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Doctor’s Degree Thesis

Development of potentiostat for human-body mounted portable diagnostic devices

Graduate School of Chosun University
Department of IT Fusion Technology
Jihwan Lee

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인체 부착형 진단기기를 위한 포텐시오스텟 개발

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Development of potentiostat for human-body mounted portable diagnostic devices

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This is to certify that the Doctor's Thesis of

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Acronyms

POCT	Point Of Care-Testing
WE	Working Electrode
RE	Reference Electrode
CE	Counter Electrode
FPGA	Field Programmable Gate Array
DSP	Digital Signal Processor
MCU	Micro Controller Unit

요 약

인체 부착형 진단기기를 위한 포텐시오스텟 개발

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현재 생의학 분야에서는 많은 연구들이 진행되어, 값싸고 높은 성능을 가진 분석장비들이 연구 및 개발되고 있다. 특히 분석 장비 및 시스템은 10cm x 10cm 이하로 소형화되면서 보편화 되었다. 소형화된 분석 장비들은 낮은 전력과 작은 수량의 부품을 사용하며, 값싼 비용으로 제작할 수 있는 장점을 가지고 있다. 전기화학 센서에서 신호를 검출할 수 있는 장치들은 MCU를 사용하여 신호를 다각적으로 분석할 수 있게 되었다. 휴대하기 쉽도록 개발 상용장비는 i-STAT 분석기, Sandia’s MicrochemLab biotoxin detector, 혈액 분석기 등을 예로 들 수 있다. 소형 분석 장비들은 삶에 편리함을 제공하며, 위험에 처한 사람들을 빠르게 도와줄 수 있고, 생활 환경을 분석하는데 사용되기도 한다. 휴대용 포텐시오스텟은 기본적으로 회로의 부품의 수를 최소화하고 크기도 소형으로 제작되어야 하며, 저전력으로 작동되도록 개발되어야 한다. 이러한 선행연구결과들로 휴대형 디바이스는 낮은 가격으로 제조가 가능해졌으며, 내부 USB, 블루투스, 시리얼포트를 이용하여 스마트폰과 컴퓨터등 다양한 통신 방법으로 분석이 가능해졌다. 인체 부착형 포텐시오스텟이 아닌 기존 선행연구 결과들로 개발된 포텐시오스텟에

는 동시에 다수의 마커를 분석할 수 없는 단점을 가지고 있다. 선행연구의 멀티포텐시오스텟은 다수의 공간에서 동시에 사용하여 측정가능 하지만 한 개의 공간에서 다수의 마커를 측정하기는 어려운 실정이다. 본 연구의 고감도 포텐시오스텟은 동시에 4개의 작업전극에서 측정이 가능하며, 10㎕의 적은 용액에서, 22㎁까지 측정이 가능하다. 인체 부착형 진단기기로 사용할 수 있도록 센서와 신호 검출되는 포트 부분이 일체형인 포텐시오스텟을 개발하였다. 이를 통해 질병 발생 여부를 확인할 수 있는 프로토콜 및 휴대용 어플리케이션 개발의 기초 연구로 사용할 수 있으며, 초미세 신호를 증폭 및 필터할 수 있는 회로와 무선통신 장치를 하나의 모듈로 통합하여 많은 종류의 휴대용 현장진단장치 개발이 가능하다. 즉, 본 연구에서 개발한 포텐시오스텟을 이용하여 산화 환원반응을 기초로 하는 진단 및 예방 장치에 크게 기여할 것으로 기대된다.

I. Introduction

A. Background of the Portable Potentiostat

Evolving environments and continuously changing patterns in lifestyle continue to increase the prevalence of many diseases. In particular, the average age of the Korean population is rapidly growing compared to that of other countries due to an increasing life expectancy. Accordingly, health insurance for the elderly, often a form of welfare, is a growing cost issue the Korean government. Cardiovascular disease, which is the second-most common cause of death after cancer in Korea, is becoming a serious problem due to the increases in stress, dietary imbalance, and intake of high cholesterol foods, as well as sudden environmental changes. People aged 30 years and over are thus at increased risk of developing cerebrovascular and heart diseases as well as cancer. Medical devices that can detect such diseases early are being actively developed with the advance of technology.

Figure 1. Cause of death in Korea (Source: Statistics Korea, 2013)

Recently, many studies focusing on cost-effective, high-performance medical analysis devices are under continuing research and development[1–3]. with the latest tools able to easily and quickly diagnose diseases. As the paradigm of medical devices has evolved, the need for new types of sensors has been identified in industry. Moreover, sensor detection technologies has evolved while converging with information technology approaches, enabling the miniaturization of medical devices.

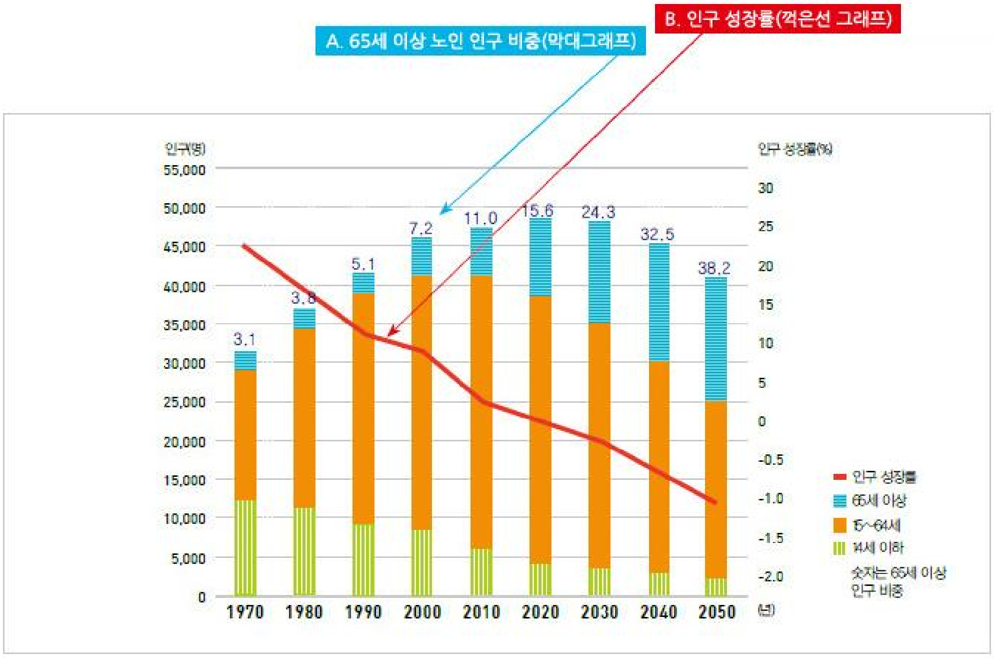


Figure 2. Population change survey (File source: Korea land and environment knowledge database)

Many such studies have been conducted in medicine, where cost-effective, high-performance analysis devices are being researched and developed. In particular, devices and systems miniaturized to smaller than 10 cm × 10 cm have become popular, since they consume little power, have few components, and can be inexpensive to manufacture. Devices capable of detecting signals from electrochemical sensors can now be used to analyze signals in multiple ways using an microcontroller unit(MCU).

Commercial devices developed for easy portability include the i-STAT analyzer, Sandia's MicroChem Lab biotoxin detector, and various blood analyzers. Small analysis devices are convenient to use, can quickly help people at risk, and can be used to analyze biotic environments.

One such device, a portable potentiostat, should be small, have a minimal number of circuit components, and operate at low power. The success of preliminary studies has allowed portable devices to be manufactured at low cost. Furthermore, the portable devices can transfer data using an internal USB, Bluetooth, or serial port through various communication protocols for viewing and analysis on smartphones or computers.

Previously-developed potentiostats that were not wearable on body surfaces could simultaneously analyze multiple markers. Later, some potentiostats capable of multiple measurements were developed that could measure multiple chambers simultaneously, but using them, it was difficult to measure multiple markers in a single chamber.

To attach a potentiostat to the human body, peripheral interference should not affect the circuit, and the detection components must be compact so as to not affect a user’s comfort. Since a potentiostat must be attached to the human body, studies must be conducted to optimize their use across diverse patterns and sensor materials.

B. Research Method of Human attachable Potentiostats

Human attachable potentiostats are capable of various types of measurements. Here we describe the use of electrochemical analysis for characterizing potentiostats, a method often used to analyze enzymes through oxidation–reduction reactions.

1. Definition of Electrochemistry

Electrochemistry is an analysis method that transfers electrons generated by the interaction between a source of electricity and a substance to be analyzed. Electrochemical analysis cannot be conducted without electron transfer, movement, relocation, or redistribution. Any chemical reaction in which the reaction energy is converted to heat or light after transmission is not included in the category of electrochemistry. Electrochemical analysis methods are used in numerous areas of electrochemistry, such as metal plating, corrosion, smelting, action, decomposition, substance concentration, and dissolved oxygen concentration.

2. Electrochemical reaction method

Electrochemical reactions can be classified into two types: spontaneous and nonspontaneous. A spontaneous chemical reaction releases energy through chemical reactions without stimulation, and include galvanic and voltaic reactions. In contrast, electrolysis is a nonspontaneous chemical reaction. For other examples of spontaneous and nonspontaneous reactions, secondary batteries can recover their original state using electrical energy from oxidation–reduction reactions, whereas primary batteries cannot. The Daniel cell is a representative voltaic or galvanic cell based on spontaneous reaction.

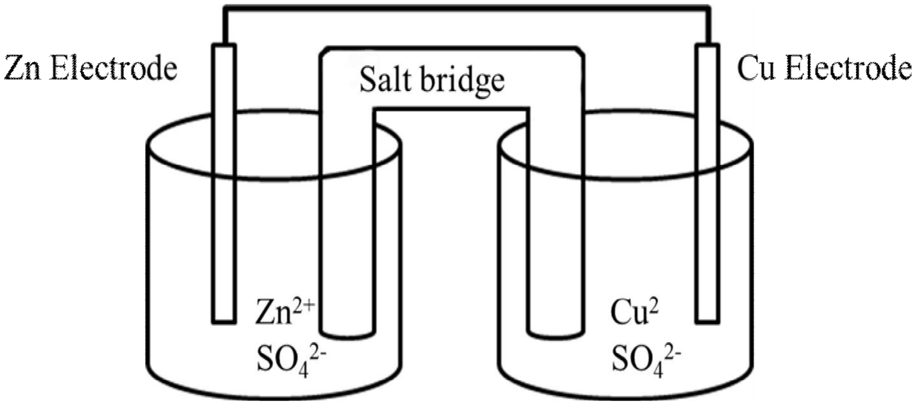


Figure 3. Daniel battery structure

$$Zn + Cu^{2+} -> Zn^{2+} + Cu$$

In the Daniel cell, the Zn electrode comes in contact with the $ZnSO_4$ solution to conduct the oxidation reaction.

$$Zn -> Zn^{2+} + 2e$$

Meanwhile, a Cu electrode in contact with a $CuSO_4$ solution starts are duction reaction at the sensor.

$$Cu^{2+} + 2e \rightarrow Cu$$

In the above-mentioned schematic diagram, the electrons flow from the Zn electrode where the oxidation reaction takes place to the previous electrode. The oxidation reaction occurs in the Zn electrode, and the reduction reaction occurs in the previous electrode. The Brassiere is filled with an electrolyte solution, such as K^+Cl^-, using an N-shaped tube, and the membranes at both ends only allow the electrons to move. In the solution containing the Zn electrode, the number of positive ions increases as the Zn^{2+} ions dissolve. In the case of a solution containing the Cu electrode, the negative charge increases as the C^{2+} ions decrease and then disappear from the surface of the electrode. A nonspontaneous electrolytic cell is a typical electrolytic cell and is different from the Daniel cell. The following reaction occurs when electrons are moved to the cathode by indirectly applying electrical energy in an opposite direction in an external circuit connecting two electrodes. In daily life, this nonspontaneous reaction is used for electroplating.

$$Zn^{2+} + Cu \text{ -> } Zn + Cu^{2+}$$

C. Electrochemical analysis method

The detection of enzymes relies on electrochemical analysis for detection through oxidation–reduction reactions. Electrochemical analysis converts the water mass of a sample to be measured into an analog signal, and then to a digital signal using an analog-digital converter (ADC). An electrochemical sensor uses a reference electrode (RE) operating independently from a working electrode (WE) while maintaining the a given potential. An important aspect of electrochemical analysis is that the detection limit can change due to the difference between electrode systems.

Generally, two electrochemical analysis methods are available, one using two electrodes (RE and WE) and another use three electrodes (RE, WE, and a counter electrode). In generic electrochemical analysis, two electrodes can be used to analyze and inspect a sample. However, a voltage drop may occur due to the resistance of the sample solution, and the voltage of the WE may become lower than the original voltage. This problem arises when a highly-resistive organic solution is used. However, when an aqueous solution is used, the voltage drop is typically less than 1 mV. If an organic solution is measured using a two-electrode system, the current flow between the two electrodes should be significantly reduced to decrease measurement errors and obtain accurate data. A three-electrode system adds a CE to the two-electrode system to measure the sample. The CE usually uses an inert metal such as platinum.

