

Impedance Estimation Read-out System for Biomedical Sensors

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Abstract. An impedance estimation read-out system for biomedical sensors to detect cancer biomarkers using TSMC 0.18 μm mixed signal CMOS process is proposed in this investigation. Without disadvantages such as long detection time, and high cost of conventional methods, this system integrates bio-electrical impedance analysis (BIA) technique with a read-out system is a solution of high accuracy of the least impedance ($< 0.292\%$) and phase error ($< 0.1\%$) in the widest frequency range (10 Hz – 2 MHz).

Keywords: impedance estimation, biomedical sensor, read-out system, BIA, tumor marker, ELISA, RIA.

1. Introduction

Cancer is one of the top causes for death in modern society. More and more people are suffered from cancer than ever. However, according to the research of biomedical immunity society, cancer can be detected from human blood or urine by sensing the concentration of tumor markers. Tumor markers, e.g., CEA, PSA, AFP, ALP, are all proteins generated from the cells in human bodies, regardless the cells are normal or not. Therefore, detecting the concentration of specific tumor marker is the first step of curing. Today, two main methods to detect tumor marker concentration are ‘Enzyme linked immune-sorbent assay’ (ELISA) [1-4] and ‘Radioimmunoassay’ (RIA) [5-7]. These two methods are based on optical theory, which have some issues on reagents consumption ($> 25\ \mu\text{L}/\text{well}$), long detection (120-150 min), and cost ($> \text{NT } 300,000$). By contrast, ‘Bio-electrical impedance analysis’ (BIA) [8] is a better solution to attain real-time, low cost, low reagents consumption, and portable analysis, where BIA relies on the detection of electrical characteristics (impedance, admittance, phase, and frequency response) of biomedical sensors. Besides, the read-out system for BIA technique is needed, which will be disclosed below.

2. Impedance Estimation Read-out System Design

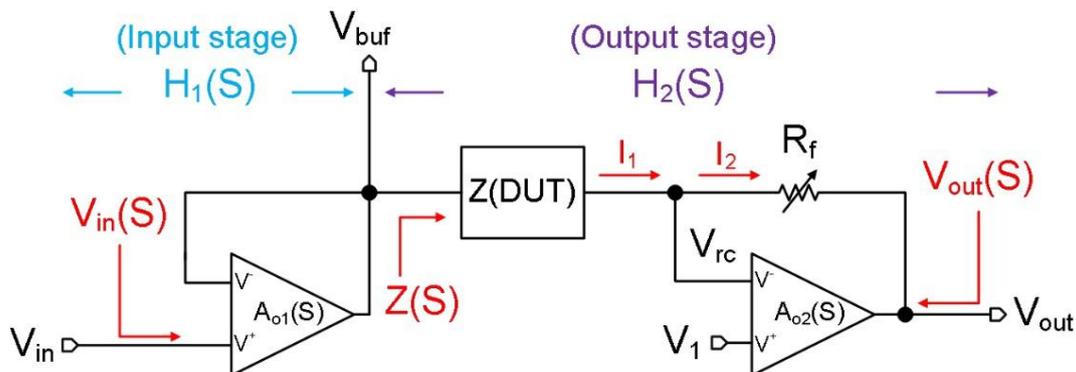


Fig. 1: Block diagram of proposed impedance estimation read-out system.

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2.1. Overall circuit

Fig. 1 shows the block diagram of the proposed impedance estimation read-out system, consisting of 2 OPAs, 1 VR (Variable Resistor, R_f), and 1 DUT (Device Under Test). V_{in} is the input sinusoid testing signal with various frequency and 2 V amplitude. OPA1 is a unit gain buffer, which provides high input impedance and low output impedance to reject the loading effect from the testing signal. DUT is the biosensor, where its impedance will be changed according to the frequency of the input signal. As for R_f , it will be a variable resistor to make V_{out} adjustable in Output stage (inverting amplifier) to avoid distortion.

