CHAPTER 2

LITERATURE SURVEY

2.1 Introduction

The motive of this chapter is to render background information on the factors to be considered here and also it stresses to check if the there is any resemblance in the work carried out by other authors.

The gravimetric biosensors use thin piezoelectric Quartz Crystals Microbalance (QCM), either as resonating crystals, or as bulk SAW device. A system is described, in which acoustic waves are launched in very thin (25 microns) polymer films to produce an oscillatory resonant device. A theoretical equation for this system is almost equal to the Sauerbrey equation used in the QCM method. A system using a PVDF film was tested in protein detection. Results showed that the PVDF film can act has a microbalance. Currently, a new system using a PVDF Immobilon-PIPVDF film, to be used in protein detection is being tested. Results for the PVDF system and current work with the new system are presented.

The use of thin quartz crystal for the detection of small additions of bound mass to its surface has been reported over a period of more than 40years. Due to its piezoelectricity, the crystal can be made to oscillate using simple electric circuitry in a shear mode and at a natural frequency which is inversely proportional to the crystal thickness. The addition of mass bound to the surface will reduce this frequency. This illustrates a related technique where a film of a piezoelectric polymer and a membrane (Immobilon-P, from Millipore Co.) with a high protein binding capacity are used.

2.2 Literature Survey

Piezoelectric sensors have been developed based on very established theories in electricity, mass, and visco-elasticity and with commercially available instruments, such as QCM. Piezoelectric sensors have shown their advantages over other sensors in terms of sensitivity, versatility, label free, low cost and simplicity. They have been applied to the biomedical area mainly in the forms of immune-sensors and geno-sensors for rapid detection of bacteria, viruses and proteins and DNA/RNA hybridization, respectively.

Reindl *et al* [1] suggests how the SAW devices can be used for passive wireless sensors, where these types of radio sensors make it conceivable to peruse estimation at the remote areas by considering its values. The definitive advantage of this type of sensors is that their passive operations with no requirement for a different force supply, and falls in the likelihood of wireless establishment at especially inaccessible areas. It is also by fact that these sensors are free from maintenance and the waves that travel along the surface can be used to detect the presence on the chemical compound by change in the properties of the wave. This paper also helps in comparing various type of SAW sensors (reflective delay line, resonators and dispersive) and their equations for sensitivity calculation and also provides example for different applications.

The paper provides the application of the SAW sensor which are temperature sensor (to detect temperature), sensors van can be used to detect mechanical properties (pressure, acceleration) and physical and chemical properties (to detect different chemical). The dispersive based sensor has greater advantage as it has adjustable sensitivity.

Now having learnt the application of SAW sensor from the previous author the Pohl *et al* [2] define one such application where the SAW sensors are used to monitor the tire pressure in cars/ road vehicles and this monitoring is continuous as it is done at even period of driving. The authors provide a prototype of the application and also provide the enhanced version of the interrogation setup. This paper concludes that SAW sensors are best for vehicular application for tire pressure measurement and the sensors are maintenance free.

Buff *et al* [3] has developed a remote sensing device for detection of temperature and pressure using SAW sensor, here the two frequency outputs of the SAW resonators are for temperature and pressure measurement. These sensors have two resonators placed on a single substrate with different wave propagation directions, if there exist any variations in the velocity of the wave then desired parameters are detected. The prime aim is to reduce the noise that gets added up due to RF link between interrogation unit and sensor. The output signal is in the form of difference in frequency. Thus it is concluded that the disturbance in the RF link is removed and the accuracy is improved to 51.5 dB.

Pohl *et al* [4] has improved the work carried out by the author [2], where, in the previous work only the tire pressure was monitored here in the paper [4] the author monitors both tire pressure and also the thread wear and temperature. Thus, the author calls it an intelligent tire. The key factor is the contact amongst the tire and surface of the road, while portraying the acceleration, deceleration and to steer the vehicle. Therefore, the contact becomes imperative for modern vehicle control system. It is also seen that the friction co-efficient can be measured by assessing tire's mechanical strain using the contact.

Greve *et al* [5] describes the use of SAW devices in harsh environment, where the author has used langasite as the material to detect the temperature and gas concentration. It provides the information on oxygen gas sensor implementation. The experimental results are also provided for the langasite SAW oxygen sensor. The sensing layers for these sensors are made of tin oxide. It also provides the information on the resistivity of ZnO and tin oxide, also the designing and fabrication of the sensor is mentioned.

Zakaria *et al* [6] defines the designing and fabrication of the transducer in SAW sensor using the conventional lithography technique. Here the author investigates the importance and the conduct of the fingers in the IDT that can be used for biosensor application, here the conventional lithography technique is used, and also it provides the combination of substrate and IDT material to be used. It is suggested that in order to get good result concerning frequency response and electrical characterization a blend of ZnO piezoelectric substrate and aluminium IDT must be considered. It also suggests that increasing the number of IDTs in a sensor will provide a better sensitivity with increase in the center frequency up to 2.40 MHz. This has helped by providing explanation of theoretical background, where different relations were obtained and also the paper defined IDT fingers (N), width of fingers and spacing between IDT, aperture length (W) and wavelength (λ).

The device was also fabricated, in order to fabricate the complete device, the mask must be designed. The mask is designed by using AutoCAD software. The sensing area is in the shape of a rectangle where the size was 4800 μm x 3000 μm. This concludes that higher the center frequency better will be the sensitivity of the biosensor device. The two models were prepared one with 10-finger IDT and other with 16-finger IDT. The center frequencies were 1.92MHz and 2.40MHz respectively so the IDT design with 16-finger IDT has a higher sensitivity.

