A Fast FPW-based Protein Concentration Measurement System

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***Abstract*— A fast protein concentration measurement system with two-port FPW (flexural plate wave) biosensors using a frequency-shift readout technique is presented in this paper. The proposed frequency-shift readout method employs a peak detecting scheme to measure the amount of resonant frequency shift. The frequency sweep range of the linear frequency generator is limited in 2 MHz to 10 MHz according to the characteristics of the FPW biosensors. The proposed frequency-shift readout circuit is verified on silicon using a standard 0.18 μm CMOS technology. The power consumption of the proposed protein concentration measurement system is 48 mW given a 0.1 MHz system clock. The protein concentration measurement is read out in less than 10 minutes.**

***Keywords*—IgE antigen, frequency-shift readout circuit, FPW, resonant frequency, peak detection.**

I. Introduction

With the booming demand of the biomedical electronics, *in vitro* bio-analytical applications are quickly developed to help medical staffs to perform POC (point of care) pathologic analysis. More specifically, many people have been suffered by different allergic diseases, e.g., allergic rhinitis, which may cause extremely uncomfortable feeling and poor quality of life. Clinically, the concentration of immunoglobulin E (IgE) protein is one of the most important indicators to reveal the allergic level in human serum [1]. Conventionally, many commercial allergy measurement techniques are available to analyze IgE concentration, e.g., enzyme-linked immunosorbent assay (ELISA) [2], surface plasmon resonance (SPR) [3], quartz crystal microbalance (QCM) [4] sensing techniques, and chemiluminescence immunoassay (CLIA) [5], etc. Unfortunately, all the above mentioned commercial allergy measurement instruments require multifarious testing samples, long operation time for sampling analysis procedures, and expensive analysis instruments. These equipments might not be available in remote areas, or even those clinics in suburban areas. Therefore, an inexpensiveness, short analysis time, and high precision for allergic level estimation is very much needed for those who are suffered in these areas.

Recently, the flexural plate-wave (FPW) devices are found to be appropriate for bio-analytical applications. Moreover, since the FPW device can be fabricated by semiconductor technology, it allows batch processing such that it is very cost effective. In this paper, we propose a novel frequency-shift readout system for a pair of two-port FPW biosensors. The FPW allergy biosensor adopts the Cr/Au-based IDTs to be a Tx(transmitter) and a Rx(receiver), which are, respectively, placed on the right and left side of a thin plate [7]. Notably, the resonant frequency shift of the FPW allergy biosensor is roughly anti-proportional to the purified human IgE antigen concentration. Therefore, the FPW-based allergy biosensor provides another IgE antigen concentration measurement method. The proposed frequency-shift readout system is realized by a standard 0.18 μm CMOS technology.

II. FPW allergy biosensor characteristics

The FPW allergy biosensor propagates an acoustic wave via a mechanical thin plate. The resonant frequency, f_0, of the FPW sensor is given by the following equation,

$$f_0 = \frac{V_p}{\lambda} \tag{1}$$

where λ is the acoustic wavelength and V_p is the phase velocity [7]. The mass loading of the Si/SiO2/Si3N4/Cr/Au/ZnO floating thin plate which results in resonant frequency shift is expressed as follows,

$$\frac{\Delta f}{f_0} = S_m \Delta m = S_m(MW \times C_S) \tag{2}$$

where Δf is the change of the resonant frequency due to a change in mass per unit area, Δm, and S_m is the mass sensitivity of the FPW allergy biosensor. MW is the molecular weight and C_S is the surface concentration of the absorptive moleculars. Therefore, Δf can be changed by C_S as well as the IgE antigen concentration.

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According to the phenomenon of FPW allergy biosensor's frequency shifting, we propose a novel frequency-shift readout circuit to estimate the amount of the frequency shifting. Referring to Fig. 1, when the input frequency is equal to the resonant frequency, the output signal amplitude of the FPW allergy biosensor will be maximum according to the resonant principle. Therefore, a high sensitive peak detector is required to detect the maximum peak voltage and generate an enable signal to trigger a register to snapshot the frequency value from the oscillator control signal. Thus, the frequency-shift value is attained as well as the amount of the IgE antigen concentration by calculating the difference between resonant frequencies of sensor1 (Experimental group, with antigen) and sensor2 (Control group, without antigen).

III. Frequency shift readout circuit design

Besides FPW sensors, the proposed frequency-shift readout system is composed of a 8-bit up-counter, a 8-bit DAC (digital-to-analog converter), an OTA-C oscillator, a pair of peak detectors, two registers, and a subtractor as shown in Fig. 1. The detailed description of each subcircuit is explained in the following text.