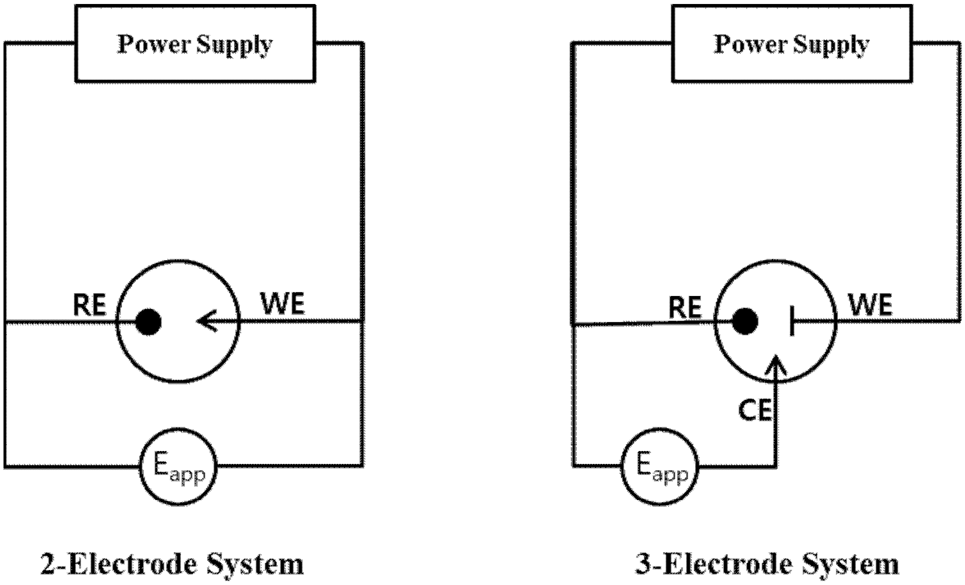


Figure 4. Electrochemical sensor system (2-electrode system and 3-electrode system)

Unlike a two-electrode system, where current flows between the RE and WE, in a three-electrode system current flows from the WE to the CE, and a constant voltage is maintained at the WE. This allows the current to flow to the CE through the indicator and auxiliary electrode.

Typical examples of measurement sensors that use electrochemical methods include potential difference, voltage measurement, and current measurement sensors. Next, the characteristics of each type of sensor will be examined.

a. Potentiometric Sensor

A potential difference sensor measures the potential difference between the RE and the measuring electrode on the surface of an analyzed material. There are generally two potential difference measurement methods: potentiometry and the ion-selective indicating electrode (ISE). Potentiometry measures the inactive electrode potential change with respect to the RE according to the concentration distribution of the substance to be measured in the sample. The ISE method measures the potential difference between membranes that can selectively permeate or adsorb the target to be analyzed by the inner charging solution and the sample. These potential difference sensors are widely used in biomedical engineering research to develop new drugs and diagnose, research and treat diseases.

b. Voltammetric sensor

Voltage measurement sensors are widely used to analyze various samples through a current-voltage relationship. Sensors can be classified as using repetitive, stripping, or square-wave voltage measurement methods.

c. Amperometric sensor

A current measurement sensor is a type of label immunosensor that measures the change in a labeling agent as an electrical current. A representative example is the enzyme immunosensor that uses an enzyme such as catalase or glucose oxidase as a labeling agent. The current measurement device embedded in an immunosensor is usually an oxygen electrode. The sensor is built by attaching an antibody immobilization membrane to the oxygen electrode. The competition method (antibody-1) is used to label a target antigen, and the sandwich method (antibody-2) is utilized to label the antibody. The amount of any labeled enzyme is determined by the change in the oxygen reduction current with the addition of a certain amount of enzyme substrate. The response time needed to achieve a steady current is 10–30 s, which is a remarkably short period of time compared to that of the conventional enzyme immunoassay.

D. Research Purpose

The POCT market is steadily and rapidly expanding. This study aims to develop a human blood-analysis potentiostat that simultaneously analyzes multiple. Existing potentiostats can analyze multiple markers at the same time, but are not portable due to their size. To date, portable potentiostats have not been capable of analyzing multiple, low-concentration markers due to limited device performance. Therefore, the present study was conducted to develop a portable potentiostat that does not affect detection results even when attached to a human body.

E. Article composition

This paper is organized as follows. Chapter 1 introduces the background and research method of potentiostats and explains its purpose and necessity. In Chapter 2, the functional design, hardware and software design, implementation and algorithms used to implement the potentiostats are described. Chapter 3 explains the experimental setup and method for the proposed potentiostat development method in this study. In Chapter 4, the experimental results are explained and analysis results are discussed. Finally, Chapter 5 presents the conclusions.

II. Implementation of human body-type potentiostat

A. Potentiostat Hardware Implementation

1. Potentiostat function

To develop the potentiostat proposed in this study, a sensor that detects simultaneous signals is created, and a snall analog signal detected by the sensor is converted to digital by an amplifier, filter, and ADC converter, and is then entered into a MCU. The result is configured to confirm analysis results from an outside environment using Bluetooth and a serial port.

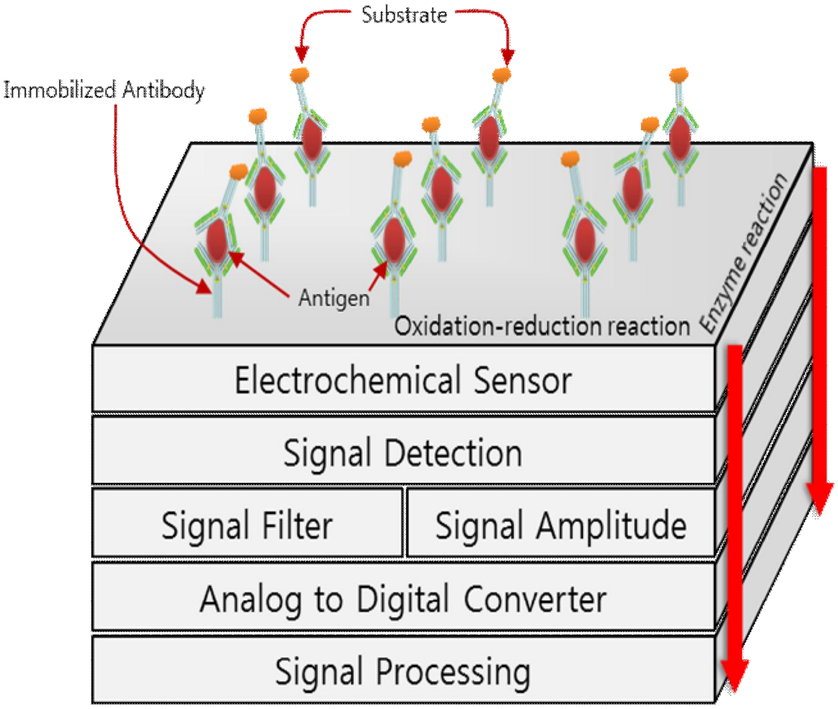


Figure 5. Schematic diagram of the signal processing using electrochemical sensors

2. Potentiostat performance on the human body

In the present study, the potentiostat circuit maintains a constant voltage. Voltage maintenance does not always refer to a constant voltage but a circuit that maintains a voltage that remains proportional to a voltage input provided by the user. In addition, this potentiostat simultaneously detects four signals to allow for a multi-marker analysis. The developed potentiostat has a detection error of < 5% when compared to existing devices sold on the market. The target detection limit is less than 1 year.

3. Human body-type potentiostat design

The on-body potentiostat is designed based on an ARM processor to generate signals from electrochemical sensors. The WE is used to directly detect signals from the sensor, and the detected signal is configured to amplify the detection signal through the an op-amp. In addition, a low-pass filter is added to detect the desired signal. The detected signal is converted from analog to digital through an amplifier and filter. The ARM processor is designed to control the counter electrode (CE) and RE. A fixed voltage was used for the RE, and a step was given to the CE. The ARM processor was used to construct an algorithm that can determine the current intensity over time. The ARM processor is designed to easily connect with smartphones and various applications using a Bluetooth module and USB connector.

4. Potentiostat firmware design

a. Definition

The new potentiostat proposed in this paper was based on an MCU and can control and detect each electrode. Thus, a program that can restrict such a potentiostat is necessary. To communicate with a smartphone and PC, USART communication can control Bluetooth and send data to a USB connector. In addition, the voltages of the RE and CE, which are the most important, can be controlled, and the current generated from the WE can be detected.

b. Methods

The current generated from the WE enters as analog data through the sensing portion of the potentiostat. Then, it is converted into a digital signal using an ADC, and the converted data are processed into a data type that can be visually confirmed. Since self-monitoring of the small potentiostat is not possible, two methods are available to transfer the data to a computer and smartphone. First, data are transmitted to the computer via a USB connector using UART. Second, data are saved and then sent via Bluetooth when data detection is completed. When communicating with a computer using USB, real-time detection can be confirmed on the monitor. However, with smartphones, data reliability may be low due to limitations in Bluetooth communication speed. Therefore, data are first saved in the MCU memory prior to transmission when communicating using a smartphone.

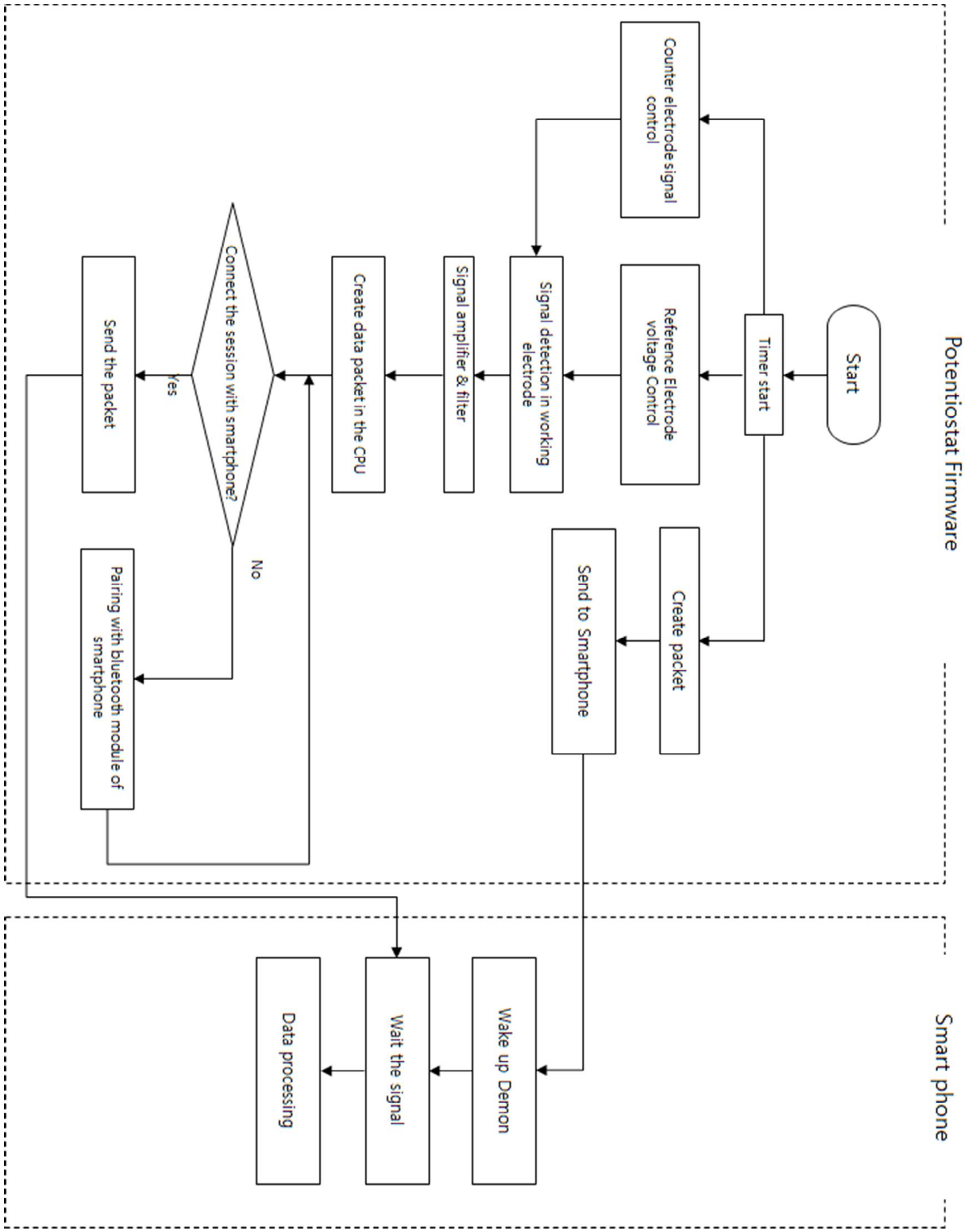


Figure 6. Potentiostat - Smartphone firmware block diagram

Figure 6. Hardware firmware block schematic for data transmission between potentiostat and smartphone. When the potentiostat begins to detect, it not only controls the RE and CE, but also begins pairing with the smartphone. The smartphone runs the application daemon and opens a port in preparation to receive the packet. After the potentiostat has completed data sampling, data can be transmitted if a session with a smartphone connects.

