Printed Organic Transistor-Based Impedance Biosensor

Authors: Qi Huang, Kai Jin, Yukun Huang, Zhe Liu, Linrun Feng, Xiaojun Guo, Hanbin Ma, Hanbin Ma

Date: 2020-04-05T00:00:00+00:00

Abstract

Electrochemical impedance biosensors measure impedance variations in solution during biochemical processes, thereby enabling label-free biological detection. However, the biological signals to be detected are extremely weak, thus necessitating signal amplification circuitry. Printed organic thin-film transistors (OTFTs) exhibit numerous advantages, including low cost, mechanical flexibility, and biocompatibility, rendering them suitable for biological detection. In this study, an amplification circuit for electrochemical impedance testing was developed based on OTFTs, and test samples comprising phosphate buffer solution (PBS) at various concentrations were measured using the aforementioned circuit. The results demonstrate that the OTFT-based circuit effectively achieves signal amplification, thereby establishing a foundation for the application of printed OTFTs in electrochemical impedance biosensors.

Full Text

Printed Organic Transistor-Based Impedance Biosensor

Qi Huang[1,†], Kai Jin[1,†], Yukun Huang[2], Zhe Liu[3], Linrun Feng[3], Xiaojun Guo[2], and Hanbin Ma[1,*]

[1] CAS Key Laboratory of Bio-Medical Diagnostics, Suzhou Institute of Biomedical Engineering and Technology, Chinese Academy of Sciences, Suzhou, 215163, China; huangqi@sibet.ac.cn (Q.H.); kj902@acxel.com.cn (K.J.)

[2] Department of Electronic Engineering, Shanghai Jiao Tong University, Shanghai, China; x.guo@sjtu.edu.cn (X.G.); wjh1056@sjtu.edu.cn (Y.H.)

[3] Hangzhou LinkZill Technology Co., Ltd., Hangzhou, China; linrun.feng@linkzill.com (L.F.); zhe.liu@linkzill.com (Z.L.)

† These authors contributed equally to this work.

- Author to whom correspondence should be addressed; mahb@sibet.ac.cn; Tel.: +86-512-6958-8081; Fax: +86-512-6958-8081.

Abstract

Electrochemical impedance biosensors measure impedance variations in solution during biochemical processes, enabling label-free biological detection. However, the biological signals to be detected are typically very weak, necessitating signal amplification circuitry. Printed organic thin-film transistors (OTFTs) offer numerous advantages including low cost, mechanical flexibility, and biocompatibility, making them well-suited for biological sensing applications. This work demonstrates an amplification circuit for electrochemical impedance testing based on OTFT technology. Different concentrations of phosphate buffer solution (PBS) were measured using this circuit. The results show that the OTFT-based circuit effectively amplifies signals, establishing a foundation for the application of printed OTFTs in electrochemical impedance biosensors.

Keywords: electrochemical impedance biosensors; OTFT; impedance testing; signal amplification circuit

1. Introduction

With advances in biological detection technology, biosensors such as bioluminescent sensors are trending toward higher sensitivity, selectivity, and stability [1]. These fluorescence-based biosensors can be specifically designed for various applications including clinical medicine, food safety, and environmental testing. However, for rapid diagnostics and point-of-care (PoC) applications, sensor cost and user-friendly operation become increasingly important considerations, provided that basic detection requirements are met. Meanwhile, due to the complexity and cumbersome operation of existing optical immunosensor systems, it is difficult to satisfy the demand for convenient and rapid detection in everyday applications such as food bacteria and pesticide residue testing [2]. Reducing the size and operational complexity of sensing systems represents an urgent challenge.