A. Linear frequency generator

A sine wave frequency generator is required for the FPW allergy biosensors to generate the frequency sweep signal in the pre-defined range. Referring to Fig. 1, the counter is a typical digital 8-bit counter generating 0 to 256 counting signal to drive the DAC (digital-to-analog converter). The 8-bit DAC utilizes a typical current-steering structure, which requires only 8 current sources with binary-weighted sizes instead of $2^8 - 1$ sources. The schematic of the tunable OTA-C oscillator is shown in Fig. 2 [8]. OTA_vb is biased externally to ensure correctness of the OTA's functionality. Gm1, Gm2, Gm3, and Gm4 are the typically identical operational transconductance amplifier (OTA). Referring to Fig. 2, Gm1-C1 and Gm2-C2 constitutes a 2nd-order RC oscillator with a positive feedback to generate an oscillation signal. On the other hand, Gm3 and Gm4 are used to keep the peak-to-peak amplitude of the generated sine wave. The frequency tuning range of tunable OTA-C oscillator is limited from 2 MHz to 10 MHz according to the characteristics of the FPW allergy biosensor.

B. Peak detector

The output signal of each FPW allergy biosensor in Fig. 1 will reach its peak voltage when the input frequency equals to the resonant frequency. A peak detector is, then, used to detect the maximum peak from the FPW allergy biosensor output and the determine the corresponding frequency. Fig. 3 shows the proposed peak detector. The detailed operating steps of the peak detector is listed as follows.

Step1: Initially, RESET1, RESET2, and RESET3 are biased at high to discharge C3, C4 and reset the D flip-flop.

Step2: The sine wave from FPW allergy biosensor's output is fed to VIN (vpeak_in1 or vpeak_in2 in Fig. 1). When VIN is higher than VPEAK_new, OPA1 will turn on MN603. Then, C1 is charged until VPEAK_new = VIN.

Step3: MN603 is off to isolate VPEAK_new from VPEAK_max. If VPEAK_new is higher than VPEAK_max, OPA2 will trigger the D flip-flop. Then, EN (En1 or En2 in Fig. 1) is pulled high to turn MN603 on. Hence, VPEAK_max is pulled close to VPEAK_new through MN603. If VPEAK_new is not higher than VPEAK_max, VPEAK_max keeps the prior high voltage value.

Step4: When VPEAK_max is equal to VPEAK_new, RESET3 will be pulled up high to reset the D flip-flop to set EN=0. VPEAK_new and VPEAK_max are isolated again by MN603.

By the above steps, the peak detector can generate the enable signals, EN (En1 or En2 in Fig. 1), to enable the registers (reg1 or reg2 in Fig. 1), respectively, and store the respective counting numbers therein. Therefore, the resonant frequencies of the FPW allergy biosensors are stored by the proposed peak detectors. By the subtraction the contents in reg1 from that in reg2, the frequency-shift variation, $\triangle$f, can be derived.

IV. Implementation and measurement

Fig. 4 shows the implemented FPW sensor using micro-electromechanical systems (MEMS) technology and the total fabrication processes. Notably, the IgE antigen concentration of allergy patient is usually higher than 100 IU mL^{-1}. The proposed frequency-shift readout circuit for FPW allergy biosensor is fabricated on silicon by TSMC (Taiwan Semiconductor Manufacturing Company) standard 0.18 μm CMOS technology. Fig. 5 shows the die photo including I/O PADs of the proposed prototype chip. The chip area of the proposed frequency-shift readout circuit is 1678×1328 μm^2.

The pair of FPW sensors are coupled to the proposed readout system as shown in Fig. 6. We utilize an FPGA (field-programmable gate array) experiment board to generate the control signals for the proposed frequency-shift circuit. When the frequency-shift measurement is done, the amount of the frequency-shift will be displayed on the LCD monitor. For instance, the LCD monitor displays the resonance frequency of the Control group FPW allergy biosensor (sensor2) is 9.1 MHz and the amount of the frequency shift of the Experimental group FPW allergy biosensor (sensor1) is 0.11 MHz. Thus, we can derive the concentration of IgE protein by a frequency to concentration conversion table.