Kirschner *et al* [7] provides a general idea of the SAW sensors where the author describes the concepts that are important while designing and fabricating the SAW sensors. The author gives a clear idea how one must start with the designing in the series of step where the author first explains the basic theory of operation of such sensors. It is seen that first the RF source is applied to the input IDT and the input signal is converted into mechanical wave due to compression and tension. The IDT has two terminals in which one acts as input terminal and other acts to be grounded, due to this terminal configuration a sinusoidal wave is created and the waves propagate along the surface of the substrate. Then the wave reaches the sensing area which is coated with certain antibody, when the antibody detects the desired antigen and stick to the antibody the propagating will undergo change in velocity, phase, amplitude and frequency. The wave reached the output IDT and the waves are converted to electrical parameter. Therefore, the changes in the wave properties are measured in order to detect the presence of certain antigen. The author explains how the piezoelectric materials are selected and the Rayleigh wave velocity concept, as both this factors are interconnected with one another, here the authors also explain how the material are selected for IDT and the effect of using the same materials.

The fabrication processes are also mentioned which have been useful in fabrication of the device. The processes are lift-off and etching process respectively. Finally explains few applications of the SAW sensors for the detection of various properties like physical and chemical. The main restriction to the utilizations of a device with SAW is in scope to materials that experience an adjustment in measurement or mass within the sight of a phenomenon.

Thus the author [7] concludes that the information of the important configuration parameters and material affect the assembling and sensor operation, a SAW sensor are intended to satisfy for detecting numerous applications. As interest for detecting advances (and specifically, dispersed, remote detecting systems) builds, it also hopes to view the utilization and scope of uses of sensors using SAW to increment.

Wang *et al* [8] articles about the SAW based gyroscope using $LiTaO_3$ substrate. The SAW gyroscopic impact can be explored by assigning a successful permittivity technique with the administration of little proportions to the speed of rotation and SAW frequency. The hypothetical examination shows that a larger shift in velocity was seen from the pivoted substrate of X-112°Y $LiTaO_3$. In that point, two reverse course SAW delay lines and 160 MHz operation frequency are manufactured on an equivalent chip of X-112°Y $LiTaO_3$ as an input of two SAW oscillators, that go about as sensor component.

The Single Phase Uni-Directional Transducer (SPUDT) and brushed transducers are utilized for delay line structure to enhance frequency steadiness of oscillator. Subsequently, the assessment of the sensor execution, in the interim, the differential structure was executed to two fold the sensitivity and make up for temperature impacts. Utilizing an exact rate table, the execution of the manufactured SAW gyroscope was assessed tentatively. A great linearity was observed. Thus, the author concludes that the figured results show that among normal substrates of piezoelectric, a bigger sensor reaction was seen from the rotated X-112°Y $LiTaO_3$ and the linearity was acquired.

Filipiak *et al* [9] provides a study on SAW vibration sensors, these type of sensors are used in electronic warning system, where the setup is collected from linked structure of SAW vibration in view of a delay line SAW fabricated over piezoelectric plate surface. The plate vibrations are changed to electric signals that permit sensor identification and limitation of risk. The hypothetical investigation on vibrations of sensor drives straightforwardly isotropic model with one level of opportunity. This model permitted an express depiction of the plate of sensor development and recognizable proof of the sensor vibration. Examination of frequency reaction of the sensor plate made of ST-cut quartz and a damping rate of its motivation reaction has been directed. The examination above the premise to decide the scopes of vibrating plates parameters that are valuable in electronic warning system.

Frequencies of stage changes are equivalent to reverberation frequencies of sensors vibrating plates. The adequacy of these stage changes is corresponding to the sufficiency of a sensor plate vibration. Both bits of data might be consigned and recorded together by a straightforward electrical unit.

Gaso *et al* [10] reviews about the biosensor for the detection of the pathogens using surface generated acoustic wave technique. This survey displays a profound understanding into Surface Generated Acoustic Wave (SGAW) innovation for the applications of bio-sensing, taking into account over 40 years of innovative and exploratory advancements. In the most recent twenty years, SGAWs have been pulling in the consideration of the biochemical academic group, because of the way that a few of such devices - Shear Horizontal Surface Acoustic Wave (SH-SAW), Surface Transverse Wave (STW), Love Wave (LW), Flexural Plate Wave (FPW), Shear Horizontal Acoustic Plate Mode (SH-APM) and Layered Guided Acoustic Plate Mode (LG-APM) - have shown a larger sensitivity in the recognition of bio-relevant particles in fluid media.

The expansion corresponding endeavors to enhance the sensing of the films that have been done amid these a long time. Every one of these advancements have been made with the point of accomplishing, in future, a profoundly delicate, minimal effort, little size, multi-channel, convenient, solid and financially built up SGAW biosensor. A setup with such components could altogether add to future advancements in the wellbeing, sustenance and ecological commercial enterprises. The second reason of this work by author is to portray the best in class pathogens locations using SGAW biosensors, this point is an issue of great degree of significance for the human wellbeing.

The authors also provide information on the designing the IDT and also provides the better insight in understanding few terms like pitch, synchronous frequency and periodicity. It also signifies different electronic configurations of the SGAW sensors like the delay line, dual channel delay line and resonators. After understanding the electronic configurations, the paper also specifies the SGAW measurement techniques like vector voltmeter, oscillator and network analyzers. There is a need for proper material to be selected, substrate cut and orientation for the biosensor applications. So here different types of waves are also mentioned they are SH-SAW, STW, LW and SH-APM.