5. Development of the human body-type potentiostat

In order to develop a miniaturized potentiostat, several studies have endured trial and error, improving technologies while identifying problems at each developmental stage.

a. Development of Potentiostat V1.0 circuit

The first potentiostat was developed to implement functions, and was not focused on size. To determine whether four markers could be detected simultaneously, six electrodes were tested, consisting of four WEs, one CE, and one RE.

Although the CE and RE were separately controlled, all the electrodes were connected using a single connector.

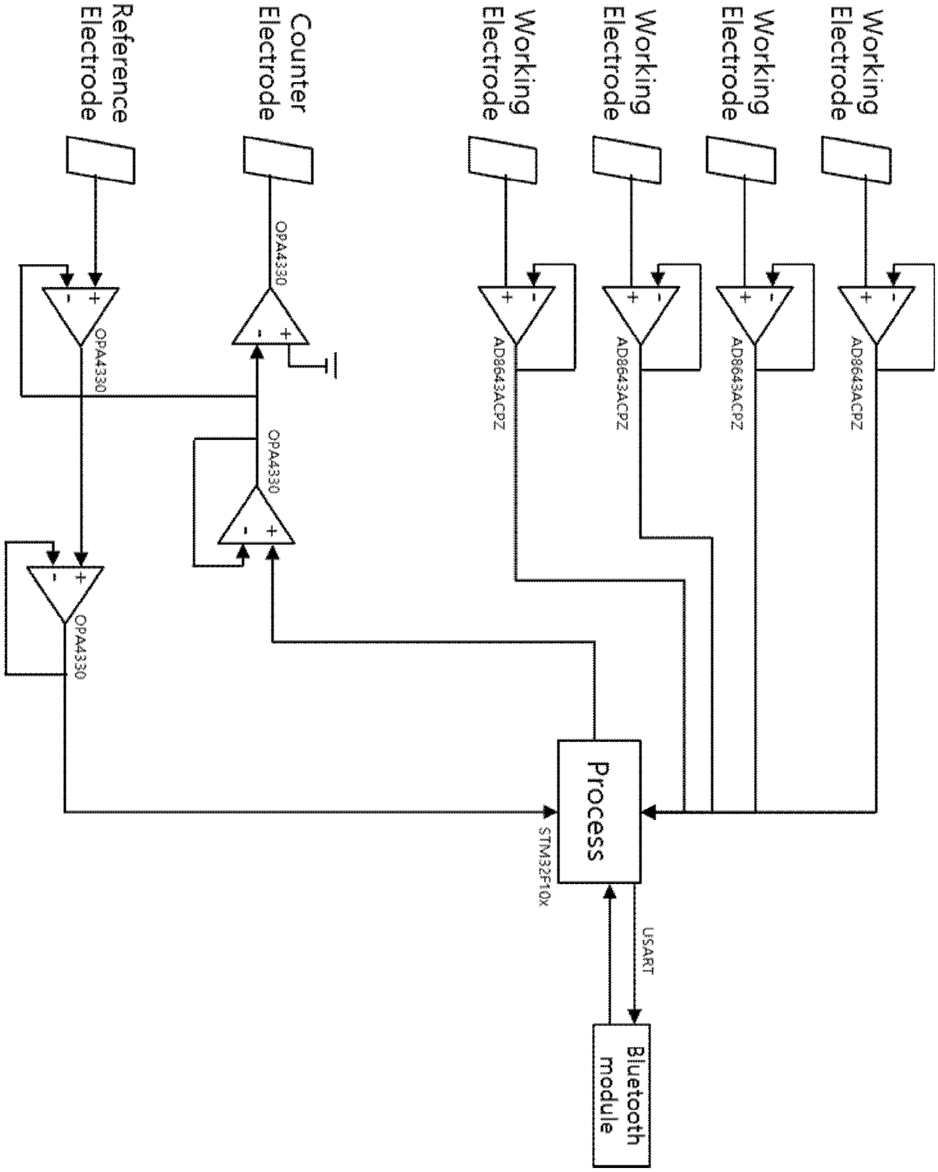


Figure 7. Schematic diagram of the first potentiostat hardware design

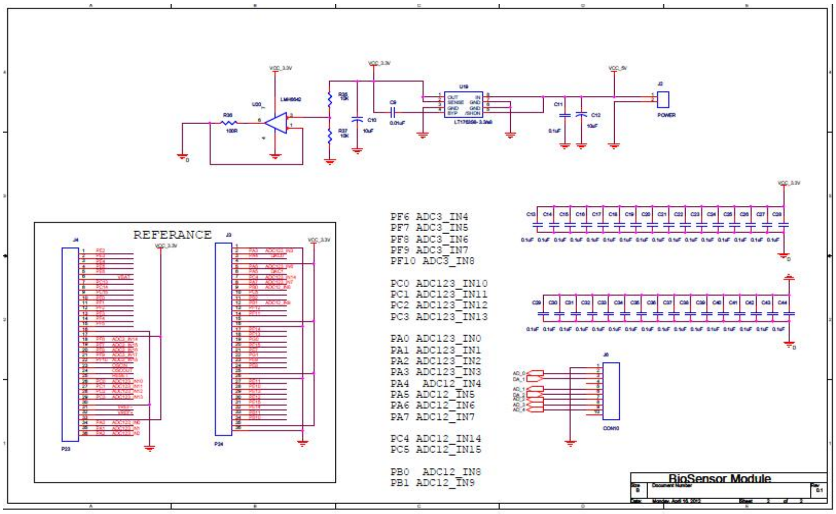


Figure 8. Design of the power supply circuit

The input voltage was changed from 5 V to 3.3 V and then to 1.65 V, which is a basic step in maintaining each electrode at a constant voltage. When using a high voltage, the voltage drop was carried out because of electrode damage.

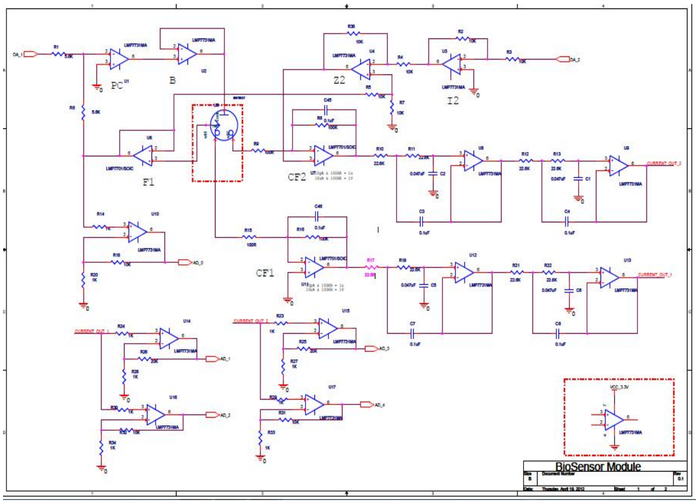


Figure 9. Potentiostat amplifier and filter architecture

The two ADCs were configured to supply voltages to the RE and CE. We designed a low-pass filter to identify the detected signal and an amplifier to amplify the signals since there was a possibility of loss.

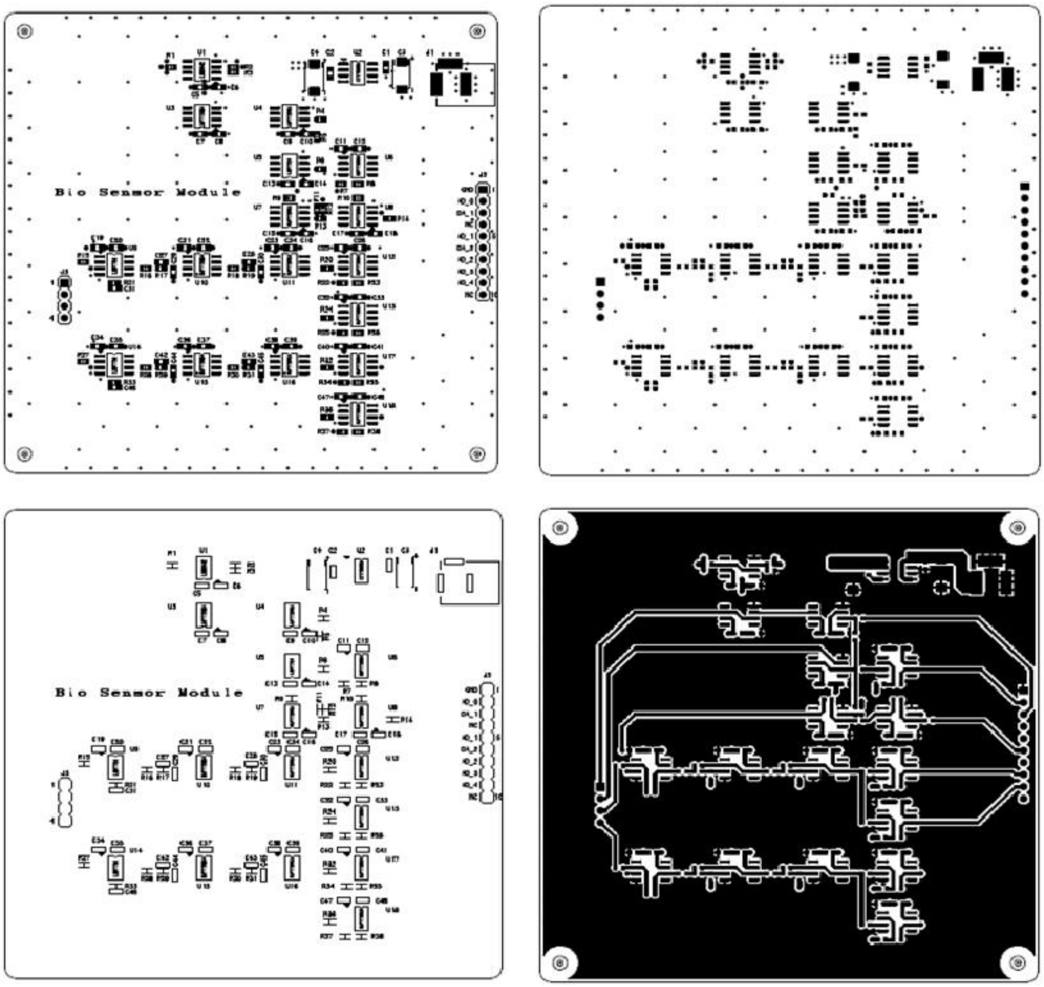


Figure 10. Prototype potentiostat Gerber format

The prototype potentiostat Gerber is composed of 4 layers, and the right part of the figure is connected to the RE, WE, and CE of the electrochemical sensor. Through signal amplification and the use of the filter in the middle part of the figure, the output signal is transferred to the processor through the right processor connector.

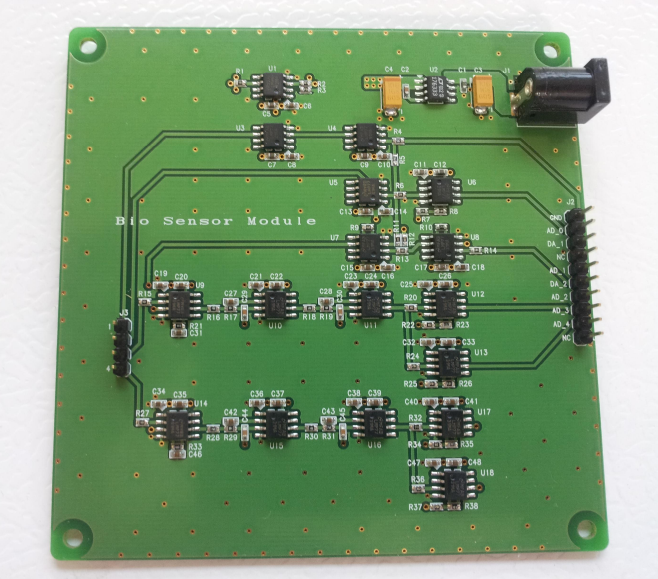


Figure 11. First potentiostat test PCB board

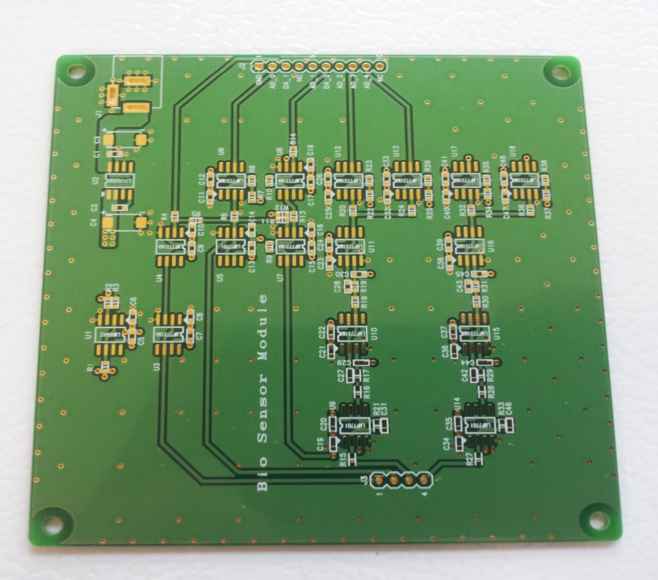


Figure 12. First potentiostat test PCB board (Blank)

b. Development of Potentiostat V2.0

The second production potentiostat was both similar and different to the first. Several problems were observed with the first potentiostat. It generated too much noise in the detection data due to peripheral interference, even though the control data was extracted or controlled through one connector.

