Implantable Sufficiently Integrated Multimodal Flexible Sensor for Intracranial Monitoring

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***Abstract*—Traumatic brain injury (TBI) is a global health problem, and real-time monitoring of intracranial physiological and biochemical information in patients with TBI remains a challenge. In this study, we report a flexible multimodal sensor based on polyimide, which has the potential to be implanted into the skull to measure cerebral cortical discharge, intracranial temperature, brain tissue oxygen content, sodium and potassium in cerebrospinal fluid, and intracranial pressure. In addition, this sensor has good flexibility and can be implanted into the brain smoothly. The proposed technique provides a novel insight for real-time monitoring of intracranial physiological and biochemical information and is of great significance for the diagnosis of TBI.**

Keywords—integration; intracranial; physiology; biochemistry; flexible sensor;

I. INTRODUCTION

Traumatic brain injury (TBI) is a global health problem with high mortality, caused by severe brain injury caused by traffic accidents, industrial accidents, personal accidents, and so forth [1]. The fatality rate of severe TBI is above 20%, and the disability rate of severe TBI is above 50% [2]. Clinical manifestations of TBI can be predicted by various intracranial physiological and biochemical indicators [3], such as intracranial pressure (ICP) [4], O_2 content of brain tissue, intracranial temperature (ICT), Na^+/K^+ concentration of cerebrospinal fluid [5], and intracranial electroencephalogram (iEEG) [6]. Real-time monitoring of these changes can not only early determine the occurrence of secondary TBI, but also quantify the extent of TBI [7].

The gold device for monitoring intracranial physiological indexes uses an implantable sensor probe [8]. However, the current implantable sensor probes have various disadvantages, such as large wound area, infection, dispersion, inconvenient wire connection, which greatly limit their clinical applications. To the best of our knowledge, there is no monitoring method of minimally invasive integrated multimodal cortical physiological indexes.

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Here, we propose an implantable sufficiently integrated multimodal flexible sensor, which can help diagnose TBI. Specifically, we demonstrate a fully integrated platform that implements this capability to measure the intracranial physiological and biochemical information (ICP, O_2, Na^+, K^+, ICT, iEEG) in real-time. All sensing units are fabricated by Micro-Electro-Mechanical System (MEMS) process on a flexible polyimide (PI) substrate (Fig. 1(a)). The impedance of the cerebral cortical electrode is 36.28 kΩ @1k Hz. The sensitivity of the temperature sensing unit is 0.633 Ω/℃ in the range of 28~75 ℃. The detection range of the oxygen sensing unit is 3~15 ppm; the sensitivity of the Na^+/K^+ sensing units are 205 mV and 64.6 mV per decade of concentration at the concentrations of 40~180 mM NaCl and 1~16 mM KCl. The sensing range of the piezoresistive sensing unit is 2~140 mmHg. Therefore, the sensor has good flexibility and can be implanted well into the brain. This sensor can be used to gain unprecedented insight into TBI to promote biomedical knowledge and advance national science.

II. METHODS

The manufacturing steps of the flexible sensor are shown in Fig. 1, and the optical image is shown in Fig. 1 (j-l).

A. Fabrication of Electrodes Array and temperature sensing unit

As shown in Fig. 1 (a), PI was cleaned with acetone, ethanol, and O_2 plasma etching. The electrode array was patterned via photolithography and deposited with 30/300 nm of Cr/Au, followed by corrosion process in Au etching solution ($KI/I/H_2O$ = 50 g/25 g/400 ml) and Cr etching solution (Fig. 1 (b),(c)). Then 150 nm Pt was deposited via hard mask one to fabricate the temperature sensing unit, and 300 nm Ag was deposited via hard mask two to fabricate the Ag electrode (Fig. 1 (d),(e)). The electrode array and temperature sensing unit were coated with 1 μm parylene C insulation layer additionally in a vacuum deposition system (PDS2010), and the sensing electrode area was defined via photolithography. The fabricated array was further etched

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with O_2 plasma to remove the parylene C layer at the defined sensing area (Fig. 1 (f)).