This work concludes by telling albeit conventional techniques for the location furthermore, recognizable proof of contaminants (made up of microbial) can be extremely sensitive, cheap and ready to give both subjective and quantitative data, they often don’t require many days to yield dependable results. Biosensors complete a genuine contrasting option to conventional strategies, since they can offer mark free, on-line examination of antigen-antibody interaction and give the choice of a few immunoassay groups that permit expanded affectability and specificity. Water, SGAW biosensors permit fast, ongoing, and various examinations, with the extra points of interest of their cost viability and usability.

Voiculesca and Nordinb [11] have presented are view of acoustic-wave based MEMS devices that offer a promising technology platform for the development of sensitive, portable real time biosensors. MEMS fabrication of acoustic wave based biosensor enables device miniaturization, power consumption reduction and integration with electronic circuits. For biological applications, the biosensors are integrated in a microfluidic system and the sensing are a is coated with a bio-specific layer. When a bio-analyte interacts with the sensing layer, mass and viscosity variations of the bio-specific layer can be detected by monitoring changes in the acoustic wave properties such as velocity, attenuation, resonant frequency and delay time. Few types of acoustic wave devices could be integrated in microfluidic systems without significant degradation of the quality factor.

Satapathy *et al* [12] review the SAW sensor for biosensor application using MEMS technology. This technology has been promising for the advancement of delicate, compact, constant biosensors. MEMS manufactures biosensors that uses acoustic wave empowered device scaling down power consumption, diminishment and assimilation of electronic circuits. For application organics, the biosensors are coordinated in a micro-fluidic system.

The sensing part is covered with bio-specific layer. At the point when a bio-analyte associates along a sensing part, mass and viscosity varieties of the bio-specific layer can be recognized by checking variation in the properties of acoustic waves, for example, speed, attenuation and delay time. Few sorts of devices made of acoustic wave may be incorporated in micro-fluidic system without huge debasement of the quality component. The MEMS device made of acoustic wave are disclosed in writing as biosensors and exhibited as film in this review are mass Film Bulk Acoustic Wave Resonators (FBAR), SAW resonators and SAW delay lines. Diverse ways to deal with the acknowledgment of FBARs, SAW resonators and SAW delay lines for different biochemical applications are exhibited. Techniques for mix of the acoustic wave MEMS device in the micro-fluidic and functionalization systems will be likewise talked about.

Lec [13] has proposed about the piezoelectric biosensor technology and applications and also the challenges facing by acoustic biosensor developers in the coming decade. Modern biosensors developed with advanced micro-fabrication and signal processing techniques are becoming inexpensive, accurate and reliable. Increasing miniaturization of biosensor leads to realization of complex analytical systems such as BioChem Lab-on-a-Chip. This rapid progress in miniature devices and instrumentation development will significantly impact the practice of medical care as well as future advances in the chemical, pharmaceutical and environmental industries.

About $20 billion US per year are spent for analytical testing worldwide. Specialized laboratories located away from a patient, doctor or hospital performs nearly all of the testing causing significant time delays in reporting results. Modern piezoelectric biosensors developed with advanced micro-fabrication and signal processing techniques are becoming inexpensive, accurate, reliable and with an average detection time in order of few minutes, can significantly reduce the delay time as well as bring the testing to doctor’s offices and patient’s homes. As a result, the wide use of biosensors may lead to more individualized health care services that will be tailored for the needs of a patient and will match a specific genotype. Indeed, one may envision using biosensors for optimizing drug doses, monitoring the effectiveness of treatments and monitoring health conditions over person’s life time. In addition to decreased time delays, miniaturization of biosensors and integration with micro-fluidic devices is yielding advanced analytical micro-systems such as a BioChem Lab-on-a-Chip. Integration of several sensors on a single substrate produces transducer arrays that successfully mimic sensing properties of natural organs.

Inacio *et al* [14] proposed a new system using a PVDF Immobilon-PIPVDF film, used in protein detection. Most gravimetric biosensors use thin piezoelectric QCM either as resonating crystals, or as bulk SAW devices. A system is described in which acoustic waves are launched in very thin (25 microns) polymer films to produce an oscillatory resonant device. A theoretical equation for this system is almost equal to the Sauerbrey equation used in the QCM method. A system using a PVDF film was tested in protein detection. Results showed that the PVDF film can act has a microbalance.

It has been shown that the PVDF system can act as a microbalance, but is not suitable for protein detection. It is also showed that the PVDF/Immobilon/PVDF system oscillates when immersed in a liquid solution. Therefore, this system can be suitable for protein detection (such as antibodies and antigens). Further work with this system will be:

1) Testing the system with protein solutions.
2) Verify the adsorption of proteins with a staining protocol.
3) Establish the incubation time needed for the adsorption of proteins.
4) Improve the process of pressing the PVDF to the Immobilon, to minimize the discontinuities.
5) Improve the oscillating circuit in order to minimize frequency instabilities.

Hou *et al* [15] proposed a novel piezoelectric microbalance biosensor based on nano-crystalline PZT/quarts. Sol-gel method is utilized to bond the PZT thin films on the quartz substrate as the sensing unit. The microstructure and the surface appearance of PZT thin films on quartz substrate and the influence of cancer cells detecting with the sensing unit using PZT/quartz were studied. The XRn and AFM results show that the PZT films feature (101) preferred orientation, perovskite crystal structure, smooth surface and the crystal particle size is 20-30nm. The sensitivity of biosensor based on nano-crystalline PZT/quartz structure is improved.