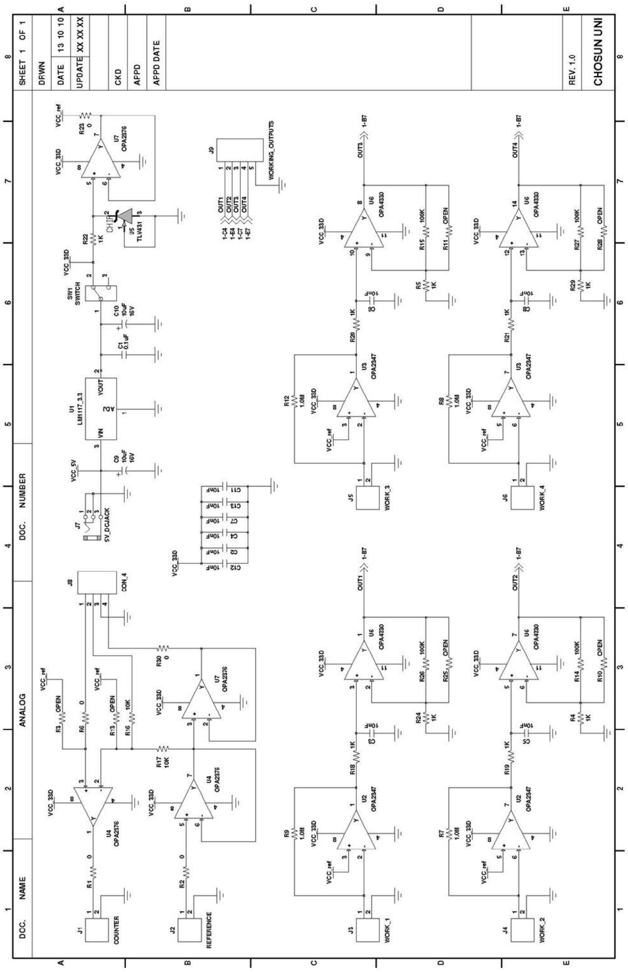


Figure 13. Design of the second potentiostat circuit

Figure 13 shows the second potentiostat circuit architecture that minimizes interference by separating each electrode module from the existing circuit and maximizing the distance between the electrode module and power control module. Furthermore, it was configured to control the amplification intensity and filtering using a variable resistor. Thus, the MCU and power control were located in the second layer, and the WE for detecting the signal was configured as an individual module to minimize ambient noise. However, the RE and CE were designed as a single module for simple control.

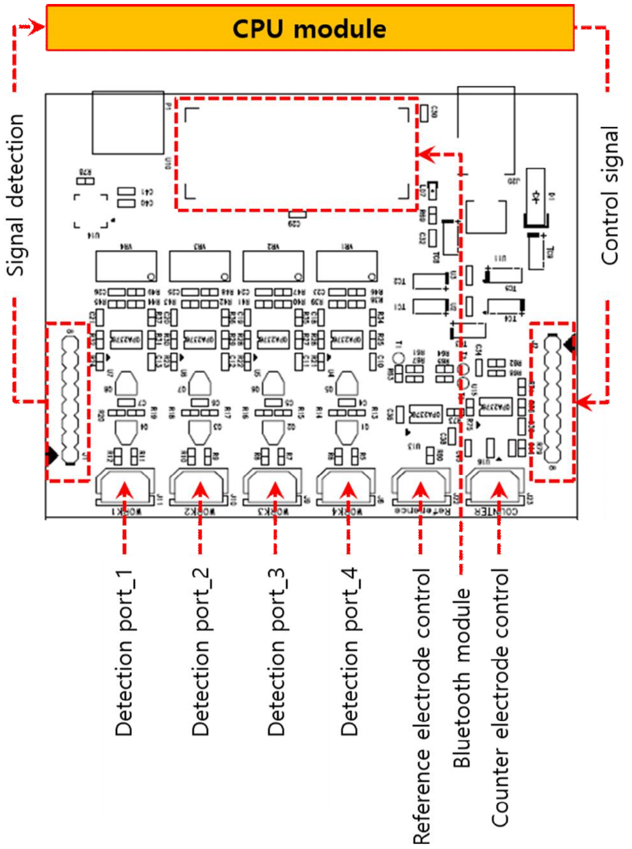


Figure 14. Second potentiostat PCB Gerber format

As shown in Fig. 14, four individual ports were created for simultaneous signal detection. The analog signal, is important in designing the Gerber model, was placed next to the detection port to avoid distortion in the signal before being transferred to the CPU module through the ADC.

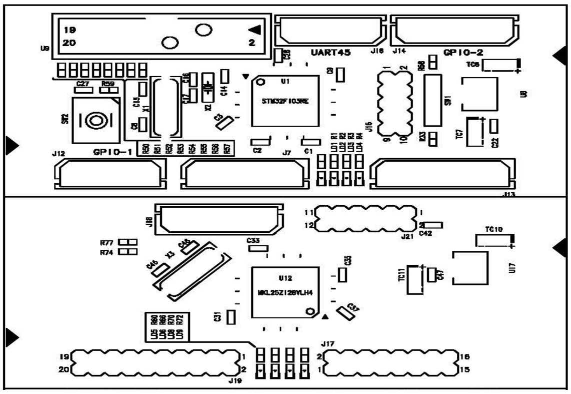


Figure 15. Gerber format using two types of MCU

In addition, the experiment was conducted with different types of MCUs, the STM32 and Freescale ARM processors. The difference between the STM32 and Freescale ARM processors is that the STM32 does not support DSP, whereas the Freescale's ARM processor does.

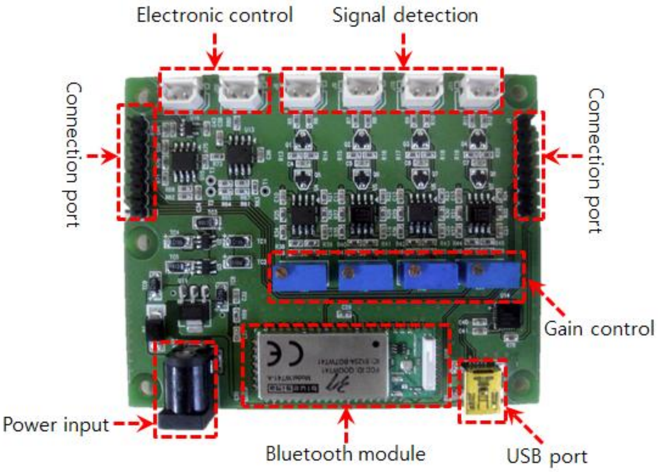


Figure 16. Second potentiostat test PCB board

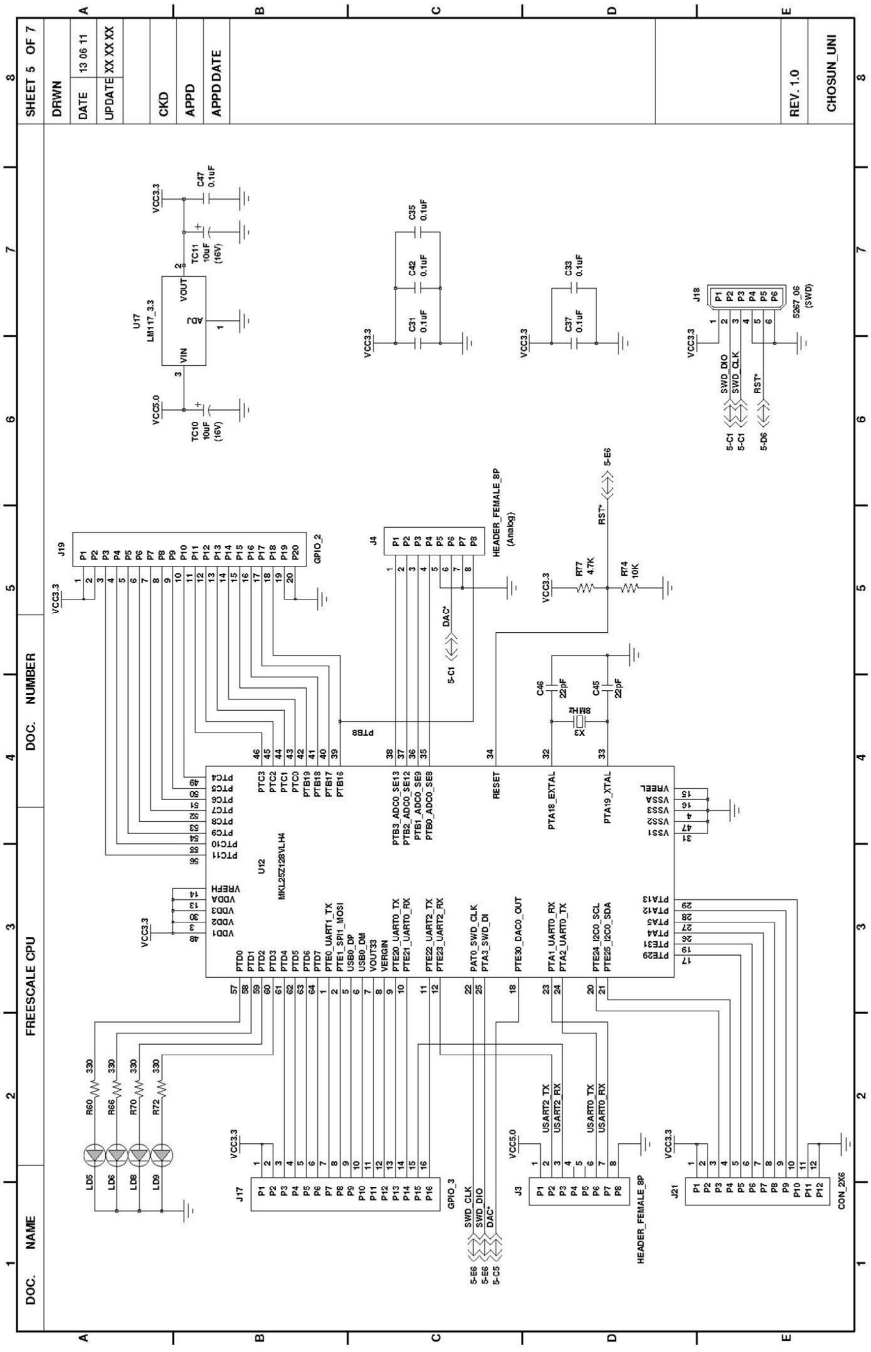


Figure 17. Freescale ARM processor architecture

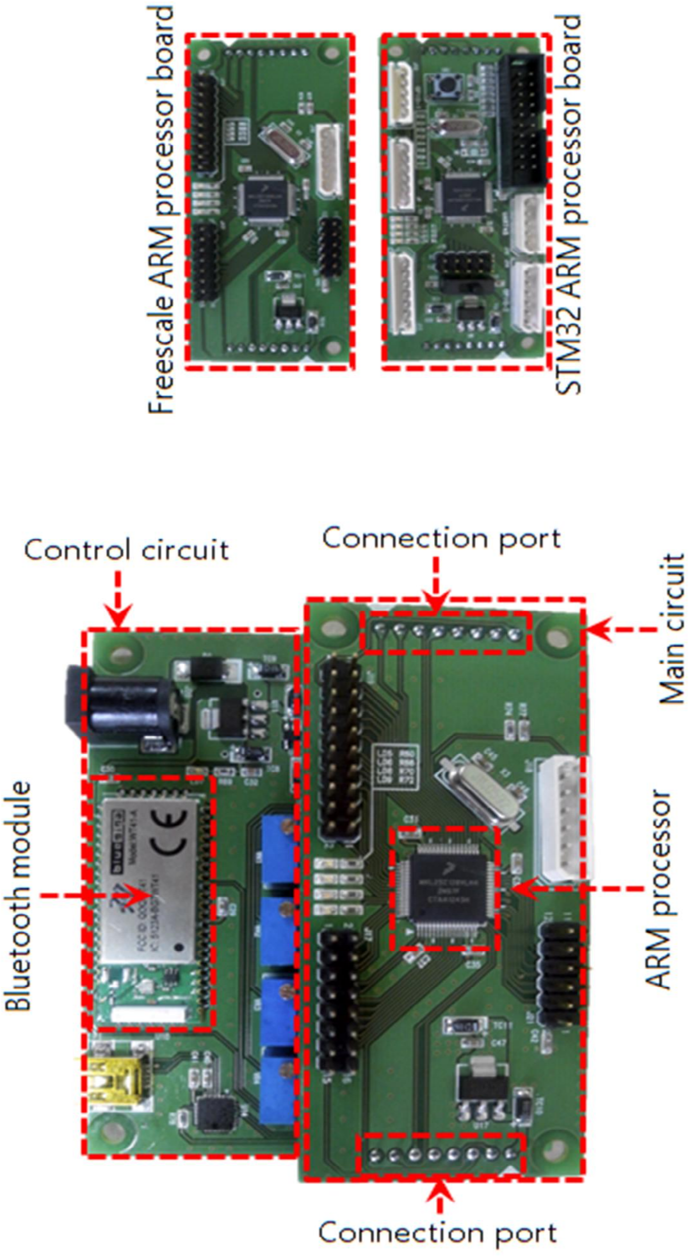


Figure 18. Development of a potentiostat using two MCUs

c. Final development of potentiostat V3.0

By solving the problems encountered during the experiment on the second potentiostat, a one with a smaller size that can simultaneously measure four markers was developed.