Electrochemical impedance testing analyzes electrode process dynamics, double-layer effects, and diffusion phenomena by measuring impedance changes across sine wave frequencies. When applied as a biosensor, sample characteristics can be directly assessed through the trend and magnitude of impedance changes at the interface between biological electrodes and samples [3]. Electrochemical biosensors feature simple structures and enable label-free analysis, attracting growing attention in the biological detection field worldwide [4-7]. Researchers have successfully applied impedance testing to major biological detection areas including cells [8], proteins [9,10], and nucleic acids [11]. However, mainstream bioimpedance testing relies on large benchtop electrochemical analyzers or impedance test boards with metal electrodes. The measured signals must travel through long wires and various connection interfaces before reaching the signal amplifier and back-end impedance analysis circuit. The parasitic noise introduced by this transmission path significantly affects the accuracy and repeatability of biological tests. Consequently, increasing research teams are focusing on the miniaturization and integration of impedance biosensors. The Andreas Demosthenous team at University College London developed a programmable wideband impedance sensor chip with high integration using complementary metal-oxide-semiconductor (CMOS) technology [12], while Arjang Hassibi' s team at the University of Texas at Austin integrated a biological functionalization electrode array into a CMOS impedance chip and demonstrated DNA sequencing using an impedance test array [13]. Nevertheless, CMOS-integrated biochips fail to meet market expectations for manufacturing cost and detection throughput of biosensors such as immunosensors. Since metals suitable for traditional CMOS processes are primarily non-biological materials like aluminum and copper, integrating gold and other biological functionalization electrodes into CMOS chips requires additional processing steps, increasing both complexity and cost. Furthermore, while the main advantage of CMOS technology is high integration—which reduces chip size and cost—electrochemical electrodes must maintain a certain size to ensure successful biological functionalization and fault tolerance. In practical applications, increasing the number of electrodes for multi-channel, high-throughput array detection is often desired, which contradicts the traditional CMOS integrated circuit (IC) design philosophy of making devices smaller and more precise.

Thin-film electronic devices have been widely applied in large-area flat panel displays, photovoltaics [14], and flexible/wearable electronics [15,16]. Printed electronics fabricates electronic devices by depositing different materials onto substrates using printing technology. As an important branch of large-area electronic circuits, printed electronics has attracted attention across various fields due to its ultra-low fabrication threshold and low cost. In recent years, the performance of printed electronic devices has advanced rapidly, particularly regarding the stability and functionality of inkjet-printed thin-film transistors [17], which now possess the capability for further integration and system-level functionality. In 2016, Tse Nga Ng' s team at the University of California, San Diego successfully fabricated a readout circuit for ferroelectric memory capacitors using printed organic thin-film transistors [18]. Also in 2016, the Sungjune Jung team at POSTECH in South Korea and the Shizuo Tokito team at Yamagata University in Japan jointly reported a circuit composed of nine 3D NAND gates integrated using inkjet-printed thin-film electronic devices [19]. Additionally, specific sensors and systems based on printed OTFTs have been reported in recent years [20-22].

In summary, with the goal of achieving portable biosensor testing, this work applies printed OTFTs to electrochemical impedance biosensors. The label-free electrochemical impedance method significantly reduces the structural complexity of fluorescence-based biosensors, while combining this approach with large-area printed electronic device manufacturing technology reduces the fabrication difficulty of impedance sensors. An amplification circuit for electrochemical impedance testing was built using OTFTs, with PBS solution serving as test samples. The results demonstrate that the OTFT-based amplification circuit enhances detection sensitivity. Furthermore, the impedance values inferred from the circuit showed good consistency with measurements from an electrochemical workstation, proving the stability of the sensor. This work establishes a foundation for the application of printed OTFTs in electrochemical impedance biosensors.

2.1 Impedance Biosensor

A system diagram of the reported impedance biosensing system is shown in Figure 1a [Figure 1: see original paper]. The impedance sensor consists of thin-film electrodes and a printed OTFT-based circuit. The biological sample under test is placed on the electrodes, and the sensing signal is amplified directly by the OTFT-based circuit. A function generator produces sinusoidal signals at various frequencies, while the amplified sensing output is recorded by an oscilloscope.

