

A Fast CEA Analyzer Prototype for Point of Care Testing

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Abstract – A CEA (carcinoembryonic antigen) concentration analyzer prototype using a pair of two-port FPW (flexural plate-wave) sensors is proposed in this paper. The proposed prototype utilizes a frequency-shift readout method based upon a peak detecting scheme to measure the resonant frequency shift. The frequency-shift readout circuit is integrated on silicon composed of a linear frequency generator, two peak detectors, two registers, and a subtractor. The frequency scanning range is from 0.9 MHz to 22.4 MHz according to the characteristics of the FPW biosensor. The sensitivity of the peak detector is 5 mV. The proposed frequency-shift readout circuit is verified by a PCB-based prototype, where the CEA serum titration is stabilized after 10 minutes and the linearity of the concentration vs. frequency shift is 97.72%.

Key word: CEA measurement, frequency-shift readout circuit, FPW, resonant frequency, point of care testing (POCT).

I. INTRODUCTION

565,650 USA citizens died in 2008 because of cancers, while 1,437,180 new cancer cases were found in the same year. Cancer has become the top 2nd cause of death for years. In human serum, the concentration of CEA, which is an important tumor marker for various cancers, including colorectal cancer, cervical cancer, carcinoma of the rectum, etc. It has been recognized as a critical indicator to show the stake of cancers [1]. Many commercial CEA or tumor marker measurement instruments are available, e.g., enzymelinked immunosorbent assay (ELISA) [2], and radioimmunoassay (RIA) [3], etc. Unfortunately, these commercial tumor marker measurement devices require multifarious testing samples, long operation time for sampling analysis procedures, expensive analysis instruments, and lot of analysts. They are mainly available in large hospitals rather than clinics, let alone home usage. To reduce and even prevent the stake of cancers, “cancer screening” is by far now more demanding than traditional “disease progression”. Namely, POCT (point of care testing) is the trend of future medicare [4]. Therefore, a low cost, fast, and accurate tumor marker measurement device for clinic level usage, or even home usage, is very much needed.

A two-port biosensor based on an ultrasonic flexural plate-wave (FPW) technique was proposed in [5], [6]. The FPW biosensor consists of Cr/Au interdigital transducers (IDTs), where cystaminie-glutaraldehyde is coated on the surface such

that it is able to catch CEA and make a bond therewith. Notably, the resonant frequency of the FPW biosensor is roughly anti-proportional to the CEA concentration. In this investigation, a frequency-shift readout system for the two-port FPW biosensor is presented to reduce the operation time and overall cost. According to the resonant basics, the output signal amplitude of the FPW biosensor will be maximum when the input frequency meets the central resonant frequency. Therefore, a high sensitive peak detector is needed to detect the maximum peak voltage and generate an enable signal to snapshot the resonant frequency. By calculating the difference between resonant frequencies of Sensor 1 (with CEA) and Sensor 2 (without CEA), the frequency-shift amount is attained such that the CEA concentration is derived.

II. FREQUENCY-SHIFT READOUT SYSTEM

The FPW biosensor propagates an acoustic wave via a mechanical thin plate [5]. We use FPW Sensor 1 to be the experimental group, while FPW Sensor 2 is the control group. Fig. 1 shows the conceptual diagram of the proposed system. Human blood drop will be placed at the hole of the serum separation micro-fluidic channel to drive the serum flowing into the cavity of Sensor 1, while Sensor 2 remains empty to serve as the base of CEA concentration measurement.

