## COMPACT, LOW-POWER MICROELECTRONIC INSTRUMENTATION FOR WEARABLE ELECTROCHEMICAL SENSOR ARRAYS IN HEALTH HAZARD MONITORING

By

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## A DISSERTATION

Submitted to Michigan State University in partial fulfillment of the requirements for the degree of

Electrical Engineering – Doctor of Philosophy

2016

#### ABSTRACT

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Biological and chemical hazards threaten human health and are of growing world concern. Wearable sensors offer the potential to monitor local exposure of individual users while enabling distribution across a global scale. However, achieving this goal is challenged by the lack of autonomous high performance sensors with the power and size features required for wearable implementation. Wearable sensors need sensing techniques having high-performance in power, sensitivity, and selectivity for biological and chemical hazards within a small volume. The autonomous operation of wearable sensors demands electronics to intelligently analyze, store, and transmit the data and generate alerts, within the strict constraints of power, and size. Electrochemical sensors have many characteristics that meet the challenging performance requirements of wearable sensors. However, the electrochemical instrumentation circuits are too heavy, bulky, expensive and consume too much power for wearable applications. Modern complementary metal-oxide-semiconductor (CMOS) technology provides an ultra-small, low-cost, low-power and high-performance solution for wearable sensors. This dissertation investigates CMOS circuit design for wearable electrochemical sensor arrays in health hazard monitoring. Multiple electrochemical modes provide orthogonal data to sensor array algorithms to improve sensor sensitivity and selectivity. A unique multi-mode resource-sharing instrumentation circuit was developed to integrate amperometric and impedance sensing abilities, and share electronics components

among recording channels, with reduced size, cost, and power. A wearable sensor array can measure multiple hazardous targets in a wide range of concentrations. To address the wide dynamic range of such a sensor array, a new CMOS amperometric circuit that combines digital modulation of input currents and a semi-synchronous incremental  $\Sigma\Delta$  ADC was developed. The new circuit simultaneously achieves a combination of wide dynamic range (164 dB), high sensitivity (100 fA), high power efficiency (241  $\mu$ W) and compact size (50 readout channels on a  $3 \times 3 \text{ mm}^2$  chip) that is not available in any existing instrumentation circuits. While the circuits above addressed key challenges in gas sensors, electrochemical biosensors offer a different set of challenges. In particular, miniaturized biosensors based on nanopore interfaces, including ion channel proteins, have great potential for high-throughput biological study and wearable biosensing. However, they require electrochemical instrumentation circuits that are compact, low power, and highly sensitive, high bandwidth. To address this need, a shared-segment interleaved amperometric readout circuit was developed, and measurement results show it has superior performance in terms of power and area compared to other known current sensing circuits for the same biological targets. This circuit achieves 7.2 pArms noise in a 11.5 kHz bandwidth, over 90 nA bidirectional input current range with only 21 µW power consumption, and allowing over 400 channels to be integrated on a single chip. The combined results of this research overcome many challenges for the development of wearable electrochemical sensor array in health hazard monitoring applications.

#### ACKNOWLEDGEMENTS

Firstly, I would like to express my deepest gratitude to my advisor, Dr. Andrew Mason, for his continued guidance and support through my PhD study and dissertation work. His knowledge, experiences and vision of biomedical applications impact my research very much. He is very patient and willing to share his knowledge and experiences. From him, I learned self-management, critical-thinking, skills of cooperation and communication, how to proactively drive a project, how to run a small team efficiently and many other things. All these knowledge and skills will help me to gain further success in the future.

Secondly, I want to thank Dr. Chuan Wang, Dr. Nelson Sepulveda and Dr. Peter Lillehoj for serving on my committee. They give me encouragement and support my dissertation work all the time. I would like to thank Dr. Erin Purcell and Dr. Xiangqun Zeng for providing their research resources to me. I also want to thank Dr. Shantanu Chakrabartty and Dr. Robert Worden for sharing their knowledge.

Thirdly, I want to thank my colleagues in AMSaC research group for their support. Thanks to Lin Li, Yuning Yang, Xiaowen Liu, Xiaoyi Mu, Yue Huang, Sam Boling, Heyu Yin, Sina Parsnejad, Ehsan Ashoori and Sylmarie Montero, Yousef Gtat and Ian Bacus.

