Proceedings of the 28th IEEE
EMBS Annual International Conference
New York City, USA, Aug 30-Sept 3, 2006

Lateral Field Excitation (LFE) of Thickness Shear Mode (TSM) Acoustic Waves in Thin Film Bulk Acoustic Resonators (FBAR) as a Potential Biosensor

Anthony Dickherber, Christopher D. Corso, and William Hunt

Abstract - **Lateral field excitation (LFE) of a thin film bulk acoustic resonator (FBAR) is an ideal platform for biomedical sensors. A thickness shear mode (TSM) acoustic wave in a piezoelectric thin film is desirable for probing liquid samples because of the poor coupling of shear waves into the liquid. The resonator becomes an effective sensor by coating the surface with a bio- or chemi-specific layer. Perturbations of the surface can be detected by monitoring the resonance condition. Furthermore, FBARs can be easily fabricated to operate at higher frequencies, yielding greater sensitivity. An array of sensors offers the possibility of redundancy, allowing for statistical decision making as well as immediate corroboration of results. Array structures also offer the possibility of signature detection, by monitoring multiple targets in a sample simultaneously. This technology has immediate application to cancer and infectious disease diagnostics and also could serve as a tool for general proteomic research.**

Introduction

Most experts agree that early detection is a key component to combating many of today's greatest public health threats. Biomolecular markers are present in individuals that suffer from cancer, tuberculosis, HIV/AIDS, hepatitis and malaria even at the earliest stages of development. The primary barrier to early detection is insufficient diagnostic processes. A detection mechanism exhibiting extremely high sensitivity and selectivity is required to identify the telling compounds that could indicate the development of a condition. Moreover, it is critical that such a detection mechanism have a process for minimizing reports of false positives or negatives. Most diagnostic procedures today require immunological lab equipment and trained medical staff to perform the procedures. This is expensive, often to the point of being impracticable, and often there is a significant delay in obtaining results. Current techniques become increasingly unfeasible for many applications that involve screening a large number of patients. The solution to these problems is to employ available technology to make cheaper and more accurate diagnostic equipment that improves and shortens the decision making process while also requiring minimal training or expertise.

Anthony Dickherber and Christopher D. Corso are doctoral candidates in the Department of Bioengineering at Georgia Institute of Technology.
William Hunt is Professor of Electrical and Computer Engineering at Georgia Institute of Technology and Adjunct Professor of Hematology and Oncology at Emory University

Microelectronic acoustic devices have long been recognized as offering great potential as biomedical sensors, specifically piezoelectric resonators. Excitation of a thickness shear mode (TSM) in a piezoelectric bulk is ideal for liquid-phase applications (*e.g.* blood or serum) as liquids cannot support propagation of a shear wave, thus minimal acoustic energy lost into the liquid media. Monitoring the changes in frequency of the resonator then becomes a highly sensitive real-time indicator of any change in surface conditions. The resonator is transformed into a biosensor by immobilization of a bio- or chemi-specific layer at the surface of the device. Binding events at the biolayer cause changes in the surface conditions resulting in a change of the resonance condition (*i.e.* resonance frequency), which is an easily monitored parameter. Many investigations over the past several years have shown success of this concept using the quartz crystal microbalance (QCM). [1-4]

The QCM is not a practical implementation of this technology, however, due to its relatively large active area (about 5 mm diameter) and low frequency of operation (between 5 and 35 MHz). The sensitivity of a resonator sensor increases exponentially with increasing resonance frequency. As we will show, it is possible to excite TSM waves in thin-film bulk acoustic resonators (FBARs) by lateral field excitation (LFE) of the piezoelectric films creating a device that resonates from a few hundred MHz to several GHz. Fabrication of thin films is a commonplace practice in the microelectronics industry, thereby making this an ideal technology for cost efficient mass production of these devices. Furthermore, these devices have a footprint of only a few hundred micrometers or smaller, so fabrication and monitoring of an array of multiple resonator sensors would be a trivial extension. The advantage of implementing an array of sensors would be to employ statistical processing towards analyzing results for a more robust decision making process. Furthermore, array structures would allow for the monitoring of multiple targets simultaneously, which would have obvious applications to cancer diagnostics.