Kim and Yoon [16] proposed a new design of a piezoelectric sensor that is miniaturized to monitor thermal problems in wide band gap power modules, which anticipated having the operation temperatures significantly higher than silicon power modules. Recent power modules, especially those employing wide band gap power devices, suffer significantly elevated temperatures. The thermal sensor proposed herein is made of miniature piezoelectric pieces (which are solder-bonded on a direct bonded copper substrate) that convert thermal stress of the substrate to electrical voltage. Compared to previous designs, this design exhibits notably smaller size (more than 70 percent size reduction) and excellent linearity (R^2 is about 0.96 close to 1.0) up to 220 degrees Celsius, which is expected to be sufficient to monitor the maximum temperature observed in wide band-gap power modules.

This achievement was enabled by (1) introducing a new piezoelectric material having a high Curie temperature, (2) improving sensor components and fabrication process, and (3) optimizing sensor locations. Power modules are one of the essential components in power electronics. This energy-conversion system is popularly used in various applications, including electrified vehicles, renewable energy power plants, smart grids and industrial applications. The power modules often exhibit a high temperature operation. The heat generated from power modules enforces critical challenges in their performance and reliability such as performance degradations, long-term fatigues and permanent damages. These problems occur because power semiconductors under operation begin to heat up, due to power loss, generating thermal stress.

Gao *et al* [17] proposed about the development of a newly designed wireless piezoelectric (PZT) sensor platform for distributed active structure health monitoring (such as aircraft wings and bridges). The developed wireless PZT-sensor network features real-time data acquisition with high sampling rate up to 12.5MSPS (sample per second), distributed lamb-wave data processing and energy saving by reducing the amount of data in wireless transmission. In the proposed wireless PZT network, a set of PZT transducers deployed at the surface of the structure and a lamb wave is excited and its propagation characteristics within the structure are inspected to identify possible damages.

The developed wireless node platform benefits from a Digital Signal Processor (DSP) of TMS320F28335 and an improved IEEE 802.15.4 wireless data transducer RF233 with up to 2Mbps data rate. Each node supports up to 8 PZT transducers, one of which may work as the actuator generating the Lamb wave at an arbitrary frequency, while the responding vibrations at other PZT sensors are sensed simultaneously. In addition to hardware, embedded signal processing and distributed data processing algorithm are designed as the intelligent 'brain' of the proposed wireless monitoring network to extract features of the PZT signals, so that the data transmitted over the wireless link can be reduced significantly.

Rajesh *et al* [18] has developed an amperometric biosensor that has been used for the quantitative determination of urea in aqueous solution. The principle is based on the use of pH-sensitive redox active dissolved hematein molecule. The enzyme, urease (Urs), is covalently immobilized on a conducting copolymer poly (N-3-aminopropyl pyrrole-co-pyrrole) film, electrochemically prepared onto an indium-tin-oxide (ITO)-coated glass plate. The covalent linkage of enzyme and porous morphology of the polymer film lead to high enzyme loading and an increased lifetime stability of the enzyme electrode. Amperometric response is measured as a function of concentration of urea, at fixed bias voltage of 0.0V vs. Ag/AgC in a phosphate buffer (pH 7.0). The electrode gives a linear response range of 0.16–5.02mM for urea in aqueous medium. The response time is 40 s reaching to a 95% steady-state current value, and 80% of the enzyme activity is retained for about 2 months.

Rasheed *et al* [19] said that an autonomous wearable biomedical sensor enables continuous human body vital signs monitoring with features such as being conformable, mobile, cost-effective and self-powered. The work on an autonomous and multi-positional sensor capable of heart rate and blood pressure monitoring. The device concept is based on a Piezoelectric-Charge-Gated Thin-Film Transistor (PCGTFT) where a PVDF piezoelectric sandwich structure is incorporated with an amorphous silicon (a-Si:H) Dual-Gate TFT (DGTFT). An analytical model and preliminary experimental results is presented along with a demonstration of a proof-of-concept sensing system for continuous multi-point heart rate monitoring.

Feng *et al* [20] presented an innovative piezoelectric thin-film based flow shear stress sensor fabricated by micromachining and stereo-lithography. The sensor has three novelties: (1) Use hydrothermal method to simultaneously grow lead zirconate titanate films on both sides of micro-machined titanium cantilever beams. This results in an approximately zero stress gradient in the thickness direction of the sensing beam due to residue stress balance. (2) Directly fabricate 3-dimensional high aspect ratio structure array on the micro-machined planar structure by stereo-lithography. This allows the measurands effectively to couple with the sensing beams. (3) Using the unique 3D photopolymer structure array for sensing coupling, the detected flow direction and the shear stress caused by measured flow are identified and evaluated.

Johnston [21] has showed that biosensors are measuring devices which incorporate a biological sensing element in conjugation with a transducer, yielding a signal useful for measurement and control. Biosensors show great potential as low-cost, easy-to-use, highly selective sensors for applications in medical diagnostics and process control. For solid-state sensors based on electrochemical detection, improvements in stability, fabrication techniques and sensitivity are required before commercial success are achieved.

