A CEA Concentration Measurement System Using FPW Biosensors and Frequency-shift Readout IC

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***Abstract*—In this paper, a CEA (carcinoembryonic antigen) concentration measurement system using flexural plate wave (FPW) biosensors and a frequency-shift readout IC is presented. The proposed frequency-shift readout method employs a programmable frequency generator and a peak detecting scheme to estimate the resonant frequency. The programmable frequency generator provides a frequency scanning range from 0.9 MHz to 25 MHz according to the characteristics of the FPW biosensors. Particularly, the proposed frequency-shift readout circuit filters and amplifies the FPW biosensors signals such that the requirements for the following voltage peak detector can be relaxed. Therefore, the sensitivity and performance of the CEA sensing system are also enhanced. The sensitivity of the peak detector is 5 mV at the highest signal rate, 50 MHz. The proposed frequency-shift readout circuit is implemented using a typical 0.18 μm CMOS technology. The power consumption of the proposed CEA concentration measurement system is 7.69 mW justified by HSPICE simulations.**

Keywords— CEA concentration, frequency-shift readout circuit, FPW biosensor, peak detector

I. Introduction

Recently, cancer has become the major cause of death in the world [1]. For example, colorectal cancer was difficult to be diagnosed before it was too late such that the treatment time would have been missed and the survival rate was quite low. If the detection of the corresponding tumor marker as well the correct treatment could have been done early, the survival rate will be much better. Clinically, the initial stage of the colorectal cancer is often diagnosed by CEA (carcinoembryonic antigen) concentration in human serum, and confirmed by further examination. Many commercial measurement instruments have been used to measure CEA concentration, e.g., enzyme-linked immunosorbent assay (ELISA) [2], and quartz crystal microbalance (QCM) [3] sensing techniques, etc. Although ELISA and QCM both have advantages of good resolution and high accuracy, these commercial measurement devices require multifarious testing samples, long operation time for sampling analysis procedures, expensive analysis instruments, and skilled personnel to operate in a laboratory. Therefore, this investigation aims at developing a high-precision, short analysis time, inexpensive solution for early detection of the CEA concentration measurement. The solution consists of the flexural plate-wave (FPW) devices and frequency-shift readout IC for early detection of CEA concentration in human serum to shorten the operation time and reduce the cost. According to the resonant basics, the output signal amplitude of the FPW biosensors will be maximum when the input frequency is equal to the central resonant frequency [4]. Therefore, a highly sensitive peak detector is used to detect the maximum peak voltage and generate an enable signal to trigger a register to snapshot the frequency. The proposed frequency-shift readout system is realized by a standard 0.18 μm CMOS technology.

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II. Flexural plate-wave (FPW) characteristics

The acoustic wave in FPW devices propagates in a very thin plate whose thickness is much less than the wavelength. The acoustic energy is present on both sides of the plate such that the entire plate undergoes mechanical deformation. Hence, the confinement of acoustic energy in such thin membranes results in a very high mass sensitivity. A typical layout diagram of FPW device designed in this work is shown in Fig. 1. The two-port FPW biosensor is composed of the Cr/Au-based inter-digital transducers (IDTs) to be a Tx (transmitter) and a Rx (receiver), which are, respectively, placed on the right and left side of the thin plate. Referring to [4], the operating frequency, f_0, of the FPW sensor for a given wavelength is low, because of the following feature,

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

where λ represents the acoustic wavelength decided by the IDT period and V_p is the phase velocity of the FPW. The mass loading of the floating thin plate which causes changes in an operating frequency is governed by the following equation,

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

where Δf denotes 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 device. C_p is the surface concentration of the absorptive molecules and MW is the molecular weight. Therefore, Δf can be changed by C_p, namely the CEA concentration.

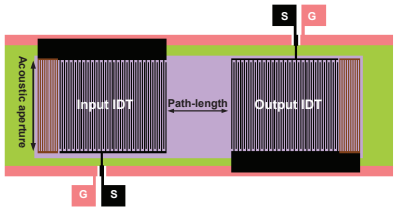

Fig. 1. Layout diagram of presented FPW device.