Lastly and very importantly, I want to thank my parents and my brother for their mental support. I also want to thank and my girlfriend, Li Cheng. She supports me all the time and encourages me so much every time I was depressed or lost.

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## 1. Introduction

## 1.1 Motivations

## 1.1.1 Global threats of pandemic diseases and air toxins on human health and traditional sensing methods

In our modern global environment, pandemic diseases and air toxins present serious health hazards to worldwide populations. Over 1.4 billion people are at risk for cholera and over 90000 people die from cholera every year [1]. In 2003, an outbreak of severe acute respiratory syndrome (SARS) spreads in 37 countries. The 2009 Influenza A (H1N1) virus outbreak killed approximately 17000 people. The 2014 Ebola virus disease (EVD) resulted in over 10000 deaths. On the other hand, air toxins can cause lung cancer, stroke, ischaemic heart disease, chronic obstructive pulmonary disease (COPD) and respiratory infections [2]. Air toxins increase the risk of cardiovascular disease for the American patients having heart or blood vessel disease, whose population is one third of all Americans. WTO reports that in 2012 around seven million people died as a result of exposure to air toxins, accounting for 12.5% of all deaths worldwide that year.

Unfortunately, pandemic diseases and air toxins cannot be effectively identified in patients during the early stages of infection or exposure. Without proactive diagnostics, most people are only able to know they are in danger after showing symptoms. The symptoms for some diseases become apparent only after a long incubation period. Take pandemic viruses for example: the incubation period for EVD is up to 21 days, of which the average fatality rate is 50%. The symptoms may become serious before individuals seek care. Furthermore, it

can take hours or days to diagnose symptoms in hospitals. As a result, pandemic viruses spread more easily and increase fatality rates. The same scenario applies diseases caused by airborne toxins. Therefore, it is crucial to identify pandemic virus and airborne toxins preemptively in order to protect people in infectious and polluted environments and to allow them receive diagnosis and treatment in time.

Although pandemic diseases and air toxins have global impact, the root causes are local phenomenon that can be addressed by monitoring local environments experienced by individuals. Diseases caused by biological agents and airborne toxins result from direct exposure; namely by directly breathing, eating, drinking or touching them. If human's natural capabilities to sense such environmental hazards in the local environment were augmented by smart electronic sensors, it would become possible for people to avoid exposure altogether. To benefit the larger population, the hazard concentrations and location information detected by an individual's augmentation electronics could be amassed in hospital databases. The resulting information could be used for alert broadcasting and disease control. However, traditional air toxin and disease agent sensing instruments are not suitable for individual use because of their large size, huge power consumption, lack of intelligence and high cost. Therefore, a wearable sensor is urgently needed to generate early danger alerts to individuals and pool all this local data to enable new means of population-level healthcare and disease control.

## 1.1.2 Wearable sensor requirements

This wearable sensor would be carried by individuals to augment natural human sensing

capabilities. The concept of such a wearable sensor is shown in Figure 1.1. The sensor measures the molecular concentrations of hazardous disease-causing agents and airborne toxins, and generates different alert signals based on perceived danger levels. The system also wirelessly uploads data to cloud-like collection nodes for disease diagnosis and hazard control.



Figure 1.1. Operation concept of a wearable sensor for biological and chemical hazards sensing. The biological and chemical hazards represent pandemic viruses and air toxins.

To facilitate portability and therefore allow the sensors to form a distributed network, the sensor needs to be wearable and suitable for individual usage. To be wearable, the sensor must meet power, size and weight constraints. To maintain marketability as a consumer device, it must be cost-effective, function in a smart and autonomous manner, and require no user training or regular maintenance. To be smart and autonomous, the system needs to automatically collect and upload data, and generate alert signals in real time.

## 1.2 Technology opportunities and challenges.

The wearable sensor uses the sensing system architecture shown in Figure 1.2 [3]. The architecture consists of four functional blocks: a transducer array, instrumentation, a digital unit, and a wireless module. The transducer array converts multiple target concentrations of

interest into a measurable energy form. The instrumentation conditions (amplifies, filters, etc.) the transducer output signal for subsequent signal processing. The digital unit is in charge of digital signal processing, system control and smart system data analysis. The wireless module includes a wireless transceiver to receive remote commands and upload data to the cloud-like collection nodes. Within this dissertation, the transducer and instrumentation together will be referred to as the sensor. With modern microelectronic technologies, many smart personal devices have been developed, such as smart phones and smart watches. The digital units of these devices have powerful computation ability, small size, and low power consumption, all of which are largely due to rapid advances in integrated circuits. Modern wireless communication module can transmit at very high data rates with low power consumption and small size. Thus, existing digital units and wireless transmission modules provide a suitable computation platform for the wearable sensor. In contrast, the development of miniaturized and highly effective sensors remains an open challenge.



