensors applied as detectors*

The theoretical and practical combination of SAW sensors with optical methods enable the simultaneous quantification of biological soft layers formed on the sensor surface under varying conditions with respect to density, viscosity,

thickness and water content [54,55]. Another possibility is the combination of different types of SAW sensors with other detection methods such as high performance liquid chromatography (HPLC) [56] or gas chromatography (GC) [57,58] or with concentration methods like pre-trapping of small aroma molecules [59,60]. The MicroChemLab system from Sandia National Laboratories, Albuquerque, NM, USA, is a system integrating the mentioned methods to measure molecules in gas phase [61,58]. The detection and biochemical analysis of interaction processes with SAW sensors can be reasonably combined with the identification of the bound proteins by mass spectrometry. Proteins bound to the S-sens® K5 sensor chip surface have been identified with matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-ToF MS).

3.2. *Physical characterization*

The mass sensitivity of SAW sensors were determined with physical techniques like etching or electrodeposition [62], often in combination with various microscopic methods, e.g. atomic force microscopy [63]. Such physical characterization methods are limited, as the physical layers are solid. The mechanical and theoretical sensitivity of the system can be determined for example for solid layers by Cu etching [64]. For the S-sens® K5, the sensitivity for solid layers was determined to be $29.6 \pm 0.8^{\circ}\,cm^2\,\mu g^{-1}$ at a guiding layer thickness of 4.7 μm and a frequency of about 174 MHz. The sensitivity for biological layers was calculated with $419^{\circ}\,cm^2\,\mu g^{-1}$ [65] and was improved to currently $515^{\circ}\,cm^2\,\mu g^{-1}$ [65]. The sensitivity remains constant over a wide mass range of proteins (for reasons, compare 1.4). The determined sensitivities for solid layers are only at less than 10 and up to 25% of the values measured with biological molecules in aqueous buffers [65–67]. This may be explained by water molecules contained and entrained within biological layers. The sensitivity of the sensor for proteins, i.e. the relation of phase shift to mass load, can be characterized using different methods (Table 1). For the S-sens K5®, the sensitivity was calculated by analysis of fluorescence labelled proteins of different size. Mass loading was determined by an imager [65]. An elegant method using radioactivity has been published by Gizeli [20]. The maximum sensitivity of the Love-wave sensor described was 11 and $31.1^{\circ}\,cm^2\,\mu g^{-1}$ for Immunoglobulin G antibody bound to silica and PMMA waveguides. She used parallel measurements to achieve the results with radioactive labelled antibody. The signal of antibody binding to the surface of the sensor system was determined in flow through. The radioactive labelled antibody was bound externally to the sensor surface to determine the mass loading on the sensor surface. The mass loading of different amounts of antibody and the resulting phase signal were plotted, resulting in a linear correlation as expected. It has to be considered that the sensitivity of the sensor might differ depending on the reproducibility of the production process of the sensor chips, or the biological modifications applied to the surface, which often cannot be standardized. Thus, the sensor signal and the binding quantities need to be (re)calibrated. The detection limit is usually calculated by assuming it to be three times the noise level. Due to improvements in sensor design and fabrication, differences in signals from sensor chips of the same design and single sensor elements are reduced and limits of detection of $<50\,pg\,cm^{-2}$ are achieved. This results in sensor systems competitive compared to other marker-free systems, e.g. the QCM E4 system from Q-sense with $1800\,pg\,cm^{-2}$, the QCM Z500 from KSV with $180\,pg\,cm^{-2}$, or the optical SPR systems as is the BIAcore system with $<100–1000\,pg\,cm^{-2}$ [68–70]. The sensitivity of the systems for oligonucleotide detection highly depends on their size and is thus not examined here. Short DNA strands behave like the deposition of a pure mass. The longer the deposited DNA molecules are, the higher the viscosity effect.

4. Substrate materials

Basic research on the SAW principle often came from new mechanical materials developed for electroacoustic devices and resonators especially in the communication market. Despite the most frequently used quartz and $LiTaO_3$ substrates, new methods for the generation of high acoustic velocity materials were developed, e.g. sapphire, diamond-like carbon, silicon, NbO_3 compounds, AlN, PMN-PT, etc. [34,46,71]. The new materials and new fabrication techniques resulted in easier manufacturing of high-frequency acoustic wave devices operating above 2 GHz [72,73]. Both materials and techniques still need to find their way into biosensor technology. The penetration depth of the sensor decreases with increasing higher frequencies, in doing so increasing the sensitivity of the sensor for smaller molecules and effects close to the surface [22,74–76]. Improvements in sensitivity may also be achieved by nanostructuring the sensor surface [77].