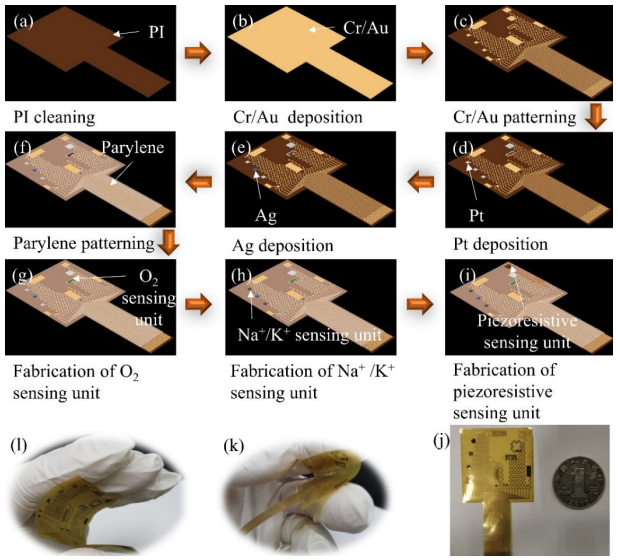

Fig 1. Fabrication process of the flexible sensor. (a) PI cleaning using acetone, ethanol, and O_2 plasma etching. (b) Cr/Au deposition. (c) Patterning of Cr/Au electrodes using photolithography. (d) Pt deposition, and fabrication of a temperature sensing unit. (e) Ag deposition. (f) Parylene insulating layer deposition, then photolithography and O_2 plasma etching of parylene in the electrode areas. (g) Fabrication of O_2 sensing unit. (h) Fabrication of Na^+/K^+ sensing unit. (i) Fabrication of piezoresistive sensing unit. (j-l) Optical image of the multiplexed sensor array

B. Fabrication of oxygen sensing unit

1 ml 5wt.% Nafion (Shanghai Macklin Biochemical Co., Ltd., China) was mixed with 0.5 ml 1.25wt.% Polyvinylpyrrolidone(PVP360, Sigma Aldrich, MO, USA) aqueous solution to obtain the proton exchange membrane (PCM) solution. 0.1ml Silane174A (Shanghai Macklin Biochemical Co., Ltd., China) solution was mixed with 5 ml anhydrous ethanol to obtain electrode surface treatment (EST) solution. The EST solution was dropped on the electrode surface and dried at 60 ℃ for 5 minutes. 2.5 μl PCM solution was titrated on the surface of the electrode and then heated at 80 ℃ with nitrogen for 20 minutes. The above steps were repeated 3 times to obtain a 15 μm PCM film. 1 g Polydimethylsiloxane (PDMS, Dow Corning Co, Midland, MI, USA) and 0.1 g curing agent were mixed to form the PDMS mixture. The PCM was coated with 20 μm PDMS mixture and cured at 60 ℃ for 2 hours (Fig. 1 (g)).

C. Fabrication of Na^+/K^+ sensing unit

The Ag electrode was cleaned for 5 s with 0.6 mol/L HNO_3 to remove Ag_2O. The Ag/AgCl electrode was prepared by injecting 10 μl 0.01 mol/L $FeCl_3$ solution on top of the Ag electrode using a micropipette for 5 s.

0.5 μl 1.5% Poly(3,4-ethylenedioxythiophene) /poly (styrenesulfonate) (PEDOT/PSS, Sigma Aldrich, MO, USA) was dripped at the Pt electrode and rest for 12 hours. Then 0.5 μl Na^+-selective membrane mixture and 0.5 μl K^+-selective membrane mixture were dropped in the corresponding position respectively, and baked at 90 ℃ for 2 hours (Fig. 1 (h)). The Na^+-selective membrane mixture was composed of bis(2-ethylhexyl) sebacate (DOS, Sigma Aldrich, MO, USA, 65.45% wt/wt), high-molecular-weight polyvinyl chloride (PVC, Sigma Aldrich, MO, USA,33% wt/wt), selectophore-grade sodium ion-carrier X (Sigma Aldrich, MO, USA ,1% wt/wt), and sodium tetrakis [3,5-bis (trifluoromethyl) phenyl] borate (Na-TFPB, Sigma Aldrich, MO, USA, 0.55% wt/wt). 100 mg of the membrane cocktail was dissolved in 660 μl of cyclohexanone. The K^+-selective membrane cocktail was composed of DOS (64.7% wt/wt), PVC (32.7% wt/wt), valinomycin (2% wt/wt), and Na-TFPB (0.6% wt/wt). 100 mg of the membrane cocktail was dissolved in 350 μl of cyclohexanone.