The power consumption is measured to be 48 mW at a 0.1 MHz clock. The curve of the frequency shift versus the IgE concentration in human serum is shown in Fig. 7. Fig. 8 shows

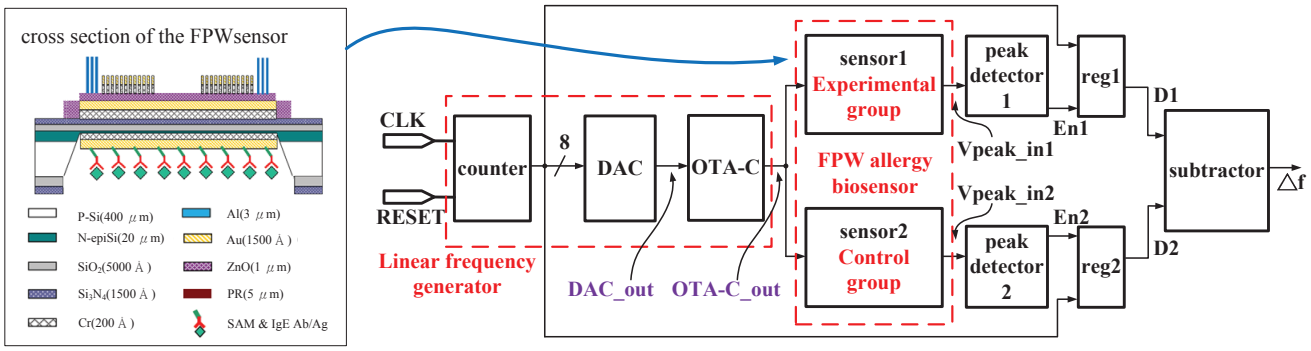

Fig. 1. Block diagram of the frequency-shift readout system

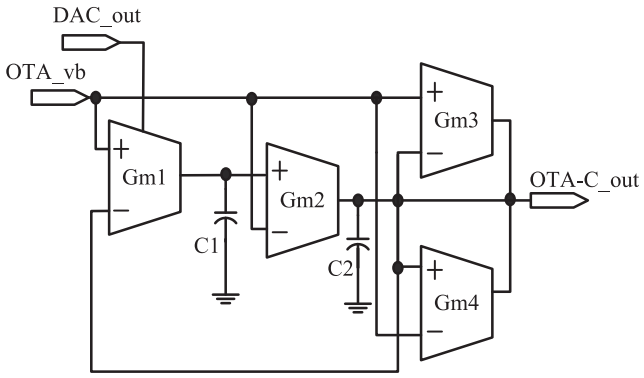

Fig. 2. Schematic of the OTA-C oscillator

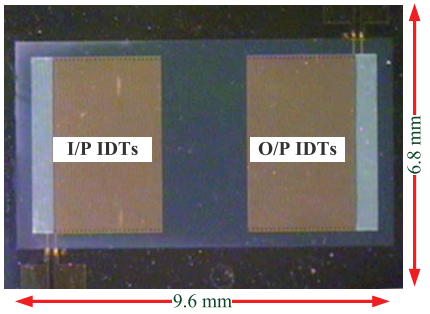

Fig. 4. Photograph of the implemented FPW sensor

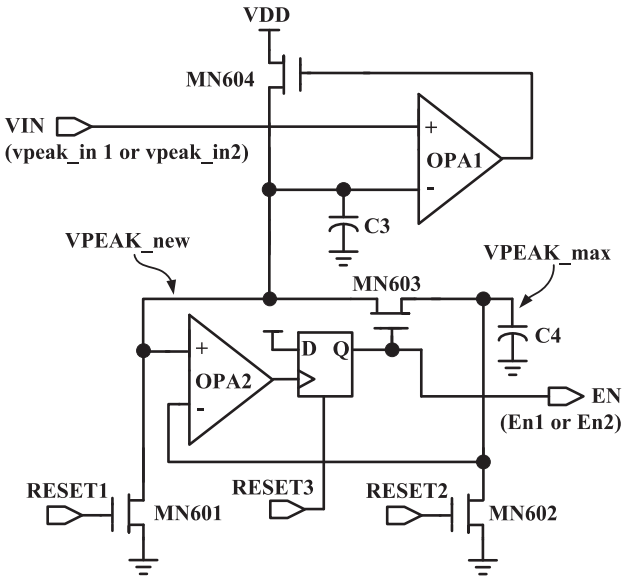

Fig. 3. Schematic of the peak detector

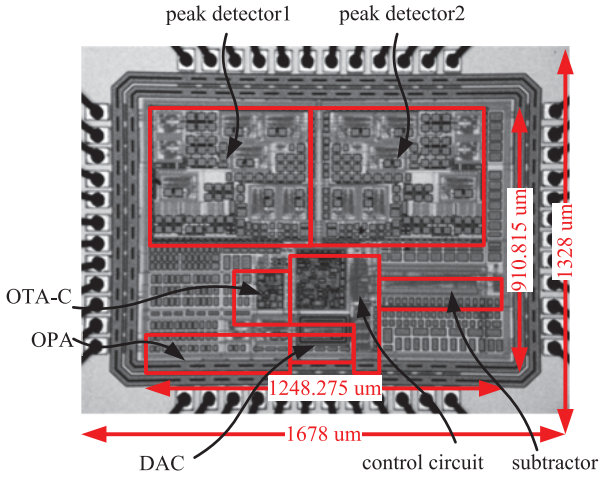

Fig. 5. Die photo of the proposed frequency-shift readout circuit

the timing behavior of the FPW allergy biosensor coated with different IgE concentrations in human serums. Notably, the frequency shift of each IgE concentration is stable after 10 minutes, which is faster than any existing IgE measurement systems, including ELISA, and CLIA, etc. The comparison with a similar prior work is tabulated in Table I.

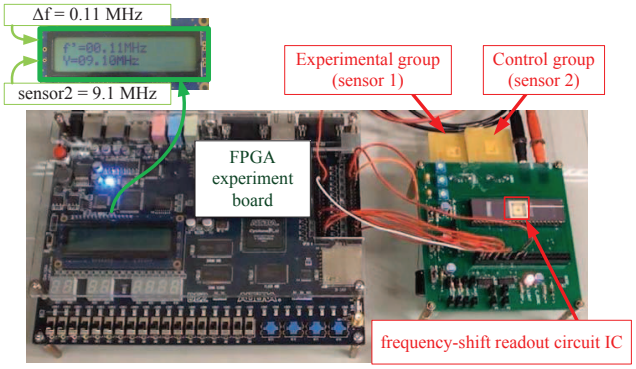

Fig. 6. Prototype of the protein concentration measurement system

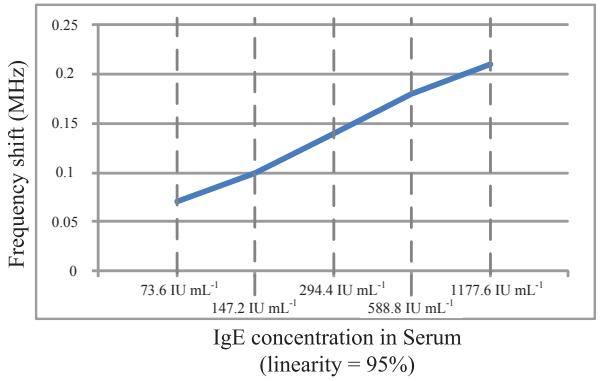

Fig. 7. Frequency shift versus IgE concentration

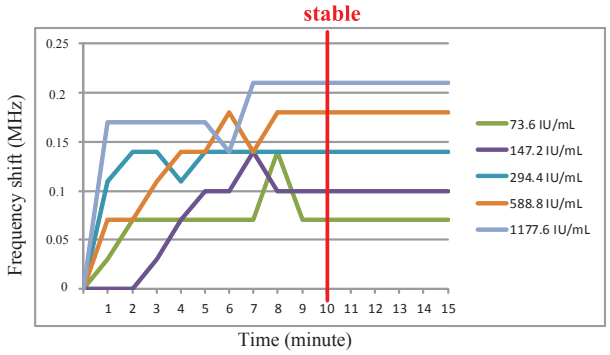

Fig. 8. Frequency shift of the FPW allergy biosensor coated different IgE concentrations in human serums

TABLE I

COMPARISON WITH PRIOR WORK

	proposed	[9]
Implementation technique	system on chip	PCB discretes
Measurement method	peak detection	phase detection
Process (μm)	0.18	N/A
Supply voltage (V)	1.8	N/A
Frequency (MHz)	0.1	4.2
Power (mW)	48	N/A
Year	2011	2008

V. CONCLUSION

This paper presents a frequency-shift readout circuit and system for a two-port FPW allergy biosensor. The linear frequency generator generates a linear frequency sweep fed into the FPW allergy biosensor. The peak detectors are used to detect the resonant frequencies of the Experimental group and Control group of the two-port FPW allergy biosensor. The detected resonant frequencies are stored in the registers, reg1 and reg2, respectively. The frequency-shift amount is measured by the proposed prototype system correctly. The proposed prototype system just needs less than 10 minutes to attain the protein concentration measurement result. Furthermore, the proposed prototype system is very cost effective compared to the traditional methods. Therefore, the proposed technique is an attractive solution for the protein concentration measurement.

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