Zakaria *et al* [22] proposed about developing the SAW device. Piezoelectric substrate is one of important factor that improve performance of a device. The materials used such as Indium Tin Oxide (ITO) or Lithium Tantalate ($LiTaO_3$) extremely affect the cost as well as the preparation methods. To overcome this problem, the material known as Zinc Oxide(ZnO) has been chosen as the thin film layer of piezoelectric in developing the biosensor. These ZnO thin film acts as piezoelectric layer that made contact with the sensing element before the signal convert from a biological signal to an electrical signal by the transducer. Sol-gel deposition technique was used and zinc acetate as precursor compound and 2-methoxyethanol as solvent to form the sol-gel.

The sol-gel is then spin coated on the SiO_2/Si substrate which will later to be anneal with oxygen to make the thin film denser, thinner and has smoother surface quality and higher resistivity. The surface morphology, electrical and optical characterization of the thin films will be studied using Scanning Electron Microscopy

(SEM) and Atomic Force Microscopy (AFM), four-point probe and UV-visible spectrophotometer. From the research, the ZnO sol-gel solution was prepared by using 2-methoxyethanol as a solvent. The prepared sol-gel was successfully coated on the silicon substrate to produce as a piezoelectric substrate. On the physical surface after undergoing AFM and SEM found that, the sample with many ZnO layers indicates that provide higher surface roughness as compared to 1 layer 2-methoxyethanol. The grain size of the thin film at a number of 5 layers was increased. Same phenomena were identified on the surface structure where the surface becomes denser due to the fact that the disappearing gap between particles resulting in the increase in size of the particle as the post annealing temperature increases.

Chen *et al* [23] presented a label-free biosensor based on a FBAR to detect one of the cancer markers of Alpha-Feto Protein (AFP). The FBAR consisted of a ZnO piezoelectric stack and works near 2.1 GHz. The monoclonal anti-AFP antibody was coated on the surface of the piezoelectric stack as the special bio-probe. Experimental results demonstrate that the FBAR based biosensor can detect AFP antigen successfully without chemical or fluorescent labeling. The minimum detectable AFP concentration of the proposed biosensor is 1 ng/ml with high selectivity. The advantages of this sensor, including the sample fabrication process, ease of detection method, low cost, high sensitive and high-throughput, mean that it has much promise in cancer diagnosis.

He has fabricated a label-free FBAR based biosensor and applied it for the detection of a cancer marker. The monoclonal anti-AFP antibody was coated on the surface of the piezoelectric stack as the special bio-probe. An obvious shift of resonant frequency was observed as the AFP antigen was attached on the device. On the basis of these results, it is expected that the FBAR based biosensor could be further developed as a handheld sensor for the detection of cancer markers.

Xu *et al* [24] investigated the effect of protein adsorption induced surface stress on the resonant frequency of ultra-thin PZT membrane (~600 nm thick) based biosensors. The resonant frequencies of the mass sensitive micro-fabricated PZT biosensors should ideally decrease after external proteins are loaded; however, they are found to increase in this work. This abnormal phenomenon is studied by micro-

Raman spectrum. The result shows that the resonant frequency change and the measured stress variation have the similar trend. This indicates that the abnormal phenomenon is attributed to the induced adsorption surface stress during the bio-immobilization process.

In the work, the adsorption induced stress on ultra-thin PZT membrane based biosensors is experimentally investigated by micro-Raman spectrum for the first time. The micro piezoelectric biosensors were fabricated by combining of sol-gel PZT thin film deposition and MEMS technology. Ideally, the resonant frequencies of the mass sensitive PZT biosensors should have frequency depression after loading the external biomaterials, however, they are found to increase in this work. To investigate this abnormal phenomenon, two similar devices were fabricated and immobilized with the same biomaterials for the micro-Raman scanning. The spectrum shift indicates the compressive stress existed inside the thin membrane. The similar trend obtained from both the resonant frequency change and the calculated stress proves that this abnormal phenomenon is attributed to the stress induced by the immobilized biomaterials.

Wang *et al* [25] proposed a mass sensitive biosensor utilizing a flexural vibration mode of a micro-machined piezoelectric micro diaphragm. The mass sensitivity of the diaphragm has been investigated with respect to the vibration modes. Theoretical analysis reveals that, for the same multilayer structure, the mass sensitivity is mainly determined by the mass per unit area of the diaphragm, the flexural mode sensor can work at a lower operating frequency than thickness mode without losing its mass sensitivity-about 30 times higher than that of a QCM. A biosensor with Q value of more than 200 has been demonstrated at a resonant frequency of as low as 120 kHz. Frequency shift in response to captured goat IgG on sensor surface has been detected. These results indicate that the flexural mode micro-machined diaphragm has a potential to be an alternative to the low-cost QCM biosensors.

The micro machined piezoelectric diaphragm has been investigated as a high performance mass sensitive biosensor platform. It is theoretically found that, for the same diaphragm structure, the mass sensitivity of the flexural resonant mode is half of that of the thickness resonant mode. However, the flexural mode sensor can work at much lower operating frequency than thickness mode without losing its mass sensitivity. The low operating frequency of the flexural mode permits the use of low cost electronics thus providing an alternative to the low-cost QCM resonators. The flexural mode biosensor with Q value of more than 200 at operating frequency of 120 kHz has been fabricated and demonstrated. A frequency shift in response to a captured goat IgG has been observed, indicating that the flexural mode of micro machined piezoelectric diaphragm has a potential to be used as a biosensor.