D. Fabrication of Piezoresistive sensing unit

7wt% Multi-walled carbon nanotubes (MWCNTs, Chengdu Organic Chemicals Co. Ltd., China，wt/wt) and 12wt% phenylmethylsiloxane (PPMS, Alfa Aesar, wt/wt) were added to Polydimethylsiloxane (PDMS, Dow Corning Co, Midland, MI, USA) to form a mixture. The curing agent (1/10 of the mass of PDMS) was added to the mixture, and the bubbles were removed through a vacuum pump to obtain the MWCNTs-PDMS nanocomposite. 150 μm nanocomposite was coated on 5-inch sandpaper (grit designation P800, Buehler Co., USA) mold and heat at 100 ℃ for 30 minutes. Finally, the nanocomposite film was cut into the desired shape to obtain piezoresistive elements.

100 μm PDMS was rotated onto a silicon wafer, solidified at 80 ℃ for 30 minutes, and then cut into the desired shape as the middle layer. The first layer of PI was placed on the platform, the middle layer was place on the first layer, the piezoresistive unit was filled in the gap of the middle layer, and then the third layer of PI was covered. Liquid PDMS was coated between the layers as an adhesive and cured at 80 ℃ for 30 minutes (Fig. 1 (i)).

III. Results and Analysis

We placed the sensor in different environments and used electrochemical workstations (CHI 760E) and multimeters (KEYSIGHT 34461A) to evaluate the performance of each sensor unit. All the characterization results are shown in Table I.

TABLE I. . Comparison Table of Standard Value and Measuring Range

Index	Normal value	Sensor range	Responsiveness
IMP	----	36.28kΩ@1kHz	----
ICT	~37℃ [9]	28~75℃	0.633Ω/℃
O_2	----	3~15ppm	----
Na^+	~143mM [10]	40~180mM	0.205V/$\log_{10}$[mM]
K^+	~2.4mM [10]	1~16mM	0.065V/$\log_{10}$[mM]
ICP	~16mmHg [11]	2~12mmHg Very sensitive, 12~140 mmHg	2~12mmHg : 47.89Ω/ mmHg ; 12~140 mmHg : 3.34Ω / mmHg

Fig. 2 (a-c) show the electrochemical impedance analysis of iEEG in PBS solutions through the electrochemical workstation. According to Fig. 2 (b), the impedance is 36.28kΩ at the frequency of 1k Hz. The small impedance indicates its capability of epileptic signal detection and electrical stimulation. Fig. 2 (c) shows that the three measurement results are consistent, indicating that the electrode has good stability.

Fig. 2 (d) displays the linear response of the resistive temperature sensor range of 28~75 °C, and the fitting equation is

$$y = 0.633\,x + 460.956 \quad (1)$$

where x stands for the temperature value and y stands for the resistance value. As shown in Fig. 2 (e), the temperature sensing unit is stable over the range of human temperature (34~42 °C), with a sensitivity of approximately 0.13% per degree Celsius (normalized to the resistance at 30 °C).

The characteristics of the O_2 sensing unit are shown in Fig. 2 (f-h). Fig. 2 (f) is the comparison curve between the fabricated oxygen sensor and the commercial oxygen sensor (Dissolved Oxygen Meter, AZ8403). The curve was measured when the initial voltage is 0 V, the fitting equation is

$$y = 0.864\,x + 10.458 \quad (2)$$

where x stands for the ground truth and y stands for the measured value. The sensor has a measuring range of 3~15ppm and is well correlated with the commercial O_2 sensor. Fig. 2 (g) shows the results of multiple measurements at different concentrations at an initial voltage of 0.6 V. It can be found that the O_2 sensing unit has good stability. Fig. 2 (h) shows the dynamic response of the O_2 sensor. Its response time is about 10 s. When the flow rate of O_2 decreases, the measured current decreases rapidly and gradually stabilizes at a certain value, but not as fast as when the O_2 is released from the solution, which takes some time.