III. Frequency-Shift Readout Circuit Design

Referring to Fig. 2, the CEA concentration measurement system is composed of several subsystems: a programmable frequency generator, FPW biosensors and peak detectors. A sine wave frequency generator is required to drive the FPW biosensors in the pre-defined frequency range to find out their corresponding resonant frequencies. The two FPW sensors are called Sensor1 (Experimental group, with antigen) and Sensor2 (Control group, without antigen) in Fig. 2. By calculating the difference between resonant frequencies of Sensor1 and Sensor2 which are detected by Peak detector1 and Peak detector2, respectively, the frequency-shift amount (Δf) is attained such that the amount of the CEA reagents (or serum volume) concentration can be estimated. Notably, subtractor in Fig. 2 is the same as the corresponding subtractor in our previous work [5]. The details of the other function blocks are described as follows.

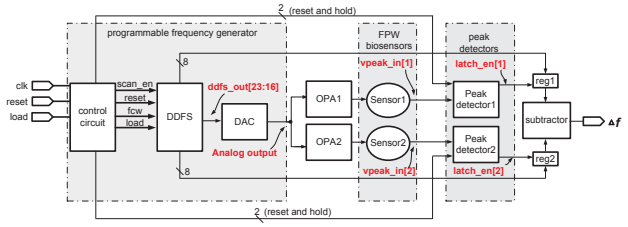

Fig. 2. Architecture of the frequency-shift readout system.

A. Programmable frequency generator

The programable frequency generator in Fig. 3 takes advantage of the direct digital frequency synthesizer (DDFS). It is composed of a phase accumulator, two complementors (1's complementor and amplitude complementor) a polynomial accumulate processer, and a digital to analog converter (DAC). A complete sinusoid can be determined by using quadrant symmetry. This approach replaces conventional ROM-based methods with a DAC to generate the sinusoid [6]. When the 50 MHz clock signal, clk, drives the system, the frequency control word (fcw) is used to accumulate the digital phase count at each clock cycle. The phase accumulator is used to translate the fcw into j-bit signals for the other blocks. The two highest most significant bits (MSB) of the phase accumulator output are used to address the quarter-wave symmetry. The most significant bit (1st MSB) and second significant bit (2nd MSB) from the output of the phase accumulator are used as upper-down symmetry and left-right control signals, respectively. Therefore, other digital codes, j-2 bits, are used to synthesize the sine wave. Besides, the scan_en from the control circuit is used to start DDFS. When scan_en = 1, the input signal, "load", is used to load the data external. The samples of the sine wave amplitude are generated by the parabolic polynomial interpolation method of the phase-to-sin mapper. The 8-bit DAC is a typical current-steering structure, where 8 current sources with binary-weighted sizes instead of $2^8 - 1$ sources are used. The frequency range of the programmable frequency generator output is from 0.9 to 25 MHz base on the characteristics of the FPW biosensors.

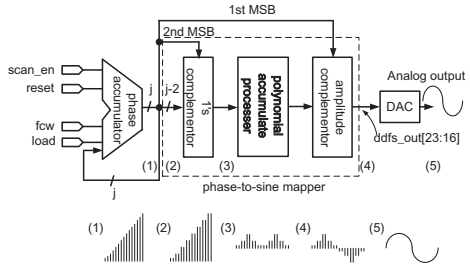

Fig. 3. Programmable frequency generator [6].

B. Peak detector

The frequency-shift readout circuit needs to filter and amplify the signal delivered from FPW biosensors such that the correct resonant frequency can be detected. As shown in Fig. 4, the proposed peak detector is composed of 3 stages, including filter stage, gain stage and compare stage. The FPW biosensor's output signal, vpeak_in[i], i= 1 or 2, is coupled to C31 such that the DC term is filtered to generate a high-frequency term, VIN. A unit gain buffer, UNI_1, is needed to keep VIN isolated from the loading effect caused by the following 8th order VCVS low pass filter (LPF). The design of the 8 order voltage-controlled voltage source (VCVS) low pass filter is based on a typical LPF design [7], which rejects high-frequency AC noise. The high-gain non-inverting amplifier OPA3 amplifies the filtered signal and sends to the following compare stage. The compare stage is in charge of sampling and holding the maximum voltage peak of the filtered and amplified signal, V_new. Notably, the circuits of Peak detector1 and Peak detector2 are the same. Besides, reset and hold signals are notified by the control circuit. The detailed steps of the compare stage are explained as follows.