The transfer function of $H_1(S)$ and $H_2(S)$ are derived in Eqn. (1) and Eqn. (2), where $A_{o1}(S)$ and $A_{o2}(S)$ are the open-loop gains of OPA1 and OPA2, respectively. Therefore, the transfer function of the overall system is summarized in Eqn. (3). Then, as $A_{o1}(S)$ and $A_{o2}(S)$ are far greater than 1, the frequency response of DUT can be simplified as Eqn. (4). As we can see the last part of Eqn. (4), which is the major error of the system, can be ignored when $A_{o2}(S)$ is far greater than R_f . However, according to the bode plot of OPA, the error will increase when it comes to high frequency region. On the other hand, high gain will lead to limited bandwidth, which is also a key factor to be considered in designing such a system. Therefore, only OPA with appropriate gain and bandwidth can achieve the minimum error in the designated frequency region of the selected sensors.

$$H_1(S) = \frac{V_{buf}(S)}{V_{in}(S)} = \frac{A_{o1}(S)}{1 + A_{o1}(S) \times \beta_1(S)}; \beta_1(S) = 1 \quad (1)$$

$$H_2(S) = \frac{V_{out}(S)}{V_{buf}(S)} = (-1) \times \frac{A_{o2}(S) \times R_f}{Z(S) + R_f + A_{o2}(S) \times Z(S)} \quad (2)$$

$$\frac{V_{out}(S)}{V_{in}(S)} = H_1(S) \times H_2(S) = (-1) \times \frac{A_{o1}(S) \times A_{o2}(S) \times R_f}{[1 + A_{o1}(S) \times \beta_1(S)] \times [Z(S) + R_f + A_{o2}(S) \times Z(S)]} \quad (3)$$

$$Z(S) = (-1) \times \frac{V_{in}(S) \times A_{o1}(S) \times A_{o2}(S) \times R_f}{A_{o1}(S) \times A_{o2}(S) \times V_{out}(S)} - \frac{R_f}{A_{o2}(S)} \quad (4)$$

2.2. DUT and RC equivalent circuit

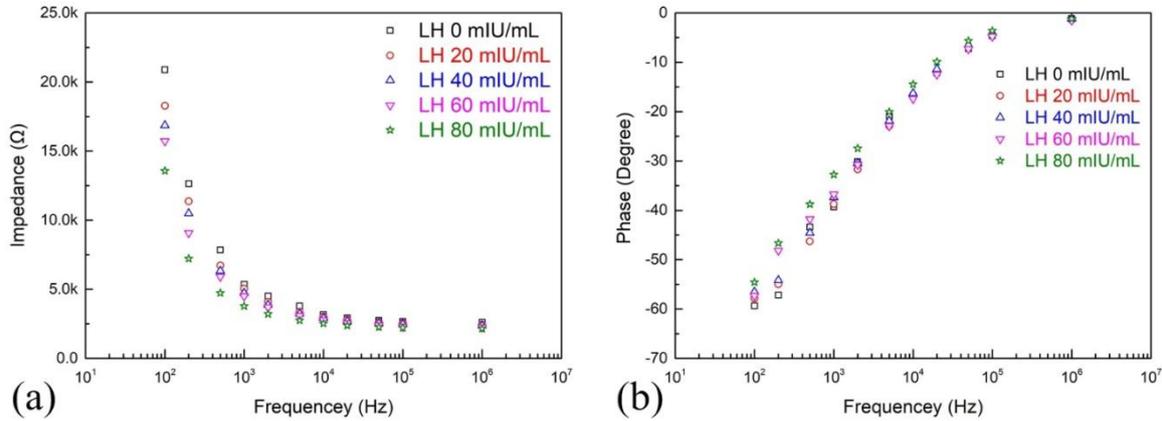


Fig. 2: (a) Impedance and; (b) phase analysis with various concentration by LCR meter.

Referring to Fig. 2 (a) and (b), it shows the measured results of impedance and phase by an LCR meter. This bio-sensor demonstrates different characteristics when various Luteinizing hormone (LH) concentrations are used. As for the impedance, it shows negative correlation with frequency, while the phase shows positive correlation with frequency on the contrary. Notably, the above test performs with designated frequency region from 100 Hz to 1 MHz.

However, in the circuit design step, an equivalent RC circuit is needed to establish the system. Therefore, as shown in Fig. 3 (a), a 3rd-order RC model is used to mimic the characteristic when LH concentration is 0 mIU/mL. The ideal impedance and phase of RC model is depicted in the red line of Fig. 3 (b), where the black line is the statistic of 0 mIU/mL for comparison. Notably, the aim of the RC model is to set up testing environment for the read-out system, but not the similarity between the RC model and the measurement results.