Electrode Design and Fabrication. Figure 1b shows a photograph of the electrode chip. The electrode chip comprises gold electrodes and a polymethylmethacrylate (PMMA) reservoir. After cleaning the glass slide using a standard procedure, a 50 nm gold layer was deposited on the surface via magnetron sputtering. A 2 mm thick PMMA sheet was purchased from Mitsubishi, Japan. In this work, we used a carbon dioxide laser to cut gold-coated glass slides for electrode preparation and to cut PMMA for reservoir fabrication. Electrode dimensions and acrylic shape sizes were designed using AutoCAD software, as shown in Figure 1d. The completed design was imported into the CO laser control software. To process the metal electrodes, the following parameters were set: laser head-to-sample distance of 7 mm, laser power of 8 W, and laser speed of 15 mm/s. For PMMA cutting to create the reservoir, only the power was adjusted to 20 W. After laser processing, the gold electrodes and cut PMMA were bonded using ultraviolet (UV) glue.

Figure 1c shows the OTFTs used in the amplifier. The gate, source, and drain are each routed to contact pads, enabling external electronic components to connect to the OTFT and form an amplifier. Figure 1e presents a microscopic photograph of an OTFT.

OTFT Fabrication. OTFTs were prepared over large areas using high-throughput coating techniques. The fabricated OFET dies were cut from the large-area substrate. Since OFET technology offers much lower cost per unit area, relatively large contact pads could be designed to facilitate external connections. The OFET die and sensing electrodes could then be connected to a carrier substrate through pre-fabricated contacts and interconnects. A blend solution of small-molecule organic semiconductor and polymer binder was deposited onto photolithographically patterned fine-resolution electrodes using a soft-contact coating technique at a rapid rate of 20 mm/s. Highly uniform crystalline channels were obtained with low sub-gap density of states over large areas through well-controlled contact-induced crystallization. The OTFT devices exhibit low-voltage electrical characteristics, excellent bias stress stability, and good uniformity across more than 100 devices [23].

2.2 OTFT Device and Circuit Parameters

The transfer and output characteristic curves of the printed OTFT used in the amplification circuit are presented in Figure 2a [Figure 2: see original paper] and 2b, respectively. The OTFT can operate at low voltage (< 3 V) with an ON/OFF ratio exceeding six orders of magnitude.

A printed OTFT-based common-source amplifier is shown in Figure 2c. Capacitor filters DC bias from the input signal. The input is biased by a DC preset stage composed of two resistors, and , which define the DC operating point of the amplifier. Resistor serves as the load for the common-source amplifier to achieve better gain. Capacitor removes the DC component from the output signal, thereby extracting the AC signal. Resistor functions as a divider resistance. The component parameters used in the amplifier are listed in Table 1 .

Figure 2d shows the frequency response of the amplification circuit. At lower frequencies, the circuit gain is approximately 13 dB, which can be further increased by adjusting the quiescent DC operating point. The gain decreases at higher frequencies due to parasitic overlap capacitance between the drain, source, and gate of the OTFT. The 3 dB bandwidth of the printed OTFT-based amplification circuit is 1 kHz.

3.1 OTFT Sensor Sensitivity Curve and Measured Results

The electrodes were tested with five different concentrations of PBS solution. Figure 3a shows the Bode plot for different PBS concentrations, while Figure 3b displays the Nyquist plot of the measurement results. The impedance of PBS solution decreases with frequency in the lower band while remaining constant in the high-frequency band, indicating capacitive characteristics at low frequencies and pure resistive characteristics at high frequencies. The tested samples show high impedance discrimination in the high-frequency region (10 kHz–1 MHz); however, the amplifier gain in this frequency region is relatively low. The excitation signal frequency from the function generator must be selected considering both amplifier gain and impedance discrimination capability, which will be discussed further below.