- Step 1: Initially, "hold" is low and reset is pulled high to discharge C1 and D flip-flop.
- Step 2: After SW_1 is on, V_new is couple to VPEAK1. "hold" is still kept low to carry out the sample mode. If VPEAK1 is higher than VPEAK2, SW_1 and SW_2 will be turned on. Then, OPA4 triggers the D flip-flop to pull high latch_en1. Hence, C1 is charged.
- Step 3: When VPEAK2, namely voltage of C1, is equal to VPEAK1 and "hold" is pulled up high, the circuit enters the hold mode. SW_2 will be turned off to keep

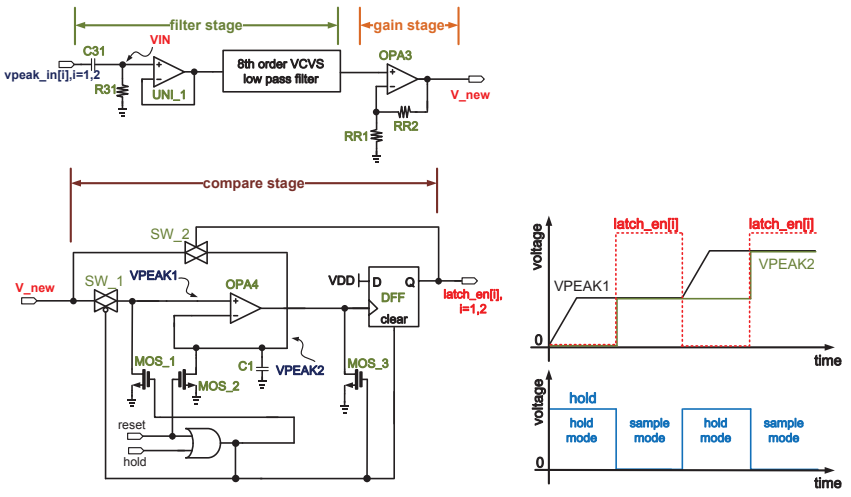

Fig. 4. Schematic of the peak detector and sample and hold illustration.

the currently highest peak voltage. In other words, when the V_new is higher than the previously stored voltage, latch_en1 is pull high. By contrast, when the V_new is lower than the previously stored voltage in C1, latch_en1 is kept low.

By the above steps, the peak detectors can generate the enable signals, latch_en[i] (i= 1 or 2 in Fig. 2), to enable the registers (reg1 or reg2 in Fig. 2), respectively, and store the frequency count from DDFS. Therefore, the resonant frequencies of the FPW biosensors are stored by corresponding peak detectors. The frequency-shift variation, $\triangle$f, can be derived by the subtractor with these two frequency counts.

C. OPA design

All of the operational amplifiers in previously mentioned schematics, including OPA1 and OPA1 in Fig. 2, UNI_1, OPA3, OPA4 in Fig. 4 are all the same. They are implemented using full-swing operational amplifier in Fig. 5. In the middle of Fig. 5, a folded-cascode stack is used to increase the output impedance. The class AB output buffer at the right most isolates the loading effect and provides a large current for driving a large load. All of required biases in Fig. 5 are provided by the beta-multiplier reference circuit in Fig. 6, and the bias generator in Fig. 7. Referring to Fig. 6, M3_5 $\sim$ M3_8 consists a differential amplifier to force the drain of M3_4 and M3_10 at the same potential such that the same current is forced through each side of the reference. M3_0 $\sim$ M3_3 consist of a startup circuit. A stable bias voltage Vx is then generated and coupled to the bias generator circuit in Fig. 7 to generate the biases, including $V_{bias1} \sim V_{bias4}$, V_{pcas}, and V_{ncas}.

IV. Implementation and Simulation Results

TSMC (Taiwan Semiconductor Manufacturing Company) 1P6M 0.18 μm CMOS process is adopted to carry out the proposed frequency-shift readout circuit. Referring to the layout in Fig. 8, the chip area is 1603 μm $\times$ 1572 μm.

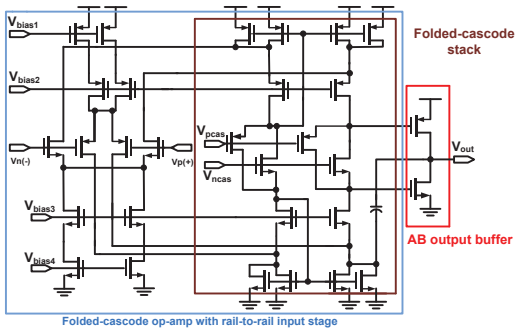

Fig. 5. Schematic of the full swing operational amplifier.

