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Lab-on-a-chip based integrated hybrid technologies for biofluids manipulation and characterization

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Abstract

The goal of this work is to develop an original and high performance hybrid lab-on-a-chip, coupling actuators and biosensors for the active control and broad range characterization of biofluids samples. These biofluids will be controlled (moved and mixed) actively by Rayleigh-Surface Acoustic Wave (R-SAW) and analysed in real-time by combining Love-SAW (L-SAW) and Surface Plasmon Resonance (SPR) technologies. A microfluidic chamber and specific transducer were designed for this application to interact efficiently with the liquid sample entrapped in the chamber and to detect modifications of its physical properties such as viscosity. AT-cut quartz and $LiNbO_3$ 36Y-X substrates were used to generate both Rayleigh and Shear-Horizontal waves and ZnO material as guiding layer. The whole system has proven is full efficiency to interact with the fluid and to detect the signal perturbations with no significant loss compared with the measurements carried out with a probe station.

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Keywords:Microfluidic; Surface Acoustic Waves (SAW); Love wave; Rayleigh wave; ZnO; AT-cut quartz; LiNbO3 36Y-X

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1. Introduction

In the last decades Surface Acoustic Wave (SAW) devices have been employed in sensor and actuator applications such as chemical and biochemical sensors and Lab-on-a chip (LOC) system. LOC are important microsystems with promising applications in point-of-are (POC) testing that are intended to be used at or near the site where the patient is located, which do not require permanent dedicated space, and which are performed outside the physical facilities of clinical laboratories. Such an approach will not replace central laboratories but it should give a first response within less time and with no need of highly trained personnel. In order to conduct chemical

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analysis, it is essential to manipulate small quantities of biofluids and immobilize probe molecules on the surface of a transducer that react with the target molecules in the sample.

LOC based on SAW devices can couple both microfluidic and sensor capabilities. The SAW device technology is relatively cost-effective because of the use of well-established MEMS microfabrication procedures. Due to their small size, they can be added into microscale system promising an excellent solution for fluid miniaturised platforms. This reduction of device scales allows the decrease of reaction times and reagent volumes, reducing the analysis cost, and enhancing the efficiency and sensitivity of analysis [1].

The aim of this work is to develop an original and high performance hybrid LOC, coupling actuators and biosensors for the active control and broad range characterization of biofluids samples. These biofluids will be controlled (moved and mixed) actively by Rayleigh-Surface Acoustic Wave (R-SAW) and analysed in real-time by combination of Love-SAW (L-SAW) [2] and Surface Plasmon Resonance (SPR) [3]. A microfluidic cell and a specific transducer have been designed for this application to interact efficiently with a biofluid and to detect a modification of its physical properties. We will first of all describe the microfluidic cell and present its efficiency in terms of SAW characterization. We will then present the design of our R-SAW and L-SAW devices based on Quartz and Lithium Niobate substrates to generate both Rayleigh and Love waves. Later, we will present our experiments to test the heating effect of the R-SAW on a fluid and to detect viscosity changes with the L-SAW sensors. All of these experiments have been carried out using the microfluidic cell that will be presented.

2. System description and Experimental set-up

2.1. Design and fabrication of a microfluidic cell and SAW devices

3D designs of the flow cell were done using the CAD software SolidWorks. The design is presented in Fig. 1a. As it was mentioned in previous works [4], one of the main challenges of L-SAW microfluidic cell design is to confine the liquid in the sensing area. L-SAW sensors do not work properly when the Interdigital Transducers (IDTs) area is covered by liquids [4]. Thus, to avoid an electrical mismatch, which produces that part of the electric signal to go through the liquid, the confinement of the liquid in the device's sensing area is required. To solve this issue, PDMS peak-end seals have been realized. These seals confine the liquid in the desire region and minimize the contact area on the sensor surface avoiding excessive perturbations.