As mentioned above, signal frequency selection for the function generator is critical in system design. Sensitivity should combine the circuit gain and impedance differences of PBS solution at various frequencies. The voltage generated by the signal generator divided by the PBS impedance is defined as the unamplified coefficient, while the unamplified coefficient multiplied by the amplifier gain is defined as the amplified coefficient. The sensitivity difference is calculated as the slope difference between the amplified coefficient and unamplified coefficient curves at specific measurement frequencies across different concentrations. The sensitivity differences at five measurement frequencies were calculated accordingly. Figure 3c shows the sensitivity difference values with and without amplification. A frequency of 1 kHz was selected as the measurement frequency because it yielded the maximum sensitivity difference while falling within the 3 dB bandwidth of the amplifier. The value of divider resistor was chosen as the average between the maximum and minimum impedance values of the tested samples at 1 kHz.

Figure 3d compares the unamplified output voltage signal with the amplified signal, demonstrating that the amplifier can boost sensitivity for PBS concentration measurement.

3.2 Calculation of Tested Sample Impedance

Sample impedance can be obtained using an electrochemical workstation, which provides a standard value for ensuring measurement accuracy. The solution impedance can also be deduced from the experimental circuit and data. This section illustrates the calculation of tested sample impedance based on the experimental circuit and data.

Figure 4 [Figure 4: see original paper] shows the small-signal equivalent circuit of the common-source amplifier in this work. The symbol represents the tested sample impedance, is the transconductance, and _ds is the channel-length modulation resistor. The AC impedance between gate and source should also be considered, as capacitive effects become significant in the high-frequency region. The impedance between gate and source is represented by _gs in the circuit. The frequency characteristics of _gs were measured using an electrochemical workstation with a bias voltage _gs of -5 V, yielding the corresponding AC impedance values at different frequencies (see Figure S1 in the Supplementary).

The tested sample impedance calculation proceeds as follows:

$$\dot{V_i} = \dot{V_{Zt}} + \dot{V_{gs}} \tag{1}$$

where $\dot{V_i}$ is the voltage from the function generator, $\dot{V_{Zt}}$ is the voltage across the electrodes containing PBS solution, and $\dot{V_{gs}}$ is the voltage across the parallel combination of , , , and _gs. $\dot{V_{gs}}$ can be obtained by:

$$\dot{V_{gs}} = \dot{V_o}/\dot{A_v} \tag{2}$$

where $\dot{V_o}$ is the output voltage recorded by the oscilloscope and $\dot{A_v}$ is the amplifier gain. The current through equals the total current through , , , and _gs, establishing the following equation:

$$\dot{V_{Zt}}/Z_t = \dot{V_{gs}}/(R_4//R_1//R_2//Z_{gs}) \tag{3}$$

By solving Equations (1), (2), and (3) simultaneously, the tested sample impedance can be deduced:

$$|Z_t| = \frac{|\dot{V_i} - \dot{V_o}/\dot{A_v}|}{|\dot{V_o}/\dot{A_v}|} \times (R_4//R_1//R_2//Z_{gs}) \tag{4}$$

Meanwhile, the voltage across resistor under different tested samples was directly recorded by the oscilloscope without using the amplification circuit. The impedance of can be deduced from Equation (5) based on the principle that the current through equals the current through :

$$|Z_t| = \frac{|\dot{V_i} - \dot{V_o}|}{|\dot{V_o}|} \times R_4 \tag{5}$$

where $\dot{V_o}$ is the voltage across resistor recorded by the oscilloscope.

The impedance of tested samples with and without the amplification circuit was obtained based on experimental data and the above equations. Figure 5 [Figure 5: see original paper] shows the impedance measurement results with amplification, without amplification, and using an electrochemical workstation. The relatively good consistency among these three methods indicates stable performance of the PBS solution impedance measurement system.