Figure 1.2. Architecture of a wearable sensor, adapted from [3].

Modern science is constantly generating new sensing methods that show promising features for wearable sensors. Among these, electrochemical sensing methods are especially good candidates because they inherently have ultra-low power consumption, low cost, simple structure, good sensitivity and selectivity, and are suitable for miniaturization. Electrochemical sensors can also sense a wide range of air toxins, such as CO, CO<sub>2</sub>, NO, NO<sub>2</sub>,

and SO<sub>2</sub>, and a wide range of biological disease agents. However, traditional electrochemical instrumentation is bulky, expensive, and consumes high power, which is not suitable for wearable sensors. Luckily, microelectronics enables the implementation of high performance, low power and low cost integrated circuits on tiny chips. Furthermore, novel integration technologies enable electrochemical transducers to be integrated monolithically with circuits on a single chip. This monolithic integration results in decreased system cost and size and improved detection limits. Complementary metal–oxide–semiconductor (CMOS) is the main technology used to implement modern integrated circuits due to its low power, low cost, and high performance compared to other integrated circuit technologies. Although many electrochemical CMOS instrumentation circuits have been developed in recent years, the key capabilities and performance metrics of existing instrumentation targets the development of CMOS electrochemical instrumentation for wearable sensing applications. Three specific challenges are to be addressed:

- The first challenge is to miniaturize and add intelligence to traditional electrochemical instrumentation, expanding on achievements of the past decade in benchtop electrochemical instruments. Novel instrumentation architectures and efficient readout methods could be employed to greatly enhance system-level performance.
- The second challenge is to expand the key capabilities and performance of miniaturized electrochemical instrumentation within the constraints of the wearable sensors. Simultaneously achieving multi-target detection, multiple sensing modes, and high detection limits in a wearable personal system raises new challenges to

instrumentation design.

• The third challenge is to develop chip-scale electrochemical instrumentation with single molecule detection capability in a high throughput sensor array. Single molecule detection is needed because many targets are hazardous in very low concentrations, and high throughput arrays are needed to allow the identification of diverse biological hazards.

## 1.3 Goals and approaches

The goals of this dissertation center around the development of miniaturized electrochemical instrumentation electronics that can uniquely address the challenges associated with implementing wearable-sensor-like devices. To explore the best system architectures and most effective readout methods, multiple system scales will be studied, from discrete commercial components to CMOS integrated circuits. Scientific contributions are expected in areas of electrochemical system architecture and high performance electrochemical instrumentation, within the constraints of wearable sensors.

## 1.4 Thesis organization

Chapter 2 summarizes the background of this research topic. Electrochemical transducer principles, structures and methods are introduced. Existing CMOS electrochemical instruments are reviewed. Chapter 3 reports the development a unique multi-mode low power electrochemical instrument. The circuit effectively integrates two electrochemical modes into one circuit, with reduced power, area, and cost. A portable system was built using this developed circuit. Chapter 4 introduces a CMOS electrochemical instrument that achieves

large dynamic range and high power efficiency, with pA level sensitivity and very compact size. This circuit enables the development of a wearable sensor array which detects multiple targets in wide concentration ranges and high detection limit. Chapter 5 presents an ultra-compact micro-watt CMOS current sensing circuit with pico-ampere sensitivity for over 400-channel biosensor arrays. Chapter 6 presents contributions and future work.

## 2. Background and Literature Review

#### 2.1 Analysis of technologies for wearable biochemical sensors

In our modern global environment, air toxins and pandemic diseases present serious health hazards to worldwide populations. Although these hazards can have global impact, the root causes are local phenomenon that can best be addressed by monitoring local environments experienced by individuals. To effectively monitor the local environment, a wearable biochemical sensor is desired. Here we define a wearable sensor as one that is required to be small (chip scale), low cost and free of maintenance, highly sensitive, highly specific, fast responding, and inherently low power. This section studies sensing methods for wearable biochemical sensors.