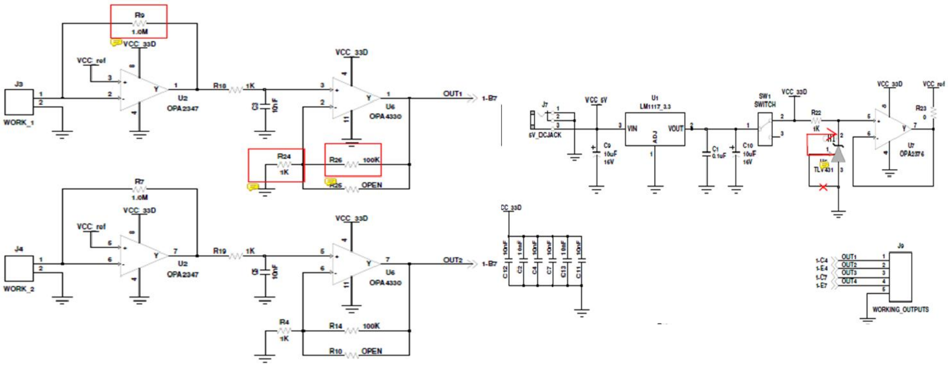


Figure 19. Complementing the second potentiostat problem

Some problems were encountered after developing the second potentiostat. First, no voltage was input at the start of the measurement, and noise was continuously generated. The cause of these problems was identified by changing the resistances of the first amplification and first filter. Data loss occurred due to the inaccurate range of the filter, and an error in the detection range occurred when detected data were monitored. The third potentiostat was developed after finding the cause and solution to these problems.

When using a conventional potentiostat, the electrode and potentiostat were connected by detecting a signal generated from the electrode through a circuit or by controlling the electrode. Through this test procedure, the effects of the noise generated by the lead wire is extremely large. To solve the problem, the third potentiostat minimizes the number of parts and designed sensor connection using a Micro-B connector.

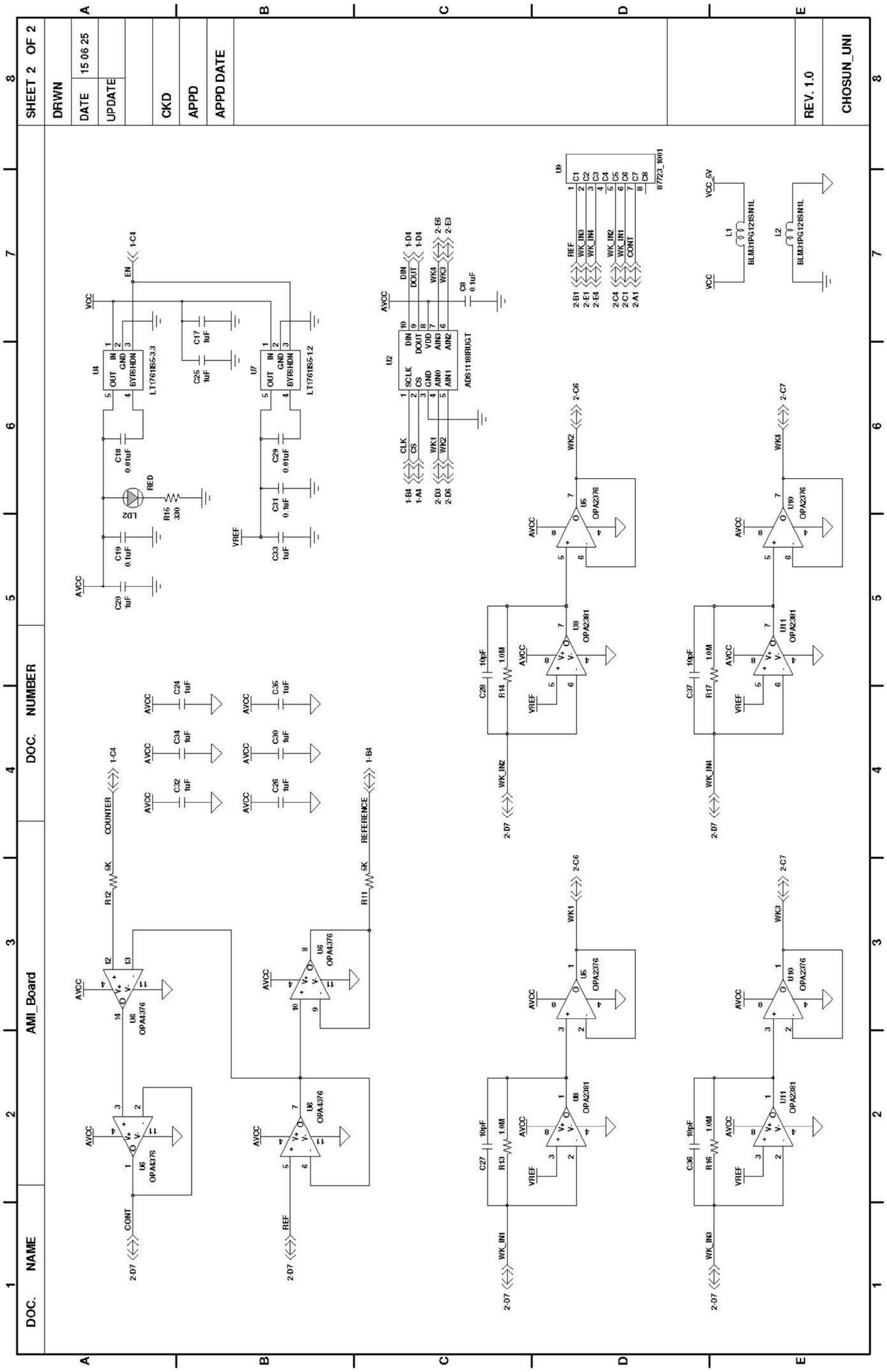


Figure 20. Potentiostat version 3 Artwork Production

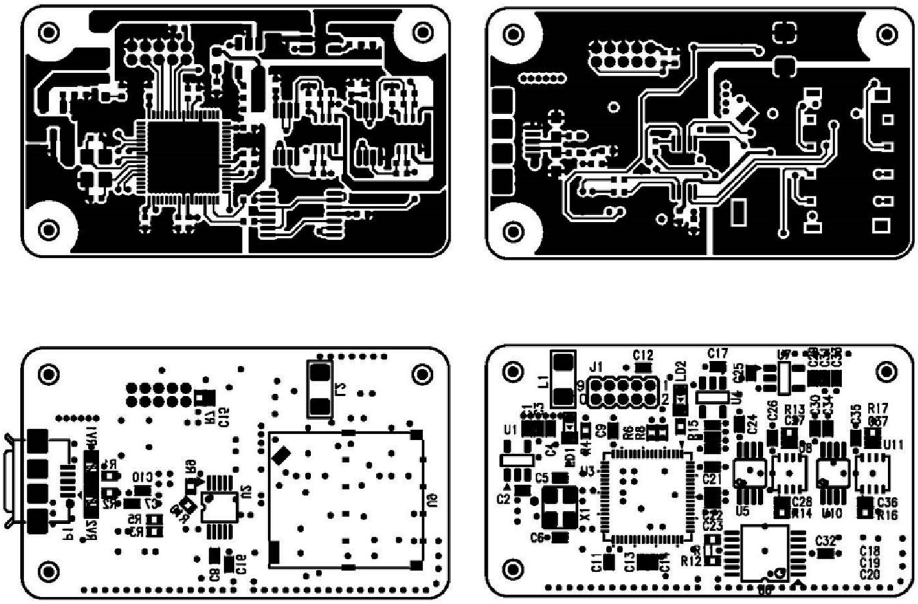


Figure 21. Potentiostat version 3 Gerber format

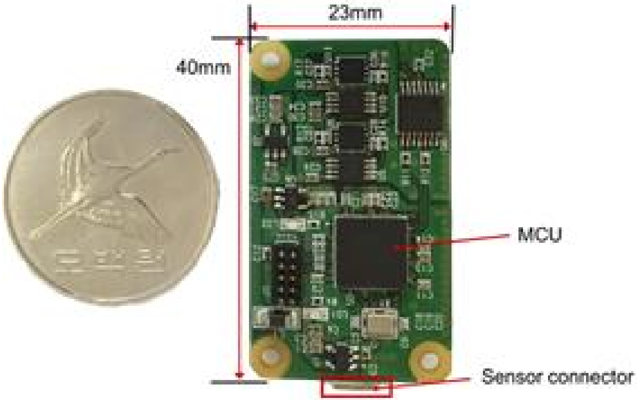


Figure 22. Size of the final potentiostat(23mm by 40mm)

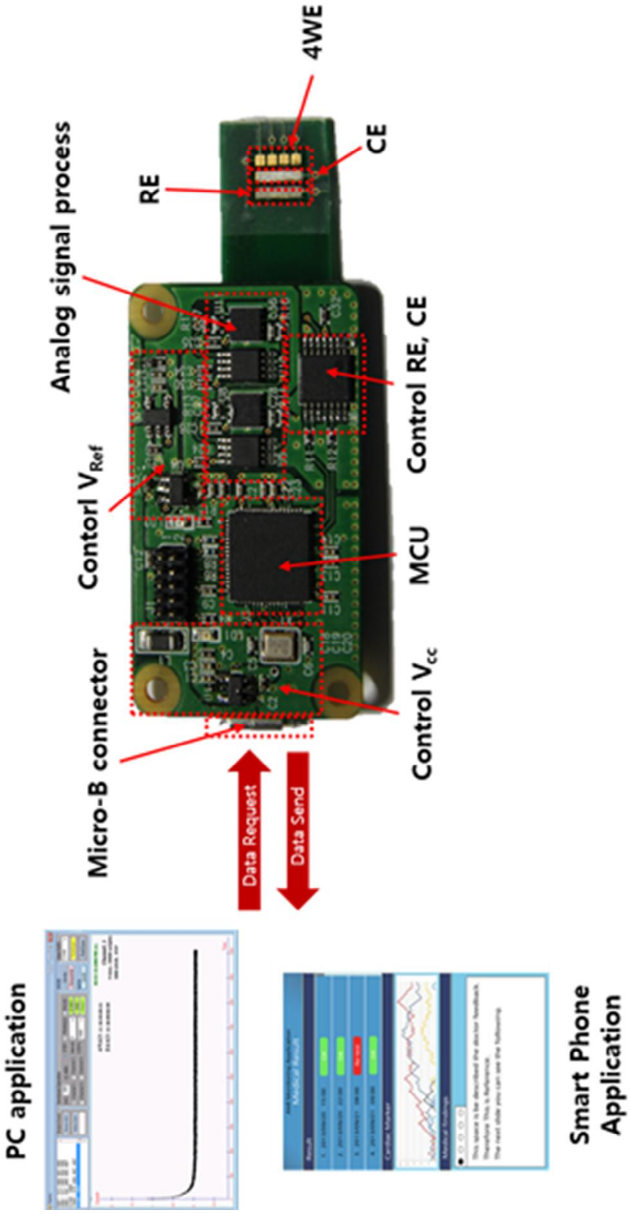


Figure 23. Final design of the third potentiostat

B. Implementation of the software Used in Data Detection and Verification

1. Functional design

We have developed a data verification program to directly check the data detected by the potentiostat. The program can check the data in real time using the USB port and also check the existing stored data. By connecting to Bluetooth, data can be stored in MCU and then be transferred to the computer for analysis.

2. Control packet structure

Control packets were diverted to a PC and smartphone using Bluetooth. The PC application requires a communication port setting because it is connected via USB. Therefore, the port setting is enabled as an internal function of the application and the data can be checked in real time.

	PC application	ARM processor	Smartphone
GET_ADC	Data detection request	-	Data detection request
GET_ADC_RTN	-	Detection completion response	-
GET_ADCM	Request detection result	Detection result sent	Request detection result
GET_ADCM_RTN	Result received	-	Result Received

Table 1. Structure of potentiostat data packet

Although the packet structure is divided into four stages, the purpose of the message changes depending on whether the Bluetooth module is used or not. The GET_ADC message is a message that indicates the start of detection. When the detection result is completed, the ARM processor sends a GET_ADC_RTN message. At this point, PC application allows real-time data transmission, and data cannot be transmitted in real time with smartphone due to the Bluetooth data transmission speed. Accordingly, the detection result is temporarily stored in the RAM of the ARM processor until the detection time is completed. When the detection process is completed, the data is divided and transmitted.