Huang *et al* [26] proposed the design, fabrication and characterization of a novel Flexural Plate Wave (FPW) micro-sensor for Immunoglobulin-E (IgE) detecting applications. The propagation membrane is constructed with SiOJSi3N4/ZnO multi-layers and are released from the silicon substrate as a floating thin-plate by using bulk micromachining technology. The ultrasonic flexural plate waves are launched and received by a pair of Cr/Au IDTs on the surface of the ZnO piezoelectric thin film. It demonstrated a high C-axis orientation ZnO piezoelectric thin film deposition, an IgE Self-Assembly Monolayer (SAM) immobilization and a FPW allergy micro-sensor with 21 MHz center frequency and 233 cm^3/g mass sensitivity. This is the first report demonstrating human IgE detection by an FPW-based micro-sensor.

Jaruwongrungsee *et al* [27] proposed that an array of QCM sensors is fabricated on a single quartz crystal substrate and attached with Poly Dimethyl Siloxane (PDMS) micro chamber for using in flow-injection system. The Cr/Au electrode array is deposited on both side of quartz substrate by sputtering through electroplated micro-shadow mask. PDMS micro chamber was fabricated by mold casting technique with SU-8 mold. Fabricated PDMS micro chamber and QCM sensor array were attached together for using in flow-injection system. Also the QCM electrodes were coated with the carboxylic Poly Vinyl Chloride (PVC-COOH) and then the carboxylic group was activated with (1-Ethyl-3-(3-Dimethylaminopropyl) Carbodiimide hydrochloride) (EDC) and *N*-hydroxylsuccinimide (NHS) for protein binding. The scanning electron micrograph showed the trapped protein on the modified sensing layer, it confirmed that our QCM sensor and PolyDi-MethylSiloxane (PDMS)micro chamber can be used as QCM biosensor array. This new QCM sensor array provide possibility of multiple detection in small amount of sample within a single quartz crystal substrate that avoid the error signal from the different properties of each sensor in an array.

The result has successfully fabricated the QCM biosensor array and confirmed by protein immobilization on the sensor's electrodes. The biosensor array provides possibility of multiple detection in small amount of sample within a single quartz crystal substrate that avoids the error signal from different properties of each sensor in an array. However, each sensor in an array should be coated in the same conditions.

Hartono *et al* [28] proposed that fabrication of PVDF films has been made using Deep Coating Machine (DCM). Preparation of samples carried out for three different solvent concentrations, five of different temperature and three different heating times. This condition is carried out to see the effect on piezoelectric properties of PVDF films. The piezoelectric properties like β fraction are discussion focus here. Piezoelectric properties of PVDF can be improved by solvent concentrations, various temperature and heating time. To obtain the diffraction pattern of sample characterization is performed using X-Ray Diffraction. The fraction of PVDF films calculated from broadening pattern of X-Ray Diffraction has been obtained to increase piezoelectric properties of PVDF films that is characterized by increasing β fraction. He has also obtained β fraction increased by 31 %, 39 % and 44.5% for solvent concentrations of 10%, 15% and 20%, respectively. For the heating temperature from 70^{0C} up to 1100C have obtained, β-fractions of 37%, 38%, 44%, 50% and 58%. Furthermore, for the heating times 10 minute, 20 minute and 30 minute the β-fractions are 34%, 48% and 60%. These results indicate that PVDF film results using deep coating method is good. These indications are shown from the β fraction obtained. From the results of sample characterization, it is known that a good percentage of solvent was 20%, heating temperature 1100C and long heating time is 30 minutes.

The experiments and calculations done, beta fractions obtained are the fraction of beta optimum solvent concentration obtained for 20% of 44.5%, for heating temperature 1100C in the amount of 58% and for the variation of warming time is 30 minutes with a beta value of the fraction of 60%. This shows that the greater the concentration of the solvent, the greater the fraction of beta and the greater the heating temperature, the greater the beta fraction obtained. Obviously the result made PVDF films exhibit good piezoelectric properties.

Kurosawa *et al* [29] proposed that piezoelectric quartz crystals have found wide applications as chemical and biosensors. The QCM is a well-known technique for mass sensing using the mass-loading transduction property for frequency shift. The behavior of the vibration displacement of the electrode surface on the QCM for various applied voltages is an important problem for understanding the physical property of the QCM, but it is very difficult to detect the displacement. The effects of resonant frequency of QCM caused by the variation of the applied voltage are studied by using the Finite Element Method (FEM) software.

The FEM that has been able to solve for the displacements of an AT-cut QCM. Full three-dimensional matrices were used. The effects of finite sized electrodes were included. In the lowest frequency fundamental mode, the displacement profile was found to be nearly circular for a circular electrode and bounded by the electrode edge. A slight ellipticity was observed, similar to the ellipticity found by Hillier and Ward. The displacement amplitudes were found to scale linearly with the applied voltage and to scale inversely with the damping coefficient.

Kao *et al* [30] proposed an 8-pixel quartz crystal resonator array with a fundamental resonance frequency of 73 MHz, he also designed and fabricated. Also established a protocol for selectively functionalizing the surface of resonator array via electrochemical desorption. The creation of hydrophobic and hydrophilic surface with methyl terminated and carboxylate terminated alkanethiols is characterized by Fourier Transform Spectroscopy (FTSR) and contact angle measurements. QCMs functionalized with hydrophobic and hydrophilic terminations show a clearly distinguishable response to ionic (buffer) solution.

The development of simple, reliable and cheap bio-analytical techniques is highly desirable and have been the focus of considerable research in the recent years. Bio-sensing applications can be broadly classified into two major categories, namely, molecular fingerprinting (identification) and quantitative bioassays. In the former case, the focus is on the identification of specific target molecule or molecular fragment and is effective for disease detection, and DNA sequencing and gene expression microarray chips when samples of adequate analyte concentration are available. The main objective is chemical identification of the presence of the analyte rather than a quantitative analysis and is based upon techniques such as fluorescent labeling, sandwich assays, and enzyme linked immunosorbent assays and so on.