Piezoelectric Resonators

FBARs offer great potential as sensors because their resonant frequency is controlled by the thickness of the fabricated film. For the case of an LFE generated TSM, the resonant frequency can be described by,

$$f_r = \frac{v_a \cdot N}{2 \cdot d} : N = 1,3,5... \quad (1)$$

where v_a is the shear acoustic velocity and d is the film thickness. A full treatment of this derivation can be found in

Rosenbaum [5]. As can be seen, fabrication of a thinner film yields a higher resonant frequency.

The QCM is excited by thickness excitation (TE), which means that the electric field is generated through the bulk of the material by electrodes on either side of the piezoelectric bulk. In our thin film devices, we employ crystals that yield a TSM acoustic wave upon LFE, as depicted in figure 1. There are several advantages to this approach. The first is that the resonant frequency of bulk acoustic wave devices is controlled by the thickness of the film, so it is simple to fabricate high frequency devices for greater sensitivity. The second is that the electrodes are no longer in the acoustic path, which would act as a means of absorbing and scattering the acoustic energy. This degrades the quality of the resonator, Q, which is defined as the energy conserved vs the energy dissipated per cycle.

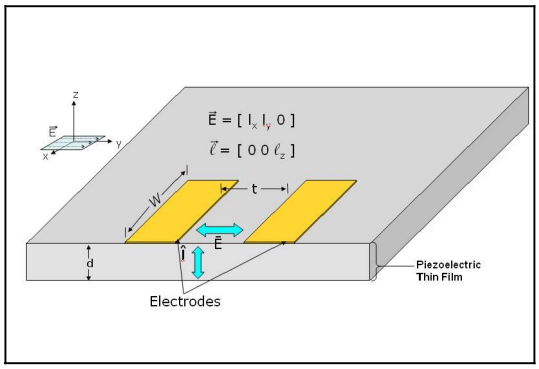

Figure 1. LFE FBAR implementation

We present two piezoelectric thin films that generate TSM acoustic waves upon LFE. The first is RF sputtered Ta_2O_5. We can verify this mode of operation by solving the Christoffel equation to predict the direction of particle displacement.

$$k^2\Gamma_{ij}v_j = \rho\omega^2 v_i \qquad (2)$$

where k is the wave number, ρ is the material density, ω is the frequency, $v_{i,j}$ represents particle velocity and direction (i,j=1,2,3 axial directions) and Γ is the piezoelectrically stiffened fourth order christoffel matrix. Γ is calculated by

$$\Gamma_{ij} = \ell_{iK}\left(c^E_{KL} + \frac{[e_{Kj}l_j][l_i e_{iL}]}{l_i\varepsilon^S_{ij}l_j}\right)\ell_{Lj} \qquad (3)$$

where ℓ is related to the acoustic propagation, c^E is the fourth order bulk material stiffness, l is the electric field direction vector and e is the piezoelectric tensor of the material. Solving for (3) for the thickness directed wave excited by LFE onto Ta_2O_5, it can be seen that regardless of the orientation of the electric field with respect to the crystal lattice structure, piezoelectric stiffening exists for the in-plane particle displacement. Since the crystal lattice symmetry is orthorhombic, the degree of piezoelectric stiffening is strongly dependent upon the orientation of the electric field. However, the important point is that for an electric field in the horizontal plane, parallel to the surface, a shear wave will be generated with a propagation direction normal to the surface (i.e. TSM wave) and that piezoelectric coupling does not occur in the direction normal to the surface. This is necessary to ensure a liquid-phase biosensor platform in which particle displacement is predominantly parallel to the surface of the device.