3. Design of the data transmission algorithm using Bluetooth

In the present study, the potentiostat uses two communication methods. First, data is transmitted and received using a USB connector. Second, data is transmitted and received using Bluetooth. Between these two methods, a data transmission algorithm using Bluetooth is designed prevent data loss.

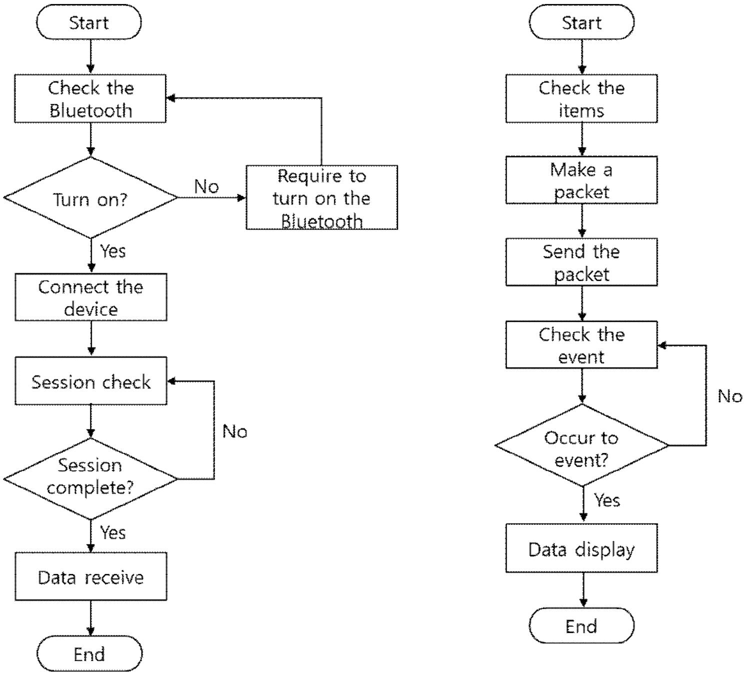


Figure 24. (Left) Bluetooth session connection method and (right) data processing method of the application

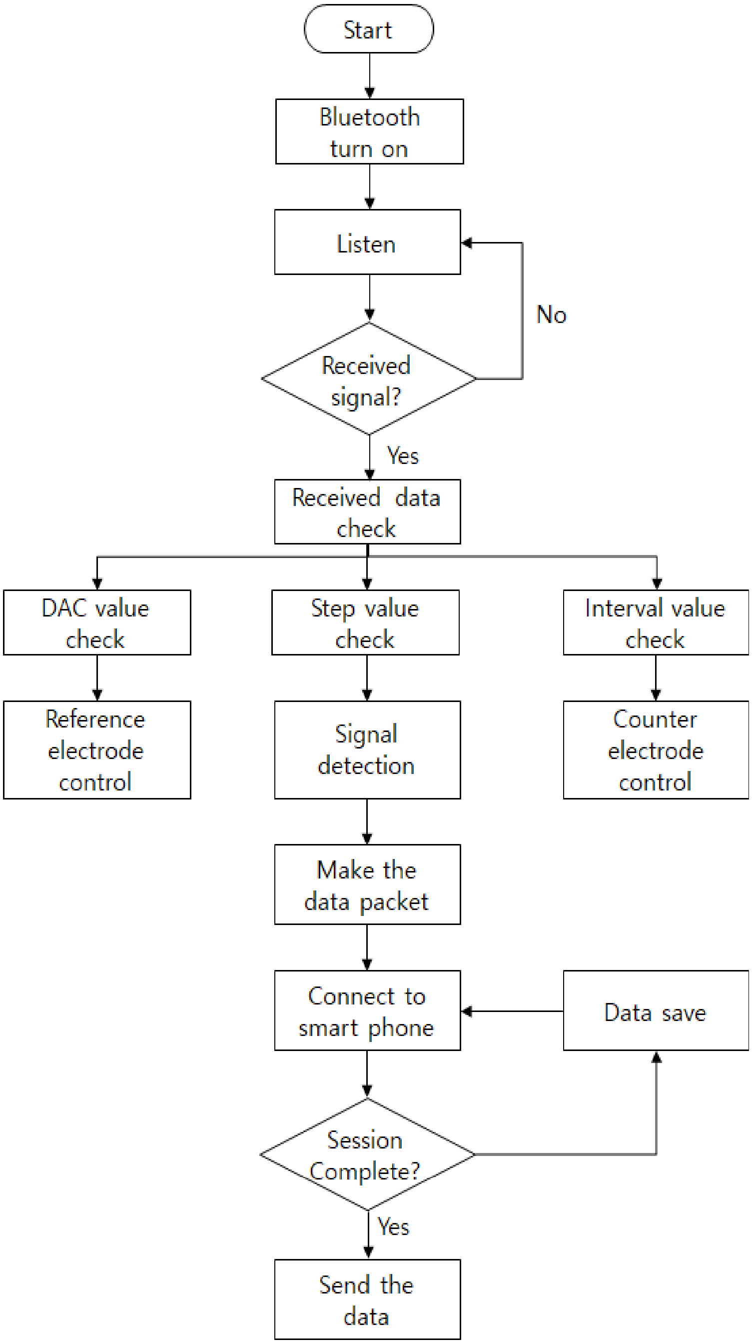
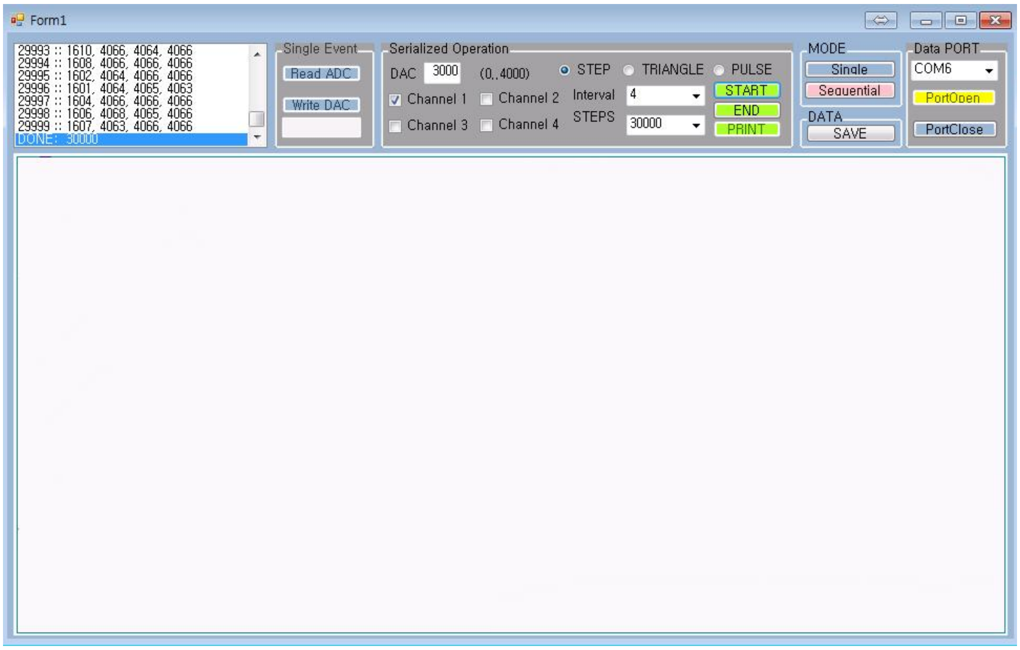


Figure 25. Bluetooth data transmission and reception method algorithm

C. Development of Software

To simultaneously detect four markers as proposed, a different graph color was assigned to each WE for easier recognition by users. Only the data value of the selected WE is displayed when the user selects the electrode of the desired number. In addition, the RE and CE electrode voltages can be controlled through the software. Moreover, the interval and step number can be set, and the voltage can be controlled by the step, triangle, and pulse methods.