In order to generate both Rayleigh and Love waves, it was required to use substrates that were able to launch Shear-Horizontal waves. Moreover, for the existence of Love waves the shear velocity of the substrate must be higher than that of the guiding layer. The guiding layer confines the wave energy on the surface providing a higher sensitivity. Two different substrates have been used to fabricate the device; AT-cut quartz Z propagating (from now on AT), due to its temperature stability and for the possibility to generate pure shear waves; and Lithium Niobate ($LiNbO_3$) 36Y X propagating (from now on LN), for its good electromechanical coupling coefficient. ZnO was used as the waveguide layer due to the relatively high velocity contrast between the guided layer material and the substrate, for its physical properties (high resistance to chemical agents, low acoustic loss and low insertion loss) and for its relatively high electromechanical coupling coefficient. With ZnO layers it is then possible to generate

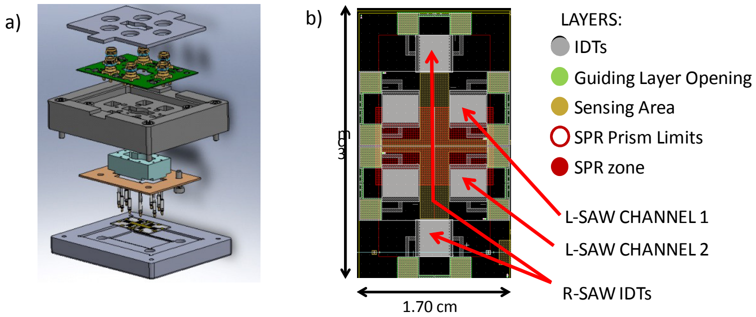

Fig. 1. (a) Exploded view of the cell. (b) Image of the mask of the SAW device.

Love waves with an effective confinement near the surface and high sensitivities [5].

The device consists of two L-SAW delay line channels (Fig. 1b), for sensing purposes and two one port R-SAW, for mixing purposes. Having two L-SAW delay lines permits to conduct differential measurements in order to suppress parasitic effects such as temperature effects or time drifts. Moreover, one channel can be functionalized and the other can be used as reference. In addition, a SPR zone was considered so the dimensions of the whole structure take into account the requirements for the future integration with a SPR system.

IDTs were patterned onto the piezoelectric substrates by aluminium deposition (200 nm) of and wet etching after a positive lithography was completed. Then, highly oriented c-axis ZnO films were deposited on the substrates by RF reactive magnetron sputtering process [6] on a positive lithography of a sacrificial layer that protected the IDTs contacts. Finally, a gold sensing area, for the immobilization of biochemical species, was placed on top of the guiding layer and in the space between IDTs.

2.2. R-SAW and L-SAW characterization experiments

To characterize R-SAW devices, an RF signal generator (Hewlett Packard HP8648C) is connected to the power amplifier (Minicircuits ZHL-5W-1) which feeds the SAW device via a directional coupler (Minicircuits ZFDC-20-1H). A power meter (Agilent Technologies E4417A) measures the injected electrical power to the IDT. An infrared camera (FLIR SC5600) is positioned above the sample with a temperature resolution lower than 30 mK, spatial resolution of 5 µm, a recording speed of 100 images per second and a spectral response between 2.5 and 5.1 µm. Dedicated software from FLIR leads to drive the infrared camera and collect data. The camera is thus used to follow the heat of the liquid deposited on the wave path in both scales: spatial and temporal.

To characterize the L-SAW sensors, glycerol-water solutions were prepared with concentrations of 0 (deionised water), 5, 10, 20, 30 and 40 %vol. The phase response of the AT/ZnO and LN/ZnO L-SAW delay lines to those different solutions (45 µl) were measured at a fixed frequency using an E5061B Agilent Network Analyzer.

3. Results

Fig. 2a presents a frequency response of one AT device tested in a probe station and in the microfluidic cell. We can see that the frequency response is affected by the seal first of all and also by the liquid deposited on the wave path (sensing area).