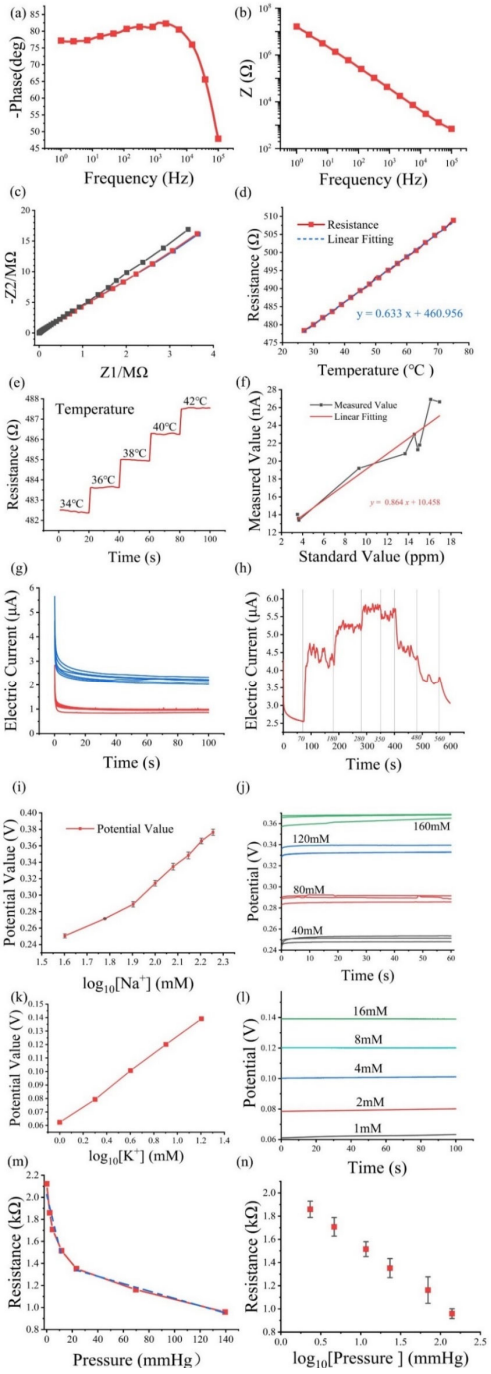

Fig 2. Experimental characterizations of the implantable highly integrated multimodal flexible sensor. (a-c) Electrochemical impedance of iEEG, (a) phase-frequency relationship curve, (b) impedance frequency relationship curve, (c) three measurements verify the stability of iEEG. (d) The resistance response of the temperature sensor to temperature changes (28~75℃). (e) The resistance responses of the temperature within the upper and lower range of body temperature (34~42℃). (f) Comparison with commercial O_2 sensors. (g), (h), the chronoamperometric responses of O_2 of static (g) and dynamic (h). (i), (k) The open-circuit potential responses of the sodium in NaCl (i) and KCl (k) solutions. (j), (l). The test in different concentrations of NaCl (j) and KCl (l) solutions. (m), (n). The resistance responses of the pressure.

Figure 2 (i-l) illustrate the open circuit potentials of Na^+ and K^+ sensors in the electrolyte solutions with physiologically relevant concentrations of 40~180 mM Na^+ and 1~16 mM K^+ respectively. For Na^+ and K^+ sensors, the sensitivity of these two ion selection sensors is 205 mV and 64.6 mV per decade of concentration. The results of multiple measurements at different concentrations are shown in Fig 2 (j) and (l), indicating their stable performance.

The piezoresistive curve of the piezoresistive sensing unit is shown in Fig. 2 (m). The sensing range is 2~140 mmHg. The piezoresistive characteristic curve can be divided into 2~12 mmHg and 12~140 mmHg. The piezoresistive material has a high sensitivity in the range of 2~12 mmHg due to its surface microstructure. The fitting curve in the range of 2~12 mmHg is

$$y = -47.98\,x + 2024 \quad (3)$$

The fitting curve in the range of 12~140 mmHg is

$$y = -3.34\,x + 1417 \quad (4)$$

where x stands for the pressure (mmHg) and y stands for the resistance value (kΩ). Fig. 2 (n) shows the sensitivity is 0.505 kΩ per decade of pressure.

IV. Conclusion and Prospect

In conclusion, we introduced a multi-modal flexible sensor with implantation potential to monitor intracranial physiological and biochemical information. The sensor is integrated with a flexible electrode array, a temperature sensing unit, an oxygen sensing unit, Na^+/K^+ sensing units, and a pressure sensing unit, and realizes the real-time monitoring of iEEG, ICP, O_2 content, Na^+/K^+ concentration, and ICP. Overall, this work establishes a technological framework for implantable intracranial biosensors and paves the way for the applications of TBI detection, disease prediction, and treatment.

In the future, we will conduct multi-sensing unit hybrid tests and implantation tests on this sensor, and realize wireless communication through Bluetooth, electromagnetic induction and other methods to advance the research of intracranial sensors.

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