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29993 :: 1610, 4066, 4064, 4066
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29995 :: 1602, 4064, 4066, 4066
29996 :: 1601, 4064, 4065, 4063
29997 :: 1604, 4066, 4066, 4066
29998 :: 1606, 4068, 4065, 4066
29999 :: 1607, 4063, 4066, 4066
DONE:  30000
```

DAC 3000 (0..4000)
● STEP ○ TRIANGLE ○ PULSE
☑ Channel 1 ☐ Channel 2
☐ Channel 3 ☐ Channel 4
Interval 4
STEPS 30000
COM6

Figure 26. Potentiostat data detection program UI design

This potentiostat has several advantages. It allows real-time inspection of the data detected with a miniaturized potentiostat, and a function to store and recall existing data has been added. In addition, a menu has been configured to print the records once they are completed.

Ⅲ. Experimental Design and Methods

A. Experimental Design

1. Sensor design

Human body-type diagnostic modules require specially fabricated sensors to be developed due to the location where they are used. Most of the sensors are made of acrylic and glass materials, and the coating of the circuit is time consuming and expensive. In this study, the sensor design was established to address these problems, and FR-4 was selected because it is cost-effective and easy to manufacture.

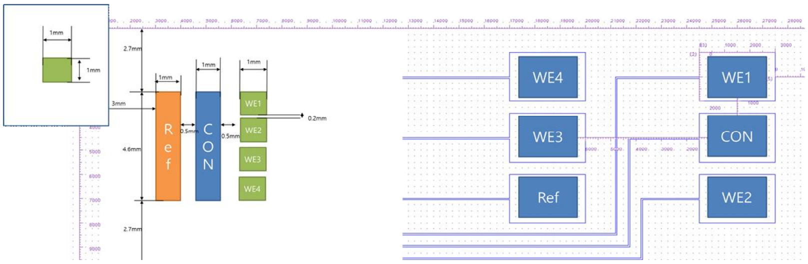


Figure 27. Electrochemical sensor diagram

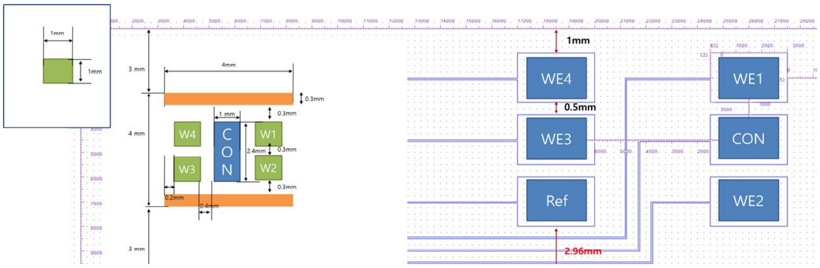


Figure 28. Sensor design in terms of RE size and proportion

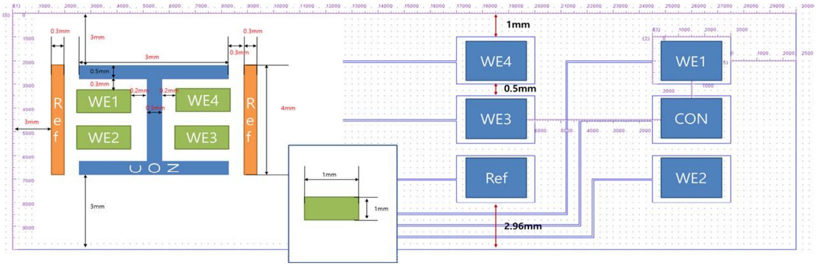


Figure 29. Sensor design depending on the position and size variations of CE and RE

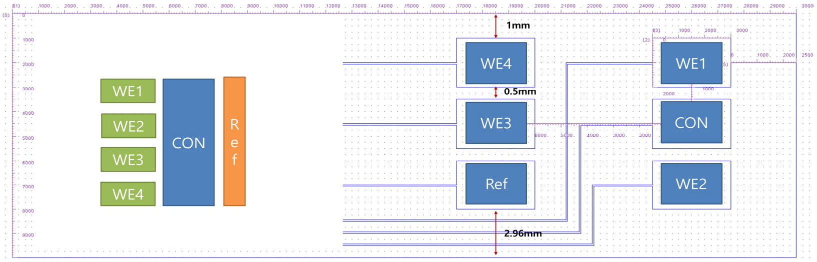


Figure 30. Sensor design according to the second batch transformation

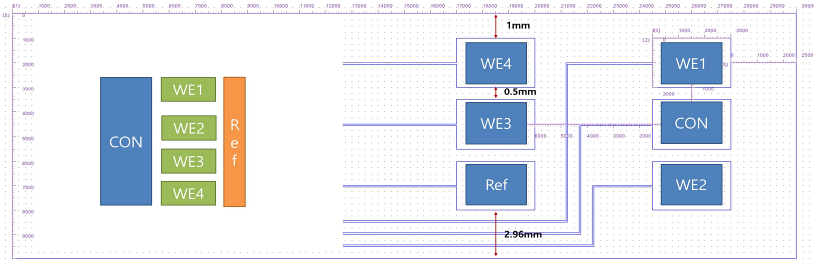


Figure 31 Sensor design according to the third batch transformation

Sensor designs were created using five methods in total. The WE was designed to be a quarter of the size of each CE and RE, and the same surface area was assigned to the CE and WE. In addition, the sensor was designed by changing the arrangement of the electrodes to obtain experimental results depending on the arrangement of the sensors.

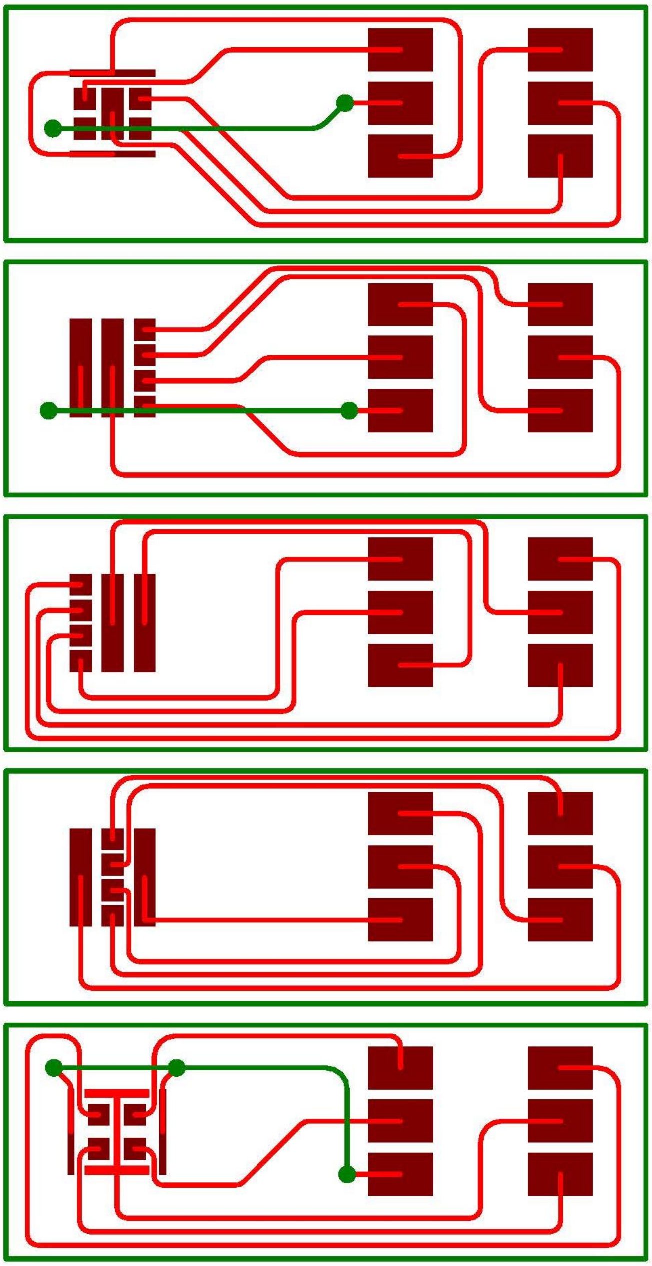


Figure 32. Artwork format of the five FR4 sensors

2. Sensor manufacturing

The sensor was designed with five different electrode patterns, and the part connected to the potentiostat was created in accordance with the Micro-B connector style. The size of the sensor is 11 mm × 30 mm, which is suitable for use with a small potentiostat.

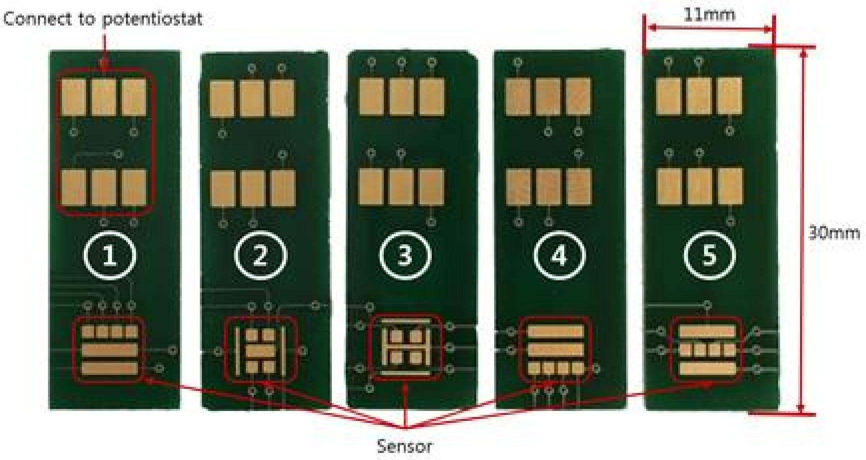


Figure 33. 5 types of sensory prototypes

To determine the sensor data in the experiment, sensors were separated from FR-4_P1 to FR-4_P5 according to the sensor pattern number. The FR-4_P1 sensor arranges the CEs in the center, with the WE and RE on the left and right of the CE, respectively. In the FR-4_P2 sensor, the RE and WE are arranged symmetrically with respect to the CE. The FR-4_P3 sensor was designed so that the size of the CE is 1.5 times larger than that of the RE, and WE is arranged between the CE and RE. In FR-4_P4, the CE and WE are arranged symmetrically with respect to the RE. In the final format, the CE and RE are arranged symmetrically around the WE.

B. Experimental Method

1. Experimental solution

The validation test of the sensor was carried out using KCL and Tris +aminophenol solution. For the solution, 1mM of KCl and hexaammineruthenium (II) chloride were used, and phosphate buffered saline was used as a buffer. For the sensor confirmation solution, 0.0013 g of reagent was added to 50 mL of buffer.

2. Experimental method

In this study, the performance of the FR-4 sensors produced in various patterns must be verified, and the following experiment should be conducted with a verified sensor. Experiments are carried out with various concentrations of $Ru(NH_3)_6Cl_3$ using the tested sensor. The experiment was conducted with concentrations at 0.01 M, 0.05 M, and 0.1 M. The RE was coated with Ag/AgCl paste, and the CE was coated with platinum (Pt). Since the WE is sensitive to resistance and noise, the sensor electrode coating was performed using gold.

C. Analysis method

1. Comparison method settings

To verify the potentiostat developed in this study, the data of the potentiostat were compared and analyzed using the commercial chemical analyzer (Emstat4). The most stable sensor among the various pattern sensors of FR-4 material was selected to detect the data results of $Ru(NH_3)_6Cl3$ solution at the same time, environment, and sampling speed using the Emstat4 comparative analysis equipment.

2. Correlation analysis

Correlation analysis was based on the relationship between the variables measured using a sequence scale, isometric scale, and ratio scale. The measured variable means the data detected by FR-4. A correlation analysis is possible because the data obtained from the potentiostat developed in this study, and the reference instrument Emstat 4 is sampled at the same rate. The data detected by the potentiostat developed in this study changes with a certain degree of correlation with the data detected using Emstat4. When analyzing the relationship between the two variables, a simple correlation is used for comparative analysis. The correlation coefficient is a numerical value summarizing the degree or direction of the relationship between data in one numerical value and expressed as an absolute value between ±1.

Correlation coefficent	Definition
$r < .2$	Very weak correlation
$.2 < r < .4$	Weak correlation
$.4 < r < .6$	Average correlation
$.6 < r < .8$	Strong correlation
$r > .8$	Very strong correlation

Table 2. Definition of correlation coefficient

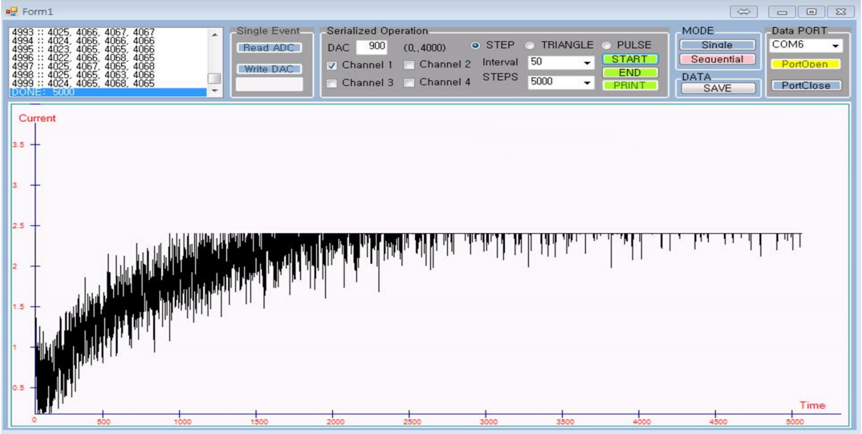
A significant correlation was observed. That is, when the detected data of the Emstat4 increases, the potentiostat variables of this study increases. The absence of an association between the two datasets even when the potentiostat variables decreases as the detected data of Emstat4 decreases can be attributed to two reasons. First, the data values that are detected or not influence other data values. Second, the correlation coefficients do not reveal a causal relationship.

Ⅳ. Experimental Results and Review

A. Experimental Results

1. Results of previous studies

We developed a final potentiostat in three stages and verified the detection results using a software application capable of showing data in real time.



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4993 :: 4025, 4066, 4067, 4067
4994 :: 4024, 4066, 4066, 4066
4995 :: 4023, 4065, 4065, 4066
4996 :: 4022, 4066, 4068, 4065
4997 :: 4025, 4067, 4065, 4068
4998 :: 4025, 4065, 4063, 4066
4999 :: 4024, 4065, 4068, 4065
DONE: 5000
```

DAC 900 (0..4000)

☑ Channel 1 ☐ Channel 2

☐ Channel 3 ☐ Channel 4

● STEP ○ TRIANGLE ○ PULSE

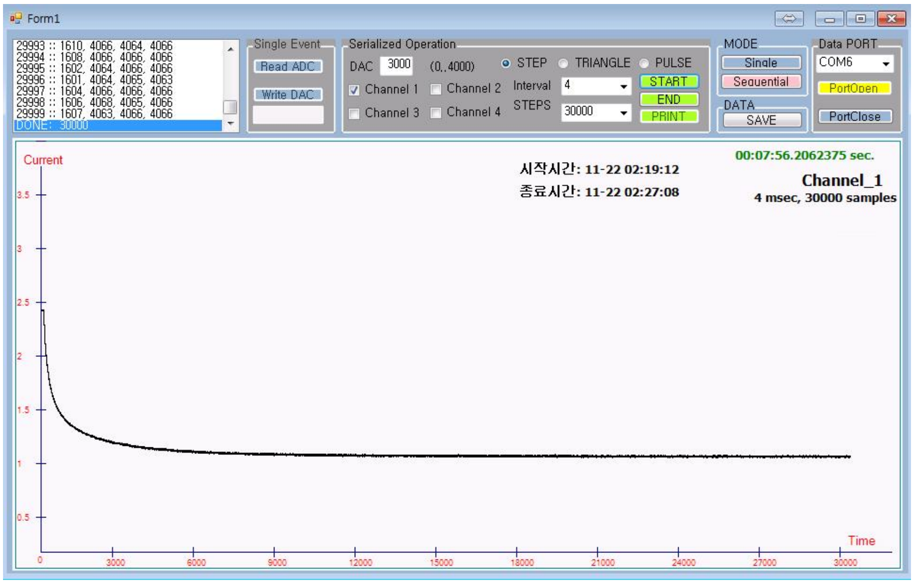
Interval 50

STEPS 5000

Data PORT COM6

Figure 34. Potentiostat V1.0 detection result

The above figure shows the data obtained with the first potentiostat by measuring the reduction reaction of the sample without considering surrounding noise or interference. However, the design of the filter was inadequate, and we observed a significant loss in the data. In addition, the figure shows a test result using one WE, and about 5000 samples were detected at an interval of 50 ms. This potentiostat had a significantly high noise level as shown in the figure, but this prototype was an improvement in that the sensor response was detected in real time.