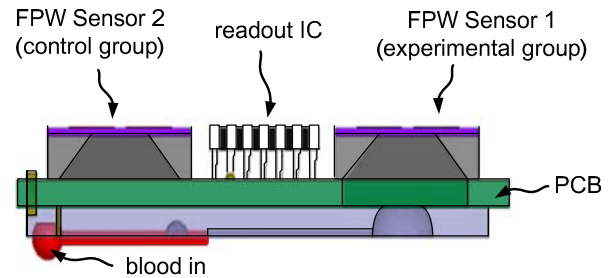


Fig. 1 Conceptual architecture of the proposed system

Fig. 2 shows all the function blocks of the readout circuit, including a Linear frequency generator, a pair of Peak detectors, two registers (reg), and a Subtractor, are all carried out on silicon. Linear frequency generator is composed of an 8-bit digital counter, an 8-bit digital-to-analog converter (DAC), and an operational transimpedance amplifier (OTA-C). The counter generates 0 to 256 up counting signal to DAC, which is based on a typical current-steering design to generate an appropriate potential to drive the following OPA (operational amplifier). The frequency scanning range of Linear frequency generator is from 0.9 to 22.4 MHz, covering the frequency variation range of the FPW biosensor (16 – 19 MHz). The generated sinusoidal signal with increasing frequency is then fed into the FPW biosensors, i.e., Sensor 1 and Sensor 2.

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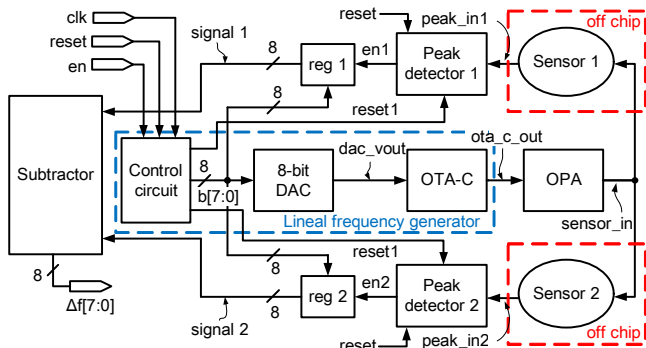


Fig. 2 Block diagram of the proposed analyzer

The output signal of the FPW biosensor will reach its peak value when the input frequency equals to the resonant frequency thereof. A pair of peak detectors are used to detect the maximum peak from the FPW biosensors' outputs and generate the enable signals, en1 or en2, to the reg 1 and reg 2, respectively, to store the corresponding counts of the 8-bit digital counter. Finally, the difference between the counts stored in reg 1 and reg 2 is calculated by the Subtractor to attain Δf , which will be used to table-look CEA concentration reading.

III. IMPLEMENTATION & MEASUREMENT

Fig. 3 shows the proposed FPW CEA analyzer prototype system. Notably, the proposed frequency-shift readout circuit for FPW biosensors is realized on silicon by standard 0.18 μm CMOS technology. The CEA concentrations under test are 0, 30, 100, 300 ng/ml. Fig. 4 shows the measured resonant frequencies, where the frequency of each readout signal is stabilized after 10 minutes regardless the testing concentration. The corresponding frequencies are tabulated in Table I. By using the MSE (minimal square error) method to derive the theoretical straight line, the derived equation is as follows.

$$y = -3.7745 \cdot x + 17991$$

Then the linearity of the concentration vs. frequency is 97.72%, which is superior to that in [4].