A similar result is obtained when solving the piezoelectrically stiffened Christoffel equation for c-axis oriented ZnO which has hexagonal symmetry. Defining the wave propagation as being normal to the surface (along the z-axis), it is possible to show that a laterally directed electric field causes particle displacement in-line with the electric field, independent on the orientation with respect to the crystal lattice. This is an interesting result because it predicts that a TSM can be excited in any direction normal to the c-axis on a ZnO sputtered wafer. Given that the bulk properties of ZnO are well known, it is simple to predict the shear wave velocity and thus the operating frequency for a film thickness equal to the Ta_2O_5 film presented in this paper. The shear wave velocity is defined as

$$v_a = \sqrt{\frac{c'_{44}}{\rho}} \qquad (4)$$

where c'_{44} is the piezoelectrically stiffened elastic coefficient for the z-directed shear propagation, and ρ is the bulk density. Using B.A. Auld as a reference [6], we get an approximate shear velocity of 2830 m/s, which yields a resonant frequency of 3.1 GHz for a 450 nm thick film. This frequency would yield a sensitivity increase of 6 orders of magnitude on QCMs.

Array Structures

Eight and 16 element array structures have been fabricated and are shown in figure 2. The arrays have been designed so as to accommodate fabrication of a flow cell structure over them while allowing active probing of the resonators. We are currently working with Professor James Landers in the Department of Chemistry at the University of Virginia on incorporating the array into a MEMS-based flow cell.

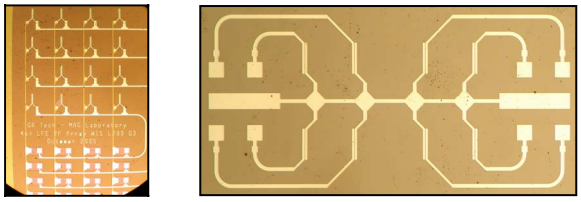

Figure 2. 16- and 8- element LFE FBAR arrays.

Surface Chemistry

There are two methods that we have used for immobilizing a biolayer consisting of two parts: a cross-linker and a biospecific molecule, on acoustic wave devices. The first method involves the implementation of a self-

assembled monolayer (SAM) as the cross-linker between the biospecific molecule and the surface of the device. Alkane-thiol carboxylic acid molecules chemisorb to the gold surface of the electrodes on the device which spontaneously orient themselves into an aligned monolayer ~30° off normal to the surface of the device. Following chemical treatment of the carboxylic acid, the immobilized molecule reacts with the antibody to form a covalent bond which fixes the antibody to the acoustic wave device. One downside to this method is that the antibody is not always oriented such that the antigen binding sites on the F_{ab} fragments of the antibody face outwards, away from the surface. Rather, the chemistry of the reaction predicts that the antibodies could bind to the cross-linking layer causing the antibody to be positioned in ways that would reduce the ability for it to bind its target.

The second method for functionalizing the surface of the device is through the use of protein A as a cross-linker. Protein A is a protein derived from the cell wall of the *Staphylococcus aureus* which binds the F_c region of IgG subclass antibodies leaving the antigen binding sites free [7]. Wild type protein A has five homologous extracellular domains which are each capable of binding an IgG molecule. The steric interactions between molecules will disallow all of the domains to be occupied by an IgG molecule simultaneously. The tradeoff, however, is that the antibodies are oriented such that the antigen binding sites are free which makes for an overall better sensor.

Non-specific binding is a critically important issue to account for. Since it is incredibly difficult to prevent random non-specific binding from proteins and other particles found in biological fluids, we attempt to isolate our relevant signal by operating the sensor in conjunction with a control sensor. This is typically a resonator that has been similarly treated as the target sensor, but with a chemistry that is specific for a target not found in the sample. This technique has proven to be successful for showing detection of mesothelin, a biomarker for pancreatic cancers, in pancreatic cancer cell line supernatant. The reference sensor was coated with anti-FITC antibodies which bind a synthetic dye molecule that should not be present in cell line supernatant [8]. The reference sensor response was subtracted from the target sensor response to give the differential response. This method allows for removing any non-binding related effects such as fluidic pressure, viscosity, *etc.* that are constant for both sensors leaving only the response due to binding of the target molecule to the sensor.