For air toxin sensing, the most common sensor technologies are metal oxide sensors (MOS), non-dispersive infrared gas sensors(NDIR), catalytic sensors, photoionization detectors (PID), flame ionization detector (FID), thermal conductivity sensor, and electrochemical sensors [4]. Among the technologies for air toxin sensing, MOS sensors and electrochemical sensors stand out as candidates for wearable systems, especially because their structures are compatible with modern microfabrication processes and are therefore suitable for low cost miniaturization [5]. Although MOS sensors have extremely long lifetimes and the ability to detect many gases over large concentration ranges, they have poor selectivity because all reducing gases in the atmosphere are detected. Furthermore, MOS sensors consume large power because a heater is needed to maintain an appropriate operating temperature. These disadvantages significantly limit the appeal of MOS sensors for wearable

systems. In contrast, electrochemical sensors have ultra-low power consumption, low cost, and good selectivity [6-8]. However, traditional EC sensors suffer from slow response time and high maintenance cost.

Monitoring for pandemic diseases and other biological hazards requires a biosensor. Many biosensors are affinity-based, using immobilized capture probe to bind the target molecule, thus transferring the challenge of detecting a bio-target into detecting a change at a localized surface [9]. Non-affinity-based biosensors do not require immobilized capture probe and binding process, and thus have simpler sensor structure and lower cost. Biosensor sensing methods can generally be divided into label-based and label-free methods. Label based methods require a label attached to the target. The amount of labels is detected and ideally corresponds to the number of targets. However, labeling a biomolecule can change the target characterizations.[10] Label-based methods also increase the sensor cost and response time because of extract label time and sample handling labor [9]. In contrast, label-free methods enable low cost and real time measurement by omitting the labeling step[11]. Label-free methods include surface plasmon resonance (SPR), surface acoustic wave (SAW), thermal, and electrochemical techniques. Compared with other label-free techniques, electrochemical technique has low power consumption, simple structure, low-cost and are suitable for miniaturization [5, 12].

Because of electrochemical sensors' advantages over other sensors, research has been done to use them for different air toxin and biological hazard targets. They can sense a wide range of air toxins such as CO, CO<sub>2</sub>, NO, NO<sub>2</sub>, and SO<sub>2</sub> [6-8]. They can detect pathogens such as cholera toxin, mycotoxins, hepatitis, bacillus anthracis, rabies virus, *E. Coli*, and bovine viral diarrhea virus [11, 13-18], and have been used for detection of biomolecules (disease indicator) such as glucose, DNA and proteins [19-22]. Because electrochemical techniques are good for personal device applications and able to sense a wide range of gas and biological targets, they provide an ideal technology starting point for development of the wearable sensor.

## 2.2 Electrochemical transducers and methods

To determine if electrochemical sensors can meet the system performance goals for wearable sensors, both the electrochemical cell and the instrumentation circuits that interrogate the sensor must be analyzed. This section describes electrochemical transducer principles and structure and analyzes electrochemical methods for performing measurements with electrochemical systems. Instrumentation will be discussed after this section.

## 2.2.1 Transducer principles and structure

The electrochemical transducer is the recognition element of electrochemical sensor. It converts electrochemical response to a measurable electrical signal. In wearable sensors, the electrochemical response represents the target concentrations of interest. The transducer is stimulated by an electrical signal and generates electrical response in the form of voltage, current or charge. The physiochemical mechanisms that occur in electrochemical sensors can be generally divided into two categories: redox reaction or target adsorption on the transducer [23]. In a redox reaction based transducer, detection targets exchange electrons with the transducer through reduction reaction or oxidation reaction. As a result, an electrical signal is

generated at the transducer output, and the magnitude of this signal is a function of the detection target concentration. In contrast, adsorption based transducers absorb or bind target molecules to the transducer's surface and causes transducer's impedance to change [23]. These two diverse mechanisms are illustrated in Figure 2.1.



Figure 2.1. Illustration of two mechanisms of electrochemical transducer: redox reaction based and adsorption based mechanisms. Redox reaction includes oxidation and reduction reaction. In a redox reaction based transducer, electric signals are generated by electron exchange between detection targets and transducer. In adsorption based transducer, the detection targets adsorption at transducer surface changes the response electric signals.