5. Sensor chip surfaces

The sensing surface by itself is not selective. Important for the development of new applications are the functional layers responsible for binding the target molecule (analyte) to a specific molecular recognition element (ligand) (Fig. 4). This selective surface is preferentially reusable. Since the SAW technology is not limited to gold, a number of materials are available enabling new binding and immobilization technologies, or even on chip synthesis. Many articles published show only minor improvements compared to well-established technologies, mostly involving gold surfaces [78]. Examples are surfaces coated with alkanethiols (Fig. 4) or in further development with carboxymethylated dextrans, often in combination with biotin/streptavidin interactions [79,50]. This technology originates from the late 1980s. A development enabling strongly localized binding are methods using photoimmobilization [80–82]. Alternatively, ZnO surfaces [83], or SiO_2 surfaces are used [67]. SiO_2 surfaces are modified by organosilanes [11,84,85] or by newly developed materials as organocelluloses [86]. A new material combination involves cellulose papers applied to the sensing surfaces [87] which might lead to the development of chromatographic techniques on the chip.

Alternative wide band gap materials with very interesting mechanical and biochemical features are used such as

intrinsic catalytical properties [88], metallic surfaces [89] or (dendritic) polymer surfaces [90–92]. These mostly were applied to detect vapor as in "electronic noses" [93,94] used for example in the detection of cocaine [95,96] and gases [97–103], to analyze food [104], or to diagnose diseases [105,106].

Integrated layers like polymers have a great potential for SAW biosensors. They will be examined in Section 7 on applications. An interesting approach included the use of fullerenes applied to a PVC-modified $LiTaO_3$ surface for the immobilization of the proteins hemoglobin and myoglobin [107].

6. Flow cells

Another field that needs improvements are the materials used for creating flow cells, packaging, and flow patterns in microfluidic channels. The development moves towards smaller flow cells using less analyte material, often accompanied by an increase in the number of flow cell elements and enhancement in the flow pattern [108,109]. The most frequently used materials are silicone-based. The fluidic cells are usually constructed with an inlet at one side, an outlet at the other, and the channels facing the sensor chip. Alternatively, a rubber O-ring is used for sealing. Those factors influence the binding efficiency and the course of binding kinetics, resulting in possible variations of the true results.

7. Applications

7.1. *Proteins and nucleic acids*

Generally, SAW sensors enable on-line interaction analysis. The data can be kinetically evaluated. An outline of possible applications was presented by Čavić et al. [110]. As molecular recognition elements or target molecules, mainly nucleotides [111–113] and/or proteins [63,78] were used. The use of antibodies (Fig. 4a) [20,42,47,50,55,83,84,107,113,114] give interesting perspectives like the detection of interleukin-6 detection by Sandia National Laboratories for medical applications. Further development is needed (i) in protein technology with biologically relevant small molecules which are unlikely to be measured in low concentrations or in mixtures with large molecules, (ii) in nucleotide technology, e.g. regarding aptamers (Fig. 4a) [115–117], or (iii) new applications to industrial needs such as enzymatic processes [118,119]. New immobilization protocols for enzymes as in photoimmobilization, are often applied to glucoseoxidase for detection of diabetes [81,78,86]. The few novel applications often were based on antibody interactions (Fig. 4a), e.g. targeted ultrasonic contrast agents for the medical field [120], or as described elsewhere in this article. Articles about applications where mass alterations are separated from viscoelastic effects (Fig. 4b) will enhance the acceptance of SAW sensor technology. An example would be rearrangement effects of drugs on bound molecules or vesicles without altering the bound mass. The usability of SAW sensors for the determination of liquid density separation from liquid viscosity has been shown for fuels and solvents [121].

7.2. *Whole cells*

Important as a reasonable application area for SAW sensors are the first works on whole cells, focusing on bacteria [11,105,106,122], bacteriophages [123] and yeasts [122]. Results with the S-sens® K5 showed that SAW sensors can be used to specifically detect viruses and eukaryotic cells with high sensitivity via selective proteins or antibodies at low concentrations, even as an alternative to Western blotting. First measurements of the adhesion of mammalian cells to sensor surfaces indicate the usefulness of SAW sensors for the characterization of advanced binding processes [110,124]. Promising results of the Sandia Laboratories (Sandia Corp.) were achieved with a Love-wave sensor applied to a stimulant of the biological warfare agent *Bacillus anthracis* [125], disclosing the possibilities of the technology for monitoring various infectious and potentially replicative bacteria, or their produced toxins as agents of terrorism and biowarfare [126], food poisoning and in medicine [122,127]. Similarly promising were the first results from measurements with *Legionella* [128], toxigenic *Escherichia coli* O157:H7 [129] and K12 with a flexular plate wave device [130]. The robust SAW sensor technology allows relatively aggressive cleaning procedures necessary during measurements involving such pathogens. This requirement will also become important upon the creation of new diagnostic tools.