---

4. Conclusions

This work established a printed organic transistor-based impedance biosensor utilizing a printed OTFT-based amplification circuit. Different concentrations of PBS solution were measured as test samples using the amplifier. The results demonstrate that the OTFT-based amplification circuit can enhance sensitivity for concentration measurement. Subsequent work calculated the tested sample impedance using experimental circuit parameters and data, with results indicating good impedance measurement stability. A common-source amplifier based on printed OTFT was successfully built. Further work is needed to apply OTFT-based impedance amplification in biological applications such as immunosensors, leveraging the advantageous features of printed OTFT technology.

Supplementary Materials: The following is available online: Figure S1: Frequency characteristics of _gs measured using an electrochemical workstation with bias voltage | _gṡ| = -5 V.

Author Contributions: Q.H. and K.J. designed and performed the experiments; X.G., Y.H., Z.L., and L.F. fabricated the OTFTs; all authors contributed to writing—review and editing; H.M. supervised the work. All authors have read and agreed to the published version of the manuscript.

Acknowledgments: This research was funded by the National Natural Science Foundation of China, grant number [to be inserted].

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Li, X.; Wu, T.; Fu, Y.; Ding, X.; Li, Z.; Zhu, G.; Fan, J. A high sensitivity background eliminated fluorescence sensing platform for hyaluronidase activity detection based on Si QDs/HA- -FeOOH nanoassembly. *Biosens. Bioelectron.* 2020, 150, 111928.

2. Ma, H.; Li, J.; Cheng, X.; Nathan, A. Heterogeneously integrated impedance measuring system with disposable thin-film electrodes. *Sens. Actuator B-Chem.* 2015, 211, 77-82.

3. Jang, B.; Hassibi, A.J. Biosensor systems in standard CMOS processes: Fact or fiction? *IEEE Trans. Ind. Electron.* 2009, 56, 979-985.

4. Cimafonte, M.; Fulgione, A.; Gaglione, R.; Papaianni, M.; Capparelli, R.; Arciello, A.; Bolletti Censi, S.; Borriello, G.; Velotta, R.; Della Ventura, B. Screen Printed Based Impedimetric Immunosensor for Rapid Detection of *Escherichia coli* in Drinking Water. *Sensors* 2020, 20, 274.

5. Malvano, F.; Pilloton, R.; Albanese, D. Label-free impedimetric biosensors for the control of food safety–a review. *Int. J. Environ. Anal. Chem.* 2019, 1-24.

6. Shaikh, M.O.; Srikanth, B.; Zhu, P.-Y.; Chuang, C.-H. Impedimetric Immunosensor Utilizing Polyaniline/Gold Nanocomposite-Modified Screen-Printed Electrodes for Early Detection of Chronic Kidney Disease. *Sensors* 2019, 19, 3990.

7. Jin, K.; Hu, S.; Su, Y.; Yang, C.; Li, J.; Ma, H. Disposable impedance-based immunosensor array with direct-laser writing platform. *Anal. Chim. Acta* 2019, 1067, 48-55.

8. Swisher, S.L.; Lin, M.C.; Liao, A.; Leeflang, E.J.; Khan, Y.; Pavinatto, F.J.; Mann, K.; Naujokas, A.; Young, D.; Roy, S. Impedance sensing device enables early detection of pressure ulcers in vivo. *Nat. Commun.* 2015, 6, 6575.

9. Peng, Y.; Zhang, D.; Li, Y.; Qi, H.; Gao, Q.; Zhang, C. Label-free and sensitive faradic impedance aptasensor for the determination of lysozyme based on target-induced aptamer displacement. *Biosens. Bioelectron.* 2009, 25, 94-99.

10. Sun, K.; Xia, N.; Zhao, L.; Liu, K.; Hou, W.; Liu, L. Aptasensors for the selective detection of alpha-synuclein oligomer by colorimetry, surface plasmon resonance and electrochemical impedance spectroscopy. *Sens. Actuator B-Chem.* 2017, 245, 87-94.

11. Tang, D.; Yuan, R.; Chai, Y.; Dai, J.; Zhong, X.; Liu, Y. A novel immunosensor based on immobilization of hepatitis B surface antibody on platinum electrode modified colloidal gold and polyvinyl butyral as matrices via electrochemical impedance spectroscopy. *Bioelectrochemistry* 2004, 65, 15-22.