An electrochemical transducer consists of at least two components: the ion-conducting electrolyte and the electron-conducting electrodes. The electrodes are immersed in the electrolyte. The electrolyte provides active ions involved in electrochemical sensing process. The electrodes provide stimulus signals on the transducer and collect the transducer output signal for further signal condition. Electrons transfer happens at the electrolyte and electrodes interface during the sensing process. The electrolyte is generally in solid phase or liquid phase. The electrodes are generally made of good conducting materials, include gold and platinum. Generally, an electrochemical transducer has two to three electrodes. These electrodes can be realized in a planar form by microfabrication process for miniaturization.

An additional layer such as a biological recognition element or chemical reaction catalyst can be coated on electrodes to improve transducer sensitivity and selectivity.

#### 2.2.2 Electrochemical methods and configurations

To understand the instrumentation requirements for electrochemical sensing, it is necessary to study the electrochemical sensing methods and electrode configurations for different electrochemical methods. Based on whether the response current type is in DC format and AC format, electrochemical methods are divided into two categories: amperometric technique and impedance technique.

## 2.2.2.1 Electrochemical methods for sensing

Electrochemical methods can be classified into four types: amperometric, impedimetric, potentiometric and field-effect method [24]. Amperometric technique and impedance technique are being used by our collaborators to develop bio/chemical transducers. Therefore, these two techniques are studied here.

Amperometric techniques are often associated with redox reaction based transducer. These methods apply a voltage on the transducer and measure the response current. The chronoamperometric technique, also known as constant potential voltammetry, applies a DC voltage on the transducer and measures the DC response current, which is ideally proportional to the target concentration [25]. The cyclic voltammetry (CV) technique applies a triangle voltage ramp on the transducer and measure the response current. The peaks that occur during oxidation and reduction provide information about target identity and concentration. A variety of other amperometric techniques that apply different stimulus voltage waveforms have been utilized to observe oxidation and reduction reactions.

Impedance techniques apply a small-amplitude AC voltage on the transducer and measure the response AC current. Sometimes a constant DC offset is also applied to establish an electrochemically active operation or increase adsorption within the cell. The absorption or bonding of targets species between transducer electrodes can generate a change in the AC response current that, ideally, is a function of target concentration. The stimulus signals can contain a single AC frequency or multiple frequencies; a broadband scan of frequencies is referred to as impedance spectroscopy.

## 2.2.2.2 Electrode configurations in amperometric and impedance techniques

Three-electrode transducers are widely used for amperometric and impedance technique. In contrast to a two-electrode configuration, the three-electrode system eliminates reference potential shift due to ion current flowing through the resistive electrolyte. This chapter will focus on review three-electrode configuration due to the advantages over two-electrode configuration. The electrochemical reaction of interest takes place on one of these electrodes called the working electrode (WE). WE is made of an inert metal that is not reactive with the electrolyte or target species. WE should also be highly conductive to effectively transfer electrons between the circuit and electrolyte. For these reasons, gold and platinum metals are highly used as WE in a miniaturized electrochemical transducer.

Both amperometric and impedance techniques require controlling the voltage on the transducer. The voltage difference between WE and the WE/electrolyte interface  $V_{cell}$ , determines the electrochemical reaction rate [23].  $V_{cell}$  needs to be accurate and stable in

value. In reality,  $V_{cell}$  is controlled by the voltage across WE and another electrode called the reference electrode (RE), as shown in Figure 2.2.  $V_{WE}$  and  $V_{RE}$  are the potentials at WE and RE, respectively, relative to instrumentation circuit ground.  $R_s$  is the solution resistance between WE and RE, *i* is the current flow through  $R_{s.}$ . A known constant voltage drop  $\Delta V$  exists between RE and the RE/electrolyte interface. Thus,  $V_{cell}$  can be represented as



Figure 2.2. Amperometric transducer potentials between RE and WE.  $\Delta V$  is the voltage drop between RE and RE/electrolyte interface,  $V_{WE}$  and  $V_{RE}$  are the potentials at WE and RE, respectively, relative to instrumentation circuit ground.  $R_s$  is the solution resistance between WE and RE, *i* is the current flow through  $R_s$ , and  $V_{cell}$  is the voltage between WE and the WE/electrolyte interface. *iRs* is much smaller than  $V_{cell}$  and  $\Delta V$  when  $R_s$  and *i* are very small.