7.3. *Membranes and vesicles*

It is surprising that the advantages of the SAW sensors for lipid research, shown already in 1996 by Gizeli et al. [18], even in combination with interactions of biotinylated antibody to membrane-bound streptavidin [19], did not lead to much further investigations in that field. Making use of the possibility to separate mass from viscosity effects [22], binding events related to vesicles and lipid bilayers and the reorganization can well be characterized ([3,131], Thomas Gutsmann, Borstel, Germany, personal communication) as has successfully been shown for QCM techniques [132–134].

7.4. *Polymers*

Polymers can be patterned for localized immobilization of molecules [80]. SAW sensors modified with polymers are employed as food biosensors [135,136], detect small organic chemicals in fluids poisonous to the environment [137–139], or determine warfare agents [140,125]. Still, the properties of the polymers have to be investigated [42,141], and it has to be shown that polymers are reliable detectors if it comes to the specificity of molecular binding. Polymers mostly were applied to sensor arrays such that more advanced analytes like oils [142,143] or alcohols [21,144,145] were detected from interacting patterns and not from specific interactions of a polymer with its analyte. Additionally, polymer layers were applied to protect the sensor chip surface from aggressive media [146], since aqueous buffers still seem to create problems for many sensors [46]. However, SAW devices are particularly useful for characterizing physical properties of liquids and for chemical sensor applications [147,7].

8. Missed opportunities

8.1. General rating

Generally, the investigation of the current literature has shown that the number of publications is increasing, however this increase is slow and on a low level especially compared to other biosensor systems (Fig. 2), limited by the relatively small fraction of indeed dedicated scientists working in this field. But it is encouraging that the gaps between physicists, engineers producing these sensors and applicants working in biochemistry or medical science are closing, amplifying possibilities and results. Often, the interdisciplinarity in teams is missing and articles are technically relevant with a proof of principle of the biological application, if any. On the other hand it is especially important for the scientist to understand, *what* physical characteristic they actually measure. This approach exemplarily has been executed by McHale et al. [9,148] and for the QCM-D technique by the group of Bengt Kasemo, University of Gothenburg, Sweden. This requirement holds just as well for the optical methods. Not publishable are the advances being made in simplicity of handling, owing to often undisclosed details of the software and sensor machines. The increasing amount and scope of biological and medical data requires mathematical and computational analysis and interpretation tools without over-interpretation of the generated data. This precaution includes predicting tools and models.

8.2. Advances of the SAW technology

Advances of SAW sensors over alternative optical sensors have not yet been sufficiently displayed. Possible starting points are (1) SAW sensors are not limited to gold or noble metals as surface materials compared to surface plasmon resonance. However, alternative materials such as other metals, polymers, or SiO_2 were not yet used sufficiently in research. The sulfur–gold binding is supplied by the majority of binding technologies. (2) SAW sensors are useful for more than the detection of mass loading onto the surface. Viscoelastic effects based on structural properties and conformational changes in the internal structures of layers can be determined by using the amplitude of the wave or its dissipation factor (Fig. 4b). (3) Protein and nucleotide research dominates the applications of the sensor field. Measurements with SPR technology using larger or highly viscous objects are not often detected properly, e.g. with little correlation between signal and concentrations. Such examples include cells, multilayers or films of materials, lipids, and even long, highly viscous DNA strands were published rarely, or not at all in the case of SAW technology.

9. Outlook

Present publications were restrained to an extremely small fraction of the possible applications, although they are desperately needed in food pathogen detection, discovery of drugs and explosives [149,150], detection of medically relevant biomolecules and environmental analyses [151]. Those types of measurement can include all possible sizes of molecules. With the adjustment of the penetration depth, the focus can be set to exceptionally small objects at high frequencies and a small penetration depth, or to large objects at low frequencies. New surface technologies based on alternatives to sulfur–gold chemistry will enable the focus on measuring only the interaction of the designated binding partners without undesired side effects, e.g. of changes in the buffer composition.

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