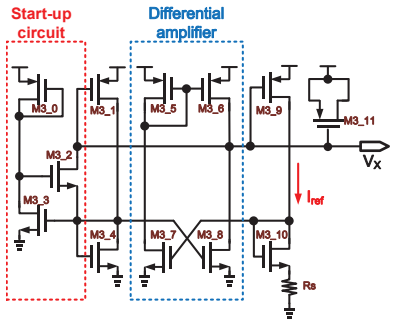

Fig. 6. Schematic of the beta-multiplier reference circuit.

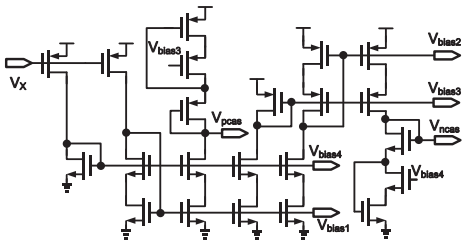

Fig. 7. Schematic of the bias generator.

Fig. 9 shows the simulation waveforms of the peak detector operating at 0.1 MHz FPW biosensor frequency, where the sensitivity of the peak detector is 5 mV. To investigate the peak detector performance at a high frequency, Fig. 10 shows the simulation waveforms of the peak detector operated at 50 MHz. The sensitivity of the peak detector is also 5 mV. Table I shows a comparison of this work and several recent works. The proposed design demonstrates the best performance and regard to sensitivity and operating frequency. Besides, the proposed design attains the best Figure-of-merit (FOM), where FOM = $\frac{\text{Sensitivity}}{\text{Operating frequency}}$.

TABLE I
COMPARISON WITH PRIOR WORK

	proposed	[8]	[5]
Year	2013	2010	2012
Power supply (V)	1.8	3.3	1.8
Process (μm)	0.18	0.35	0.18
Operating Freq. (MHz)	50	5	10
Sensitivity (mV)	5	8.4	10
Power (mW)	7.69	0.55	1.59
FOM (%)	0.1	1.68	1

† FOM = $\frac{\text{Sensitivity (mV)}}{\text{Operating Freq.}}$.

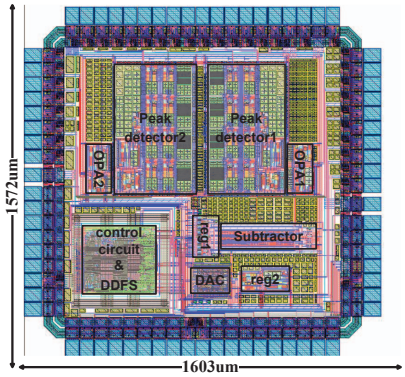

Fig. 8. Layout of the frequency-shift readout circuit.

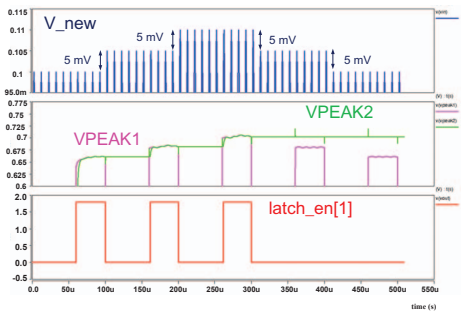

Fig. 9. Simulation of the peak detector with FPW biosensor frequency at 0.1 MHz.

V. CONCLUSION

This paper presents a CEA concentration measurement system composed of the frequency-shift readout circuit and the FPW biosensors. By replacing the conventional power MOS with full-swing rail-to-rail amplifiers and the low pass filter, the sensitivity has improved to 5 mV. Besides, the range of the FPW frequency is enlarge to 50 MHz such that the frequency-shift amount of the FPW biosensors is able to be accurately detected.

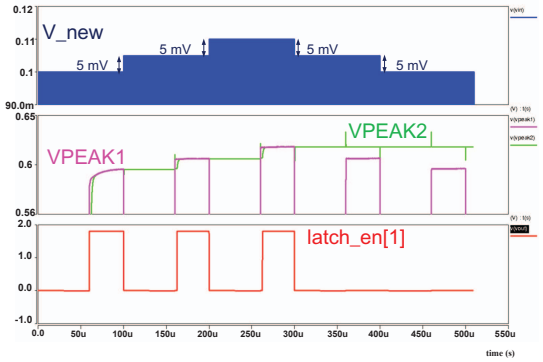

Fig. 10. Simulation of the peak detector with FPW biosensor frequency at 50 MHz.

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