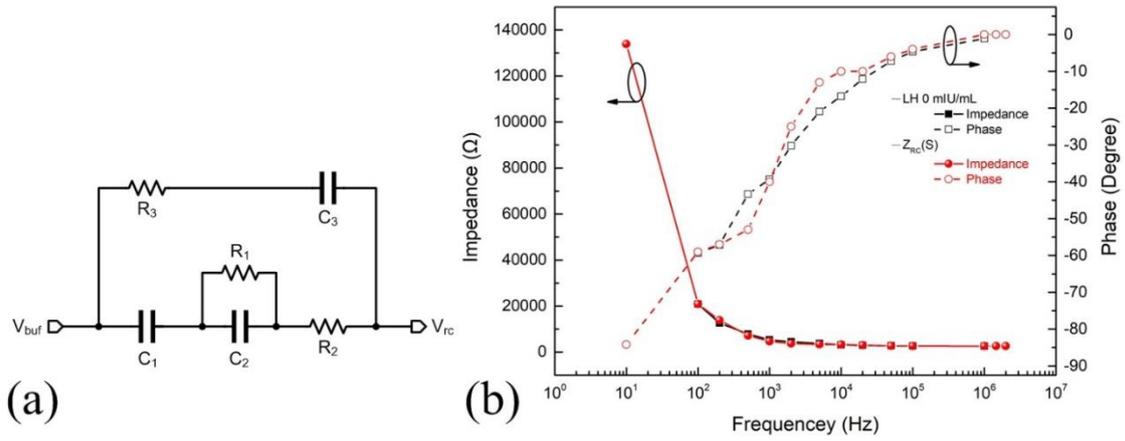


Fig. 3: (a) RC equivalent circuit, and (b) electrical characteristic comparison.

3. Simulation Results

In our system simulations, the designated frequency region is enlarged (10 Hz to 2 MHz) to ensure the reliability. Table I shows the worst case pre-layout and post-layout performance of the OPA. The worst case is at 2.97 V, SS corner, and 0 °C.

Table 1: OPA performance in pre_layout and post_layout simulation

	SR (V/us)	DC gain (dB)	Phase margin (degree)	GBW (MHz)	Output swing (V)	Input swing (V)	Max. power (mW)
Pre-layout simulation	34.96	73.06	63.92	273.3	0.195 – 3.047	0.253 – 3.263	8.608 @ 2 MHz
Post-layout simulation	30.59	73.53	55.75	262.0	0.185 – 3.061	0.252 – 3.241	7.653 @ 2 MHz

The overall system simulations are revealed and tabulated in Fig. 4 and Table II. Referring to Fig. 4, black line is the ideal frequency response of the RC model. Red line and blue line are the results of pre-layout and post-layout simulations, respectively. Table II tabulates the statistics and error of each frequency simulation. The worst case is at 2.97 V, SS corner, and 0 °C.

The proposed impedance calculation read-out system is realized using TSMC 0.18 μm mixed signal CMOS process. Fig. 5 shows the layout of this prototype system on silicon, where the overall chip size is 758×563 μm². Table III is the comparison with some prior works. Our work attains the widest frequency range, the least impedance and phase error.

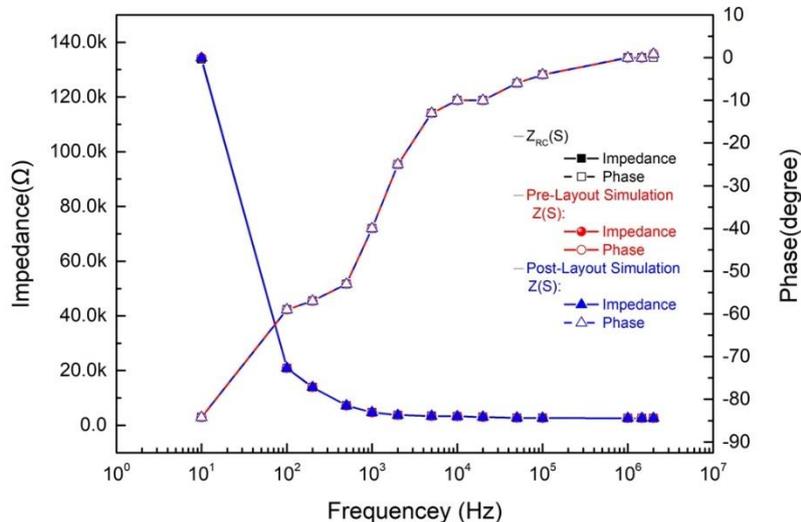


Fig. 4: Overall simulation results.