Yan [31] in his paper proposed that the piezoelectric immuno-sensor is a particular type of biosensor that utilizes the high mass sensibility of piezoelectric quartz crystal in conjunction with the high specificity of antigen-antibody immune reaction. It forms a kind of automated analysis and detection sensors and can make real-time detection for the antigen-antibody reactions on the surface of crystal blank. It is promoting immune diagnosis method to develop toward quantification. The piezoelectric immuno-sensor, which is especially suitable for the clinic laboratory diagnosis is becoming one of the novel and attractive hot researches in the field of biomedical. The fundamental principle and basic structure of piezoelectric immune sensor were briefly introduced, and the characteristics of existing piezoelectric immuno-sensor were discussed. The key technology of piezoelectric immune system was presented in detail. In addition, the existing problems in its application were summarized and the prediction on its future development direction was also made.

Piezoelectric immuno-sensor has been widely used in various areas such as clinical diagnosis, environmental monitoring, food supervisions and pharmaceutical analysis due to its diverse advantages. Meanwhile, it is also suffering from disadvantages such as the stability and the repeatability become badly in solution phase. Therefore, there is still no one ideal method that gives high immobilization yield and good stability for a certain biological material. The future directions of development of piezoelectric immuno-sensors are mainly focused on the aspects as follows: the study of immobilization method for a certain biological material, the oscillation characteristic in solution phase, the study of micro-material detection and so on.

Mehdizadeh [32] proposed the direct detection of bio-molecular adsorption events in liquid media using piezoelectric rotational mode disk resonators. Piezoelecrically transduced rotational mode silicon disk resonators with resonant frequencies in the 2.0-8.0MHz range capable of operating in liquid are utilized as direct real-time mass balances. The resonant frequency of the resonators was recorded in real-time while forming monolayers of 6-Mercapto-1-Hexanol (MCH) in aqueous solution. During one hour of exposure to the MCH solution, gradual frequency shifts up to ~3600ppm was recorded which shows the capability of such resonators as highly sensitive bio-molecular sensors. Detection of target DNA sequences has also been demonstrated using the same devices.

The highly sensitive biosensors capable of detecting and measuring smallest quantities of bio-chemicals in biological samples are needed in various biotechnology and biomedical applications. Most of the commercially available bio-sensing and bio-analysis platforms, such as the biomedical diagnostics micro-arrays are based on optical methods requiring costly and sophisticated readout instrumentation with a very complex and time consuming procedure including fluorescent labeling, incubation and hybridization steps. Furthermore, such techniques only show the end results and do not provide any real-time information, e.g. about the reaction rates and effect of different parameters on it. Therefore, label free bio-molecular sensors with fully electronic readout capable of real time monitoring of molecular absorption can be highly beneficial in state of the art biomedical science and engineering.

Handel [33] proposed that the piezoelectric sensors used for the detection of chemical agents and as electronic nose instruments are based on bulk and SAW resonators. Adsorption of gas molecules on the surface of the polymer coating is detected by a reduction of the resonance frequency of the quartz disk, subject also to fundamental quantum 1/f frequency fluctuations. The quantum 1/f limit of detection is given by the quantum 1/f formula for quartz resonators. Therefore, for quantum 1/f optimization and for calculation and improvement of the fundamental sensitivity limits, one must avoid closeness of the crystal size to the phonon coherence length, which corresponds to the maximum error and minimal sensitivity situation. Adsorbed masses below the pg range can be detected. MEMS resonators have provided a possibility for the nano-miniaturization of these sensors. Essential for integrated nanotechnology, these resonant silicon bars (fingers) are excited magnetically or electrically through external applied forces, since they are not piezoelectric or magnetostrictive. The application of the quantum 1/f theory to these systems is published here for the first time. It provides simple formulas that yield much lower quantum 1/f frequency fluctuations for magnetic excitation, in comparison with electrostatically driven MEMS resonators.

The author also demonstrated an efficient method for immobilization of functional antibodies to tile gold-coated piezoelectric quartz crystal. The results confined the stable, uniform oriented immobilization of antibodies on gold-coated piezoelectric quartz crystal employing protein A, 3APTES and glutaraldehyde. The immobilization procedure would be used reliably for the diagnosis of harmful disease biomarkers micro gravimetrically employing piezoelectric quartz crystal.

Sakong [34] proposed a SAW sensor system for detection of the immobilization and hybridization of DNA (deoxyribonucleic acid) molecules. The experiments of DNA immobilization and hybridization were performed with 15-mer oligonucleotides (probe and complementary target DNA). The sensor consists of twin SAW delay line oscillators (sensing channel and reference channel) fabricated on 36˚ rotated Y-cut X-propagation $LiTaO_3$ piezoelectric single crystals. Center frequency of the SAW oscillators is 200 MHz. The relative change in the frequency of the two oscillators was monitored to detect the immobilization of a probe DNA with thiol group on an Au coated delay line of the SAW device and the hybridization between a target DNA and the immobilized probe DNA in pH 7.4 PBS (phosphate buffered saline) solution. The target solution was continuously flowing over the probe DNA layer via micro-fluidic channels made of polyimide tubes. The exact amount of the flow was controlled by digital pumps operated by LabView software. The sensitivity was as high as 136 pg/ml/Hz. It has been normally considered that a SAW sensor is inferior in sensitivity to optical systems in detecting DNA molecules. However, in addition to the inherent advantage of being label-free, the SAW DNA sensor was confirmed by the results to have promising practical applicability in terms of the sensitivity.