Biosensor Mechanics

The pioneering work describing piezoelectric devices as possible sensors was established by Sauerbrey [9] for QCMs, where he described the change in resonance as directly related to a mass loading at the surface by

$$\Delta f = \frac{-2 f_o^2 \Delta m}{A\sqrt{\rho_q \mu_q}} \tag{5}$$

where Δf is the change in frequency, f_o is the unloaded resonance frequency, Δm is the change in mass loading at the surface, A is the area of operation, ρ_q is the quartz mass density and μ_q is the quartz elastic stiffness. The problem with the Sauerbrey equation is that it assumes the added film mass has the same density and acoustic properties of the bulk quartz. Understanding of the surface perturbation physics has evolved since Sauerbrey, especially for different mediums of operation. The Sauerbrey equation has been shown to be inaccurate for liquid phase media.[10]

Specifically relevant to the QCM biosensor setup, Hunt was able derive from the reciprocity relation through time-dependent perturbation theory [11], the following governing equation

$$t\frac{\partial \Delta\omega}{\partial t} + \Delta\omega = -\frac{\omega_u^2 \cdot h_f}{\pi\sqrt{\rho_q \mu_q}}\left[\Delta\rho_f - \frac{\Delta\mu_f}{V_S^2}\right] + i \cdot \frac{\omega_u \cdot h_f}{\pi\sqrt{\rho_q \mu_q}}\left[\frac{\partial \Delta\rho_f}{\partial t} - \frac{1}{V_S^2}\cdot\frac{\partial \Delta\mu_f}{\partial t}\right] \tag{6}$$

where the subscript "u" denotes the unperturbed field condition, ω is the radian frequency, V_S is the velocity of the shear acoustic wave, h_f is the height of the immobilized surface film and C is a constant to be utilized in satisfying the initial conditions of the differential equation. If one were to assume that $\Delta\omega$, $\Delta\rho$ and $\Delta\mu$ were independent of time, then we would find that (6) reduces to

$$\Delta f = \frac{-2 \cdot f_u^2 \cdot h_f}{\sqrt{\rho_q \mu_q}}\left[\Delta\rho_f - \frac{\Delta\mu_f}{V_S^2}\right] \tag{7}.$$

As can be seen, this equation is similar to the Sauerbrey equation with the exception that a term is included taking into account the stiffness of the surface film. This indicates that a change in the resonance condition is subject to both changes in the surface stiffness as well as mass loading at the surface. This would account for the positive frequency shift seen in past investigations of acoustic wave biosensors [1-4], unaccounted for in the Sauerbrey equation.

In the past, we have successfully implemented surface acoustic wave (SAW) sensors for vapor phase detection as well as QCM-based biosensors for liquid phase detection. Success has been established in a repeatable manner in detecting the pancreatic biomarker mesothelin with QCMs as well as the prostate cancer biomarker Sonic Hedge Hog (SHH) with the current Ta_2O_5 devices in conditioned media [8,12]. This demonstrates the ability to detect trace concentrations of target molecules in "noisy" environments. Further, our QCM detection was able to demonstrate detection at the sensitivity threshold for ELISA (Enzyme Linked Immunosorbent Assay), used as a comparison test. As can be seen from equations (5) and (7), the sensitivity of the sensor is directly proportional to the square of the

unperturbed resonance frequency. The QCMs used in the TGF-α and SHH experiments operated at 10 MHz. The Ta_2O_5 BAW sensors that we present operate at around 500 MHz, representing a potential increase in sensitivity by more than three orders of magnitude. Recall that the resonance frequency is controlled by the thickness of the piezoelectric film, offering an easy mechanism for increasing the sensitivity exponentially.

Figure 3 shows preliminary S11 impedance response results demonstrating the effects of a drop of water on the active region of our Ta_2O_5 resonator. Note that the mass loading of the water caused a significant negative frequency shift. Also notice that the water did not degrade the signal response strength. If the device resonated with a longitudinal component, as most FBARs do, then the signal would have been decimated by the water drop.