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29993 :: 1610, 4066, 4064, 4066
29994 :: 1608, 4066, 4066, 4066
29995 :: 1602, 4064, 4066, 4066
29996 :: 1601, 4064, 4065, 4063
29997 :: 1604, 4066, 4066, 4066
29998 :: 1606, 4068, 4065, 4066
29999 :: 1607, 4063, 4066, 4066
DONE: 30000
```

DAC 3000 (0..4000)
● STEP ○ TRIANGLE ○ PULSE
☑ Channel 1 ☐ Channel 2
☐ Channel 3 ☐ Channel 4
Interval 4
STEPS 30000
Data PORT COM6

00:07:56.2062375 sec.
시작시간: 11-22 02:19:12
종료시간: 11-22 02:27:08
Channel_1
4 msec, 30000 samples

Figure 35. Potentiostat's second detection result

A more stable signal was detected using the second potentiostat. Here, a 4-ms interval was possible using DSP, and it operated smoothly until 30,000 samples were detected. Furthermore, noise was significantly reduced, and the detection range was 200 nA ~ 1μA.

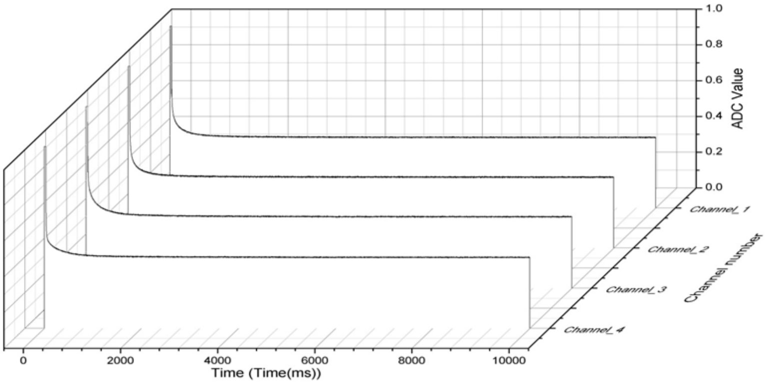

Figure 36. Simultaneous detection using potentiostat V2.0

The above figure shows the results of simultaneous detection using a WE. The amplification and low-pass filter were improved by changing the variable resistance from 1–10 MΩ to increase the detection limit.

2. Experimental Results of Potentiostat V3.0

The final potentiostat was used to carry out the experiment, which was the final product of this study.

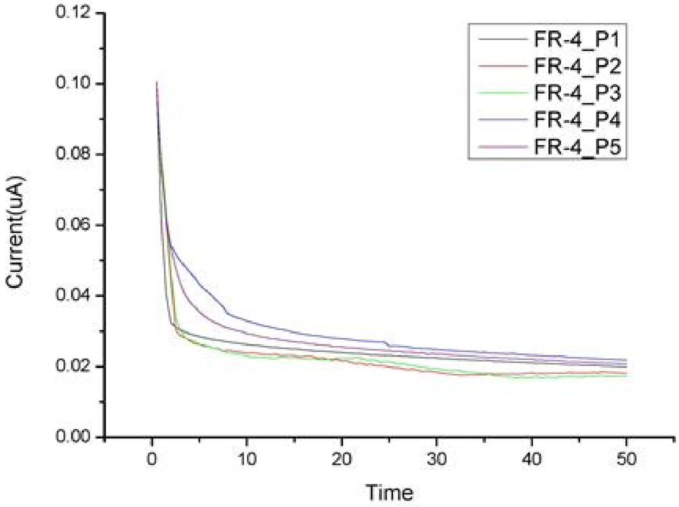

Figure 37. Experiment results using the 5 patterns of FR-4 sensor

Figure 37 shows a current detection graph for each electrode pattern with time. The response of pattern 1 was very fast. Patterns 2 and 3 show much noises and were not stable. Pattern 4 confirmed that the oxidation-reduction reaction was not uniform. Pattern 5 showed a constant reaction rate and less noise than the other electrode patterns. Therefore, sensor 5 was selected as a suitable sensor as a Human-body attachable potentiostat.

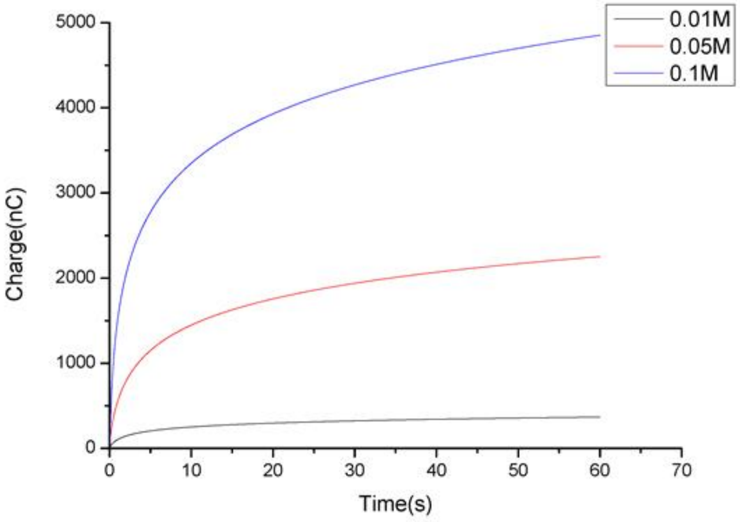

Figure 8. Comparison graph analyzing various concentrations

Figure 38 shows the sensor measurement results by concentration. $Ru(NH_3)_6Cl_3$ solutions at 0.01M, 0.05M, and 0.1M concentrations were used, and data were detected for 60 s at a scan rate of 4 ms. The results were as follows: 367 nC for 0.01 M, 2252.48 nC for 0.05 M, and 4853 nC for 0.1 M.

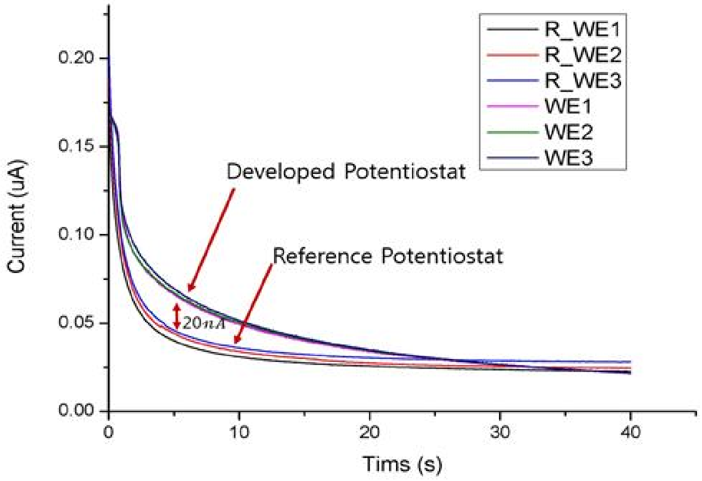

Figure 39. Comparison of the results obtained from comparing potentiostats

The above figure shows the comparison between Emstat4 and the high sensitivity potentiostat developed in this study. In this figure, WE1 to WE3 are the data detected by the final potentiostat developed in this study, and R_WE1 to R_WE3 are the data detected by the existing Emstat4. A 0.01 M solution was used, and the device was set at a scan rate of 4 ms for 40 s. In this experiment, three WEs were simultaneously measured using Emstat4 25°C, and subsequently, the experiment was conducted using the final potentiostat. The minimum detection limit was 22 nA, the resolution was 70 pA, and the detection range was 22–213 nA. The result obtained using the WE was very similar to that obtained using the reference equipment.

B. Analysis Results

	0.01M	**0.05M**	**0.1M**
0.01M	1		
0.05M	.982	1	
0.1M	.981	.991	1

Table 3. Analysis of correlation coefficient by concentration

To verify the accuracy, we analyzed the correlation using SPSS Ver.23. The data was measured at concentrations of 0.01 M, 0.05 M, and 0.1 M at 25°C for 1 minute with a scan rate of 40 ms. The result of the correlation analysis of the measured charge amounts at different molar concentrations revealed a significant correlation with a high correlation coefficient (R: 0.98).

	R_WE1	**R_WE2**	**R_WE3**	**WE1**	**WE2**	**WE3**
R_WE1	1					
R_WE2	0.994	1				
R_WE3	0.956	0.952	1			
WE1	0.947	0.954	0.936	1		
WE2	0.942	0.949	0.934	0.998	1	

Table 4. Comparison between the Emstat4 equipment and potentiostat version 3.0

To demonstrate that the detection data of the potentiostat developed in this study is reliable, we analyzed its correlation with the Emstat4 data. A significant correlation at 0.9 or higher correlation coefficient was observed between the R_WE and WE developed in this study. This result suggests that the existing and newly developed devices have the same level of performance. In addition, a correlation coefficient of 0.9 or more was observed among the three channels of the existing and newly developed equipment. Thus, a similar level of performance without malfunction was observed among the electrodes.

V. Conclusion

The future of the POCT industry is expected to evolve with the use of wearable devices that can detect and analyze signals generated within the human body, and the size of the POCT devices is expected to decrease. The miniaturization of the device can have a significant effect on the POCT industry, and reliability issues may be encountered. Although efforts have been made to improve the efficacy of wearable-type portable diagnostic devices, an electrochemical analysis device with high accuracy has not yet been developed. In addition, the development of a highly reliable circuit is costly, and a lengthy time verification procedure is required to confirm the reliability. The high sensitivity potentiostat developed in this study upgraded the problem analysis and circuit by version after the initial design, which facilitated the miniaturization of the potentiostat developed in this study. This allows simultaneous measurements of the four WEs, up to 22 nA in a small amount of 10 floating points. The technology that can detect such ultrafine data enables its use as a diagnostic device that can be attached to the human body, and we developed a sensor that can measure a small amount of sample at a low price using the FR-4 material. Recently, the potentiostat is becoming more miniaturized, and a miniaturized human body-type potentiostat may be developed by using the SoC (System on Chip) for the currently developed PCB. This can be used in basic research, particularly in the development of protocols and portable applications that can check the occurrence of diseases. Different types of portable POCT devices can be developed by integrating a circuit and wireless communication device into one module that can amplify and filter ultrafine signals.

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List of Publications

1. Journal Paper

1) J. H. Jung, Jihoon Lee, J. H. Lee and Y. T. Kim, "A smartphone based U-Healthcare system with ISO/IEEE 11073 for acute myocardial infarction", Published to International Journal of Communication Systems, vol.28, no.18, pp.2311-2325, Dec. 2015.
2) J. H. Lee, “Development of potentiostat for human-body mounted portable diagnostic devices”, Accepted to Korea Knowledge Information Technology Society, Sep, 2017

2. Conference Paper

1) Li Meina, Dinh Luan, **Jihwan Lee**, Youn Tae Kim, "In-situ Monitoring of Energy Expenditure by the Application of Wireless Patch Type Sensor Module", American Medical Association-IEEE, 28-30 Mar. 2010.
2) Dinh Luan, Li Meina, **Jihwan Lee**, Youn Tae Kim, "Algorithm for Real-time Wireless Monitoring of Heart Rate and Agility Index", American Medical Association-IEEE, 28-30 Mar. 2010.
3) **Jihwan Lee**, Jaehyo Jung, Youn Tae Kim, "Algorithm and communication protocol for mobile Cardiac Marker Monitoring System", American Medical Association-IEEE, 16-18 Oct. 2011.
4) **Jihwan Lee**, Jaehyo Jung, Youn Tae Kim, "Design and development of mobile cardiac marker monitoring system for prevention of acute cardiovascular disease", IEEE Sensors, P1724-1727, 28-31 Oct. 2011.
5) **Jihwan Lee**, Jaehyo Jung, Dong hyuk, Youn Tae Kim, "Patch Type Sensor Module for Diagnosis of Acute Myocardial Infarction", IEEE Sensors, 28-30 Oct. 2012

List of Publications

3. Patent

1) "질병진단장치 및 이의 질병진단방법, 그리고 질병진단시스템 및 이의 질병진단방법“,김윤태, **이지환**, 정재효, (Oct 20, 2014, KOR 101454719)
2) “마이크로니들 침습장치”, 김윤태, **이지환**, 정재효, 이지훈, (Jan 21, 2015, KOR 101486791)

3) "DISEASE DIAGNOSIS APPARATUS AND DISEASE DIAGNOSIS method thereof, and DISEASE DIAGNOSIS SYSTEM and DISEASE DIAGNOSIS method thereof“, Youn Tae Kim, **Jihwan Lee**, Jaehyo Jung, Youn Tae Kim, (June 14, 2012, US 13/523,345)
4) “질병진단장치 및 진단모듈”, 김윤태, **이지환**, 정재효, 이지훈 (April 11, 2013, KOR10-2013-0039867, 공개)
5) “Microneedle bio-sampling apparatus”, Youn Tae Kim, **Jihwan Lee**, Jaehyo Jung, Jihoon Lee (June 10, 2013, US 13/914,212)
6) “Diagnostic module for diagnosing disease and disease diagnosis apparatus having the same”, Youn Tae Kim, **Jihwan Lee**, Jaehyo Jung, Jihoon Lee (June 07, 2013, US 13/912,981)

ABSTRACT

Development of potentiostat for human-body mounted portable diagnostic devices

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The interesting thing is increasing about personal healthcare and an aging society. As a result, The POCT(Point-Of-Care Testing) market is growing rapidly. There are a variety of POCT devices, of which potentiostat is often used to measure precise components. Numerous potentiostats can be easily accessible. However, a portable potentiostat with the highly accurate sensor is not easily accessible. However, Potentiostat, which can be attached to a human body, has a limited range of measurement range. The high-sensitivity potentiostat developed in this study enables the measurement of multiple markers in the one chamber and the analysis data can be checked in real time. Also, It can be communication with a computer or smartphone by internal USB, Bluetooth or Serial port. and then The potentiostat developed the compact size (23㎜ x 40㎜) by minimizing the number of components through FPGA development. and then We checked the high reliability(correlation coefficient: 0.94) and row detection limited(20nA). We make the sensor by using FR-4 material and then We found the stable pattern in the variable sensor pattern. It can be useful change the pattern and connect to the line. Also, It doesn't break from high elasticity. Our device will have a positive influence on POCT and potentiostat market.