R-SAW will be used to accelerate the reaction's kinetics. This wave will interact with the biofluid, so it is of prime importance to characterize it’s effect. Fig. 2b presents the thermal effect of the wave under an injected power of 1 W and after 12 s. A rising in the temperature of the fluid reach up to 24°C and just in half of the biofluid area without being completely homogeneous. We thus consider that it will not significantly affect the biofluid. Fig. 2c presents the time response of the thermal effect in the biofluid. The steady state value is obtained after 60 s and the maximum temperature is 25.5°C. The temperature was measured near the contact of the acoustic wave with the fluid. This value will be principaly modified by the biofluid viscosity.

The phase φ of the L-SAW sensors were monitored at a fixed frequency of 102.03 MHz for the AT/ZnO device and 96.5 MHz for the LN/ZnO device. The φ of 0% glycerol solution (water) were considered as zero and were set as reference measurements (unperturbed event). Table 1 presents the sensor responses to the different concentrations of glycerol-water solutions. Both structures AT/ZnO and LN/ZnO present the same tendency and the AT/ZnO device turned to be slightly more sensitive in those specific parameters.

4. Conclusions

We have developed a whole system including a microfluidic cell integrating a sensor and actuator based on Love-SAW and Rayleigh-SAW. The microfluidic cell has proven its robust possibility to substitute a probe station. We fabricated SAW devices on AT/ZnO and LN/ZnO structures that were able to interact with the fluid without heating to much the reagents and also presented an effective sensing response to physical properties modifications of liquid samples. AT/ZnO L-SAW devices provided a slightly higher sensitivity than LN/ZnO for viscous interactions.

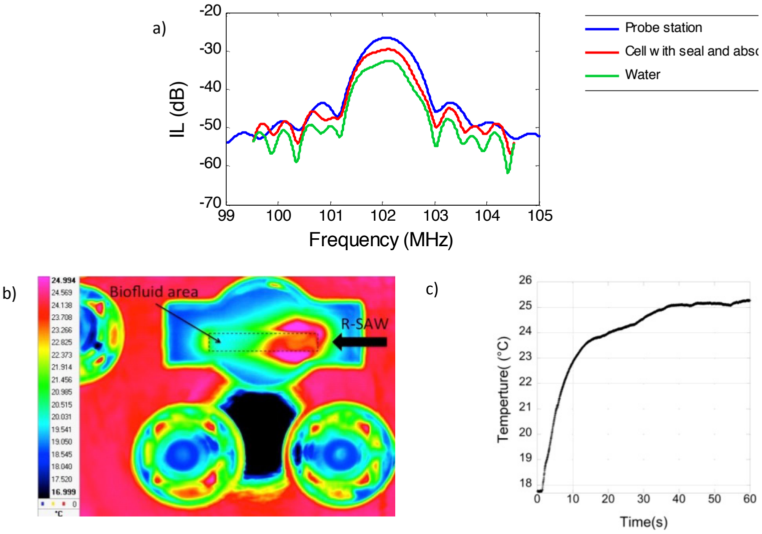

Fig. 2. (a) Frequency response of an AT/ZnO L-SAW sensor. Insertion losses produced in air with the probe station (blue line), in the cell with the seals and absorbers (red line) and in the cell in contact with water (green line). (b) Infrared image of the fluid heating (seen from the top view of the cell) under 1 W injected on the IDT and after 12 s. (c) Time response of the biofluid heating under 1 W.

Table 1. Phase responses for different concentration of glycerol-water solutions of the AT/ZnO and LN/ZnO L-SAW devices.

Glycerol %	$\|\Delta\varphi\|$ AT/ZnO (°)	$\|\Delta\varphi\|$ LN/ZnO (°)
0 (water)	0.00	0.00
5	3.54 ± 0.31	0.91 ± 0.63
10	5.96 ± 0.34	2.18 ± 0.51
20	13.09 ± 0.23	8.02 ± 1.06
30	19.62 ± 0.48	13.70 ± 1.12
40	33.55 ± 1.34	23.77 ± 1.31

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