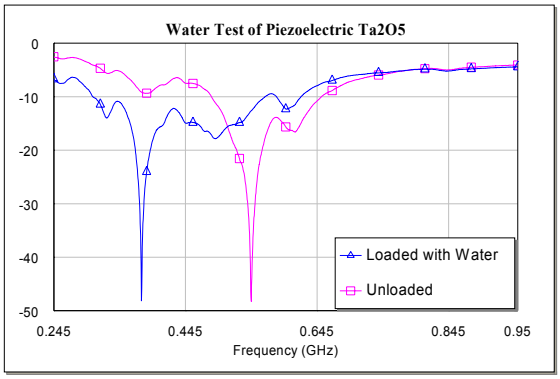

Figure 1. Frequency shift associated with water loading on a Ta_2O_5 BAW resonator.

Conclusion

As we have shown, lateral field excitation of TSM acoustic waves in a piezoelectric thin-film resonator offers great potential as a biosensor with high sensitivity. The chemi-specific surface treatment of the device attributes high selectivity to the sensor. When operated in conjunction with a reference sensor and in an array configuration, false positives and negatives should be minimized. These devices can be mass produced employing microelectronic fabrication processes yielding very low cost sensors, thereby rounding out its viability as an ideal biosensor.

References

[1] A. Shons, F. Dorman, J. Najarian, "An immunospecific microbalance" *J Biomed Mater Res* **6** (6): 565-570. 1972

[2] S.F. Chou, W.L. Hsu, J.M. Hwang, C.Y. Chen, "Determination of alpha-fetoprotein in human serum by a quartz crystal microbalance-based immunosensor" *Clinical Chemistry* **48**: 913-918, 2002

[3] Z.Y. Wu, G.L. Shen, S.P. Wang, R.Q. Yu, "Quartz-crystal microbalance immunosensor for Schistsoma-japonicum-infected rabbit serum" *Anal Sci* **19**(3): 437-440, 2003

[4] X.L. Su, Y. Li, "A self-assembled monolayer-based piezoelectric immunosensor for rapid detection of Escherichia coli O157:H7" *Biosens Bioelectron* **19**(6): 563-574, 2004

[5] J. Rosenbaum, *Bulk Acoustic Wave Theory and Devices*, Artech House, Inc 1988

[6] B.A. Auld, *Acoustic Fields and Waves in Solids*, Krieger Publishing Co. Vol 1 Apdx B, 1973

[7] D.M. Gersten, J.J. Marchalonis, "A rapid, novel method for the solid-phase derivatization of IgG antibodies for immune-affinity chromatography" *J Immunol Methods* **24**(3-4): 305-9, 1978

[8] C.D. Corso, D.D. Stubbs, S.H. Lee, M. Goggins, R.H. Hruban, W.D. Hunt, "Real-time detection of mesothelin in pancreatic cancer cell line supernatant using an acoustic wave immunosensor" *Cancer Det Prev* **30**: 180-87, 2006

[9] G. Sauerbrey, "Use of vibrating quartz for thin film weighing and microweighing" (in German) *Z. Phys* **155**: 206-222, 1959

[10] K.K. Kanazawa, J.G. Gordon, "The Oscillation Frequency of a Quartz Resonator in Contact With a Liquid" *Anal. Chim. Acta* **175:** 99-105, 1985

[11] W.D. Hunt, D.D. Stubbs, S.H. Lee, "Time-Dependent Signatures of Acoustic Wave Biosensors" *Proc. IEEE* **91**: 890-901, 2003

[12] C.D. Corso, A. Dickherber, P. Shah, A Migdal, M.W. Datta, S. Datta, W.D. Hunt, "Development of Simple Inexpensive BAW Nanosensor for Cancer Biomarkers: Detection of Secreted SHH from Prostate Cancer Cells", (Poster) *American Association of Cancer Researchers Annual Meeting 2006*, Washington DC, April 2-5, 2