Table 2: Overall simulation results

Frequency (Hz)		Pre-layout simulation	Post-layout simulation	Worst-case error	
	$Z_{RC}(S)$ (k Ω)	$Z(S)$ (k Ω)	$Z(S)$ (k Ω)	Impedance (%)	Phase (%)
10	133.868 \angle -84.2 $^\circ$	134.205 \angle -84.2 $^\circ$	134.205 \angle -84.2 $^\circ$	0.251	0
100	20.876 \angle -59 $^\circ$	20.936 \angle -59 $^\circ$	20.936 \angle -59 $^\circ$	0.287	0
200	13.888 \angle -57 $^\circ$	13.920 \angle -57 $^\circ$	13.920 \angle -57 $^\circ$	0.230	0
500	7.194 \angle -53 $^\circ$	7.189 \angle -53 $^\circ$	7.189 \angle -53 $^\circ$	0.069	0
1k	4.694 \angle -40 $^\circ$	4.698 \angle -40 $^\circ$	4.698 \angle -40 $^\circ$	0.085	0
2k	3.731 \angle -40 $^\circ$	3.738 \angle -25 $^\circ$	3.738 \angle -25 $^\circ$	0.187	0
5k	3.389 \angle -13 $^\circ$	3.389 \angle -13 $^\circ$	3.389 \angle -13 $^\circ$	0	0
10k	3.246 \angle -10 $^\circ$	3.246 \angle -10 $^\circ$	3.246 \angle -10 $^\circ$	0	0
20k	3.021 \angle -10 $^\circ$	3.025 \angle -10 $^\circ$	3.025 \angle -10 $^\circ$	0.132	0
50k	2.732 \angle -6 $^\circ$	2.740 \angle -6 $^\circ$	2.740 \angle -6 $^\circ$	0.292	0
100k	2.652 \angle -4 $^\circ$	2.651 \angle -4 $^\circ$	2.651 \angle -4 $^\circ$	0.037	0
1M	2.617 \angle 0 $^\circ$	2.622 \angle -0.06 $^\circ$	2.622 \angle -0.06 $^\circ$	0.191	N/A
1.58M	2.617 \angle 0 $^\circ$	2.619 \angle -0.10 $^\circ$	2.622 \angle 0.89 $^\circ$	0.191	N/A
2M	2.617 \angle 0 $^\circ$	2.619 \angle 0.87 $^\circ$	2.619 \angle 0.86 $^\circ$	0.076	N/A

Error = $(Z(S) - Z_{RC}(S)) / Z_{RC}(S)$

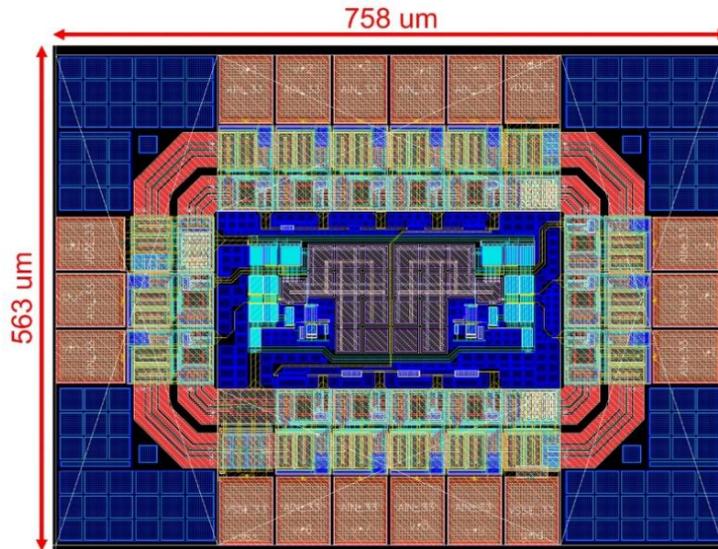


Fig. 5: Layout of the proposed read-out system.

4. Conclusions

This paper has demonstrated an impedance estimation read-out system with the widest frequency region, the least impedance and phase error, which is justified by Table III [9-11]. By integrating BIA technique with the read-out IC system, we find a better, more reliable, and quicker solution on rapid diagnostic test on cancer biomarkers. Notably, the investigation was partially supported by Ministry of Science and Technology, Taiwan, under grant MOST 106-2221-E-110-065- and MOST 106-2221-E-110-058-. The authors would like to express our deepest gratitude to CIC (Chip Implementation Center) in Taiwan, for the assistance of thoughtful chip fabrication.

Table 3: Performance comparison

	[9]	[10]	[11]	This work
Year	2015	2012	2010	2018
Publication	Journal Sensors and Actuator B: Chemical	Journal Computers and Electronics in Agriculture	Journal Microelectronics	
Implementation	Measurement	Measurement	Simulation	Simulation
Valid frequency region (Hz)	100 – 1M	100 – 1M	100 – 1M	10 – 2M
Impedance error	< 250 Ω (Eye Meas.)	< 4.96 %	< 3.68 k Ω	< 0.292 % (8 Ω)
Phase error	< 10° (Eye Meas.)	< 2.94°	< 8.28°	< 0.89°

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