12. Valente, V.; Demosthenous, A. Wideband fully-programmable dual-mode CMOS analogue front-end for electrical impedance spectroscopy. *Sensors* 2016, 16, 1159.

13. Hassibi, B.; Vikalo, H.; Hassibi, A. Method and apparatus for detection, identification and quantification of single- and multi-analytes in affinity-based sensor arrays. Google Patents: 2015.

14. Hamakawa, Y. *Thin-film solar cells: next generation photovoltaics and its applications*; Springer Science & Business Media: 2013; Vol. 13.

15. Nathan, A.; Ahnood, A.; Cole, M.T.; Lee, S.; Suzuki, Y.; Hiralal, P.; Bonaccorso, F.; Hasan, T.; Garcia-Gancedo, L.; Dyadyusha, A. Flexible electronics: the next ubiquitous platform. *Proc. IEEE* 100 (Special Centennial Issue) 2012, 100, 1486-1517.

16. Dai, Y.; Chen, J.; Tian, W.; Xu, L.; Gao, S. A PVDF/Au/PEN Multifunctional Flexible Human-Machine Interface for Multidimensional Sensing and Energy Harvesting for the Internet of Things. *IEEE Sens. J.* 2020, 10.1109/JSEN.2020.2974096, 1-1, doi:10.1109/JSEN.2020.2974096.

17. Feng, L.; Jiang, C.; Ma, H.; Guo, X.; Nathan, A. All ink-jet printed low-voltage organic field-effect transistors on flexible substrate. *Org. Electron.* 2016, 38, 186-192.

18. Ng, T.N.; Schwartz, D.E.; Mei, P.; Kor, S.; Veres, J.; Bröms, P.; Karlsson, C. Printed organic circuits for reading ferroelectric rewritable memory capacitors. *IEEE Trans. Electron Devices* 2016, 64, 1981-1984.

19. Kwon, J.; Takeda, Y.; Fukuda, K.; Cho, K.; Tokito, S.; Jung, S. Three-dimensional, inkjet-printed organic transistors and integrated circuits with 100% yield, high uniformity, and long-term stability. *ACS Nano* 2016, 10, 10324-10330.

20. Takeda, Y.; Hayasaka, K.; Shiwaku, R.; Yokosawa, K.; Shiba, T.; Mamada, M.; Kumaki, D.; Fukuda, K.; Tokito, S. Fabrication of ultra-thin printed organic TFT CMOS logic circuits optimized for low-voltage wearable sensor applications. *Sci. Rep.* 2016, 6, 1-9.

21. Nketia-Yawson, B.; Jung, A.-R.; Noh, Y.; Ryu, G.-S.; Tabi, G.D.; Lee, K.-K.; Kim, B.; Noh, Y.-Y. Highly sensitive flexible NH sensors based on printed organic transistors with fluorinated conjugated polymers. *ACS Appl. Mater. Interfaces* 2017, 9, 7322-7330.

22. Shiwaku, R.; Matsui, H.; Nagamine, K.; Uematsu, M.; Mano, T.; Maruyama, Y.; Nomura, A.; Tsuchiya, K.; Hayasaka, K.; Takeda, Y. A printed organic amplification system for wearable potentiometric electrochemical sensors. *Sci. Rep.* 2018, 8, 1-8.

23. Huang, Y.; Song, Y.; Tang, Y.; Liu, Z.; Han, L.; Zhang, Q.; Ouyang, B.; Tang, W.; Feng, L.; Guo, X. Solution Processed Highly Uniform and Reliable Low Voltage Organic FETs and Facile Packaging for Handheld Multi-ion Sensing. In *Proceedings of 2019 IEEE International Electron Devices Meeting (IEDM)*; pp. 18.15.11-18.15.14.

Note: Figure translations are in progress. See original paper for figures.