The author has developed an SH-SAW sensor to detect 15-mer oligonucleotide DNA by means of the complementary DNA hybridization mechanism. The sensor showed a good response to the change of the target DNA (5'-GAT GAT GAG AAG AAC-3') concentration in terms of its oscillation frequency change. The present work achieved sensitivity up to 135 pg/ml/Hz. It has been considered that a SAW sensor is inferior in sensitivity to optical systems. However, the results in this confirm the promising practical applicability of the SAW sensor. The developed SH-SAW sensor can be extended to the detection of various target DNA's with their complementary probe DNA immobilized on the SAW delay line.

Roh [35] proposed SAW sensors to detect human-immuno-globulin G molecule applying a particular antibody thin film on the delay line of transverse SAW devices. The mass loading effect was given by the antibody antigen bonding of the target molecules on the delay line. The sensor consists of twin SAW delay lines operating at 100 MHz fabricated on 36 degrees rotated Y-cut X-propagation LiTaO3 piezoelectric single crystals. The sensor structure was optimized to achieve the highest signal to noise ratio with the least energy leakage to the protein solution. In addition, the input IDT of the sensor was configured as a Single-Phase-Unidirectional Transducer (SPUDT) for more stable operation. The sensitive channel of the SAW sensor was coated with a gold film on which an antibody layer was immobilized. The antibody investigated was Human-immuno-globulin G (HigG) and protein-A molecules were coupled with the HigG molecules to work as an immobilizer layer to hold the antigens (anti-HigG).

The proper immobilization of the detection molecules, bovine serum albumine worked as a blocking layer to prevent the adhesion of any other molecules different from the anti-HigG to the SAW delay line. The relative change in the frequency of the two oscillators was monitored to measure the anti-HigG concentration in the protein solution. The sensor showed linear response to the mass loading effects of the anti-HigG molecules with the sensitivity up to 10.7 ng/ml/Hz. He developed SH-SAW sensor to detect anti-HigG molecules by means of the antibody-antigen binding mechanism. The sensor showed linear relationship between the oscillation frequency and the anti-HigG concentration in a protein solution. The present work achieved the sensitivity of 10.7 ng/ml/Hz. Future work will be endeavored to apply the SAW sensors of a higher operation frequency to achieve higher sensitivity. The results are quite promising and the developed SH-SAW sensor can be applied to the detection of various protein molecules with different antibody immobilization layers while maintaining all the beauties of general SAW sensors.

Augustine *et al* [36] said that SAW devices have been utilized for the sensing of chemical and biological phenomena in micro scale for the past few decades. In their study, SAW device was fabricated by electro spinning poly(vinylidenefluoride-co-trifluoroethylene) (P(VDF-TrFE)) incorporated with zinc oxide (ZnO) nanoparticles over the delay line area of the SAW device. The morphology, composition, and crystallinity of P(VDF-TrFE)/ZnO nano-composites were investigated. After measurement of SAW frequency response, it is found that the insertion loss of the SAW devices incorporated with ZnO nanoparticles is much less than that of the neat polymer-deposited device. The fabricated device is expected to be used in acoustic biosensors to detect and quantify the cell proliferation in cell culture systems.

Gil [37] proposed a detailed Several resonators have been optically and electrically characterized. High quality factors have been obtained for the in-plane anti-phase modes, what makes these devices good candidates for applications in viscous media. New resonators and circuits will be studied with the intention of achieving better quality factors. Work is in progress to analyze the device performance in liquid media, as well as the mass sensitivity of the different modes.

MEMS resonators have stimulated an increasing interest within the last years and many applications of this technology in fields such as telecommunications, inertial sensors, as well as biosensors have been demonstrated. The achievement of a high quality factor (Q factor) for these devices is a key issue to maximize their performance. Therefore, there is a continuous search for the structure and the corresponding mode of vibration that enhances the Q factor.

The wide range of possibilities, the combination of tuning fork-shaped structures and the first anti-phase in-plane mode of such structure as already demonstrated its potential in the macroscopic scale for the fabrication of oscillators. So, here, the attention is payed to piezoelectric-actuated tuning forks, but in the micro-scale. The obtained results are very promising, achieving a Q factor in air as high as 4344 for the first anti-phase in-plane mode.

2.3 Summary

This chapter summarizes the major contributions of the significant studies and a survey of existing works in the field of biosensor. The following major points are considered from the literature survey.

- The SAW sensors were used to monitor the tire pressure in cars/road vehicles and this monitoring is continuous as it is done at even period of driving.

- The research on SAW devices in harsh environment and also provided the information on oxygen gas sensor implementation

- The designing and fabrication of the transducer in SAW sensor using the conventional lithography technique.

- Among normal substrates of piezoelectric a bigger sensor reaction was the actual designing of SAW sensor technology has been reviewed. A survey of the parameters was given, which is necessary for the design of an actual sensor system.

Therefore, in order to bridge these gaps in the literature for implementation of biosensor for cancer detection the following points have been taken into consideration.

- Development of SAW sensor based on PVDF thin film using COMSOL tool.

- Design and simulation based on PVDF+ZnO composite thin film to increase the sensitivity of the biosensor.

- Implementation of the developed SAW sensor on CoventorWare.