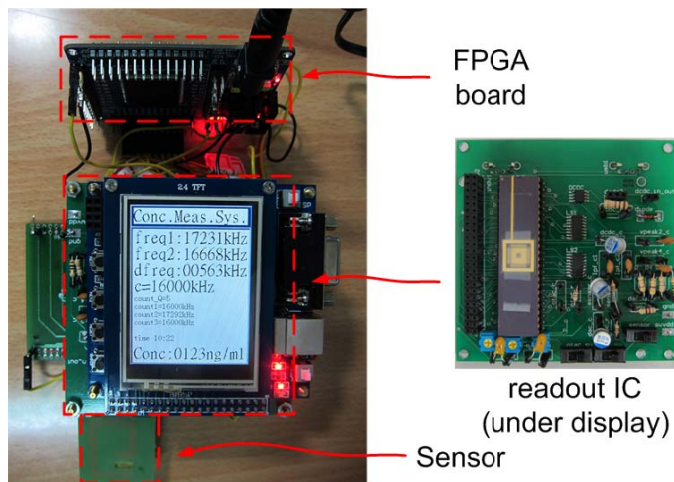


Fig. 3 CEA analyzer prototype

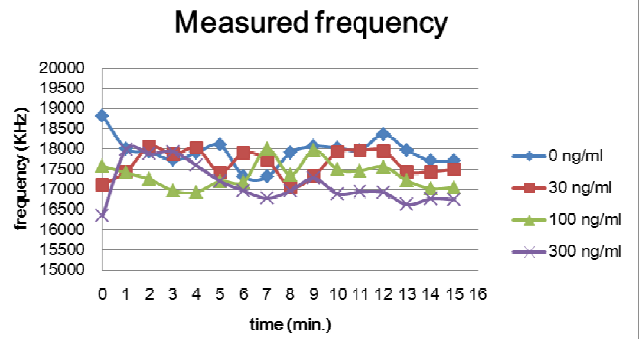


Fig. 4 Measured frequency

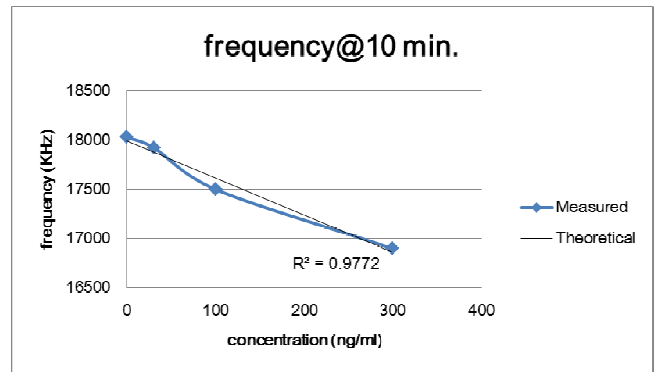


Fig. 5 Linearity of concentration vs. resonant frequency

TABLE I
READINGS OF RESONANT FREQUENCY

CEA concentration (ng/ml)	Measured Freq. (MHz)	Theoretical Freq. (MHz)
0	18.028	17.991
30	17.923	17.877
100	17.497	17.613
300	16.893	16.858

REFERENCES

- [1] A. Liang, C. Jiang, and Z. Jiang, "Resonance scattering spectral detection of ultratrace CEA using immunonanogold-VC-HAuCl₄ catalytic reaction," *2010 4th International Conference on Bioinformatics and Biomedical Engineering (iCBBE)*, pp. 1-4, June 2010.
- [2] R. M. Lequin, "Enzyme Immunoassay (EIA)/Enzyme-Linked Immunosorbent Assay (ELISA)," *Clinical Chemistry*, vol. 51, no. 12, pp. 2415-2418, Sep. 2005.
- [3] M. E. Goldberg and L. Djavadi-Ohanian, "Methods for measurement of antibody/antigen affinity based on ELISA and RIA," *Current Opinion in Immunology*, vol. 5, no. 2, pp. 278-281, 1993.
- [4] C.-H. Hsu, Y.-D. Tsai, Y.-C. Chen, M.-C. Lee, I.-Y. Huang, and C.-C. Wang, "A fast FPW allergy analyzer prototype for point of care (POC)," *2012 IEEE Inter. Conf. on Consumer Electronics*, pp. 544-545, Jan. 2012.
- [5] I.-Y. Huang and M.-C. Lee, "Development of a FPW allergy biosensor for human IgE detection by MEMS and cystamine-based SAM technologies," *Sensors and Actuators B: Chemical*, vol. 132, no. 1, pp. 340-348, May 2008.
- [6] W.-Y. Chang, P.-H. Sung, C.-H. Chu, C.-J. Shih, and Y.-C. Lin, "Phase Detection of the Two-Port FPW Sensor for Biosensing," *IEEE Sensors Journal*, vol. 8, no. 5, pp. 501-507, May 2008.