In (2.1), the solution voltage drop  $iR_s$  causes error on the voltage across the WE/analyte

interface. In order to decrease  $iR_s$  error, i and  $R_s$  need to be minimized. Minimizing  $R_s$  can be done by placing RE very close to WE. Minimizing i can be done by connection RE to a high impedance node. As a result,  $V_{cell} \approx V_{WE} - V_{RE} - \Delta V$ . Standard hydrogen electrode (SHE), saturated calomel electrode (SCE), or silver-silver chloride (Ag/AgCl) electrode are often used as RE, although single-metal "pseudo" REs of Au, Pt, Ag are becoming more popular in miniaturized and planar electrode systems.

A third electrode called counter electrode (CE) is used in a 3-electrode electrochemical

transducer to provide current needed by electrochemical reaction at WE. This ensures that the  $iR_s$  drop is minimal and  $V_{cell}$  can be accurately controlled. Inert metal with good conductivity can be used as CE. Gold and platinum are popularly used as CE in a miniaturized electrochemical transducer.

# 2.3 CMOS electrochemical instrumentation for amperometric and impedance sensing

Because electrochemical sensing techniques have been selected for system implementation, the corresponding sensor interface circuit should be developed to meet system criteria as well. Traditional electrochemical instrumentation is bulky, high cost, and high power consumption. Existing commercial benchtop electrochemical instrumentations, such as CHI760, VersaSTAT, and Genefluidics, cannot be used in personal hazard monitoring system because they are bulky, heavy, high cost (over \$10000) and large power consumption. Although Texas Instruments has developed chip-scale electrochemical instrumentation (LMP9100x), this chip only supports amperometric mode, has a very limit current input range, only has one readout channel and supports a  $V_{WE-RE}$  of less than ±1.75mV. These limitations make it unsuitable for development of a wearable sensor array. Therefore, no existing commercial instrumentation meets our wearable sensing requirements.

A wearable sensor needs a low-cost, low-power, compact and high performance instrumentation electronics. Complementary metal–oxide–semiconductor (CMOS) is a solid-state device technology for designing and manufacturing integrated circuits. The vast majority of modern integrated circuits are fabricated in CMOS technology due to its low power, low cost and high performance compared to other integrated circuit technologies. Realization of sensor instrumentation in CMOS technology can effectively decrease the instrumentation size, cost and power. To determine how well existing circuits meet the needs of wearable sensors, these CMOS electrochemical instrumentation circuits must be studied.

CMOS electrochemical instrumentation is generally composed of four functional blocks as shown in Figure 2.3. The first block is the stimulus signal generator, generating electrical waveform to stimulate an electrochemical response from a transducer. The second block is potentiostat, enforcing controlled potentials at electrodes [23, 26]. The third block is the electrochemical readout, convert current into voltage and/or amplifying the transducer response signal. The third block is signal condition and digitization circuit, extracting transducer impedance in impedance technique, and digitizing signals enabling further signal processing and smart system decision in amperometric and impedance techniques. Because the performance of the stimulus signal generator is neither critical nor challenging to achieve with CMOS circuits, this chapter will focus only on potentiostat, electrochemical readout and signal condition and digitization circuits for electrochemical sensor applications.



Figure 2.3. Function blocks of electrochemical instrumentation for amperometric and impedance sensing. The stimulus signal generator generates required stimulus voltage and waveform; the potentiostat enforces controlled potentials at electrodes; the electrochemical readout amplifies the response current and/or converts the current into voltage; the signal

Figure 2.3 (cont'd) condition and digitization circuit extracts the transducer impedance in impedance mode and digitizes the signals for further signal processing and smart system data analysis.

#### 2.3.1 Potentiostat

In this dissertation, potentiostat refers to a circuit that enforces controllable potentials at electrodes. Although some references define the potentiostat as including the readout circuit, these two functionally different circuits are discussed separately in this dissertation. The key function of a potentiostat is to control the potential difference  $V_{WE^-RE}$  between WE and RE, which is critical to electrochemical reactions [23]. Because no research-worthy challenge exists in potentiostat design or performance, this section only introduces potentiostat configurations and describes a widely used potentiostat as an example.

Three-electrode potentiostat configurations can be divided into two categories: floating-potential-CE and fixed-potential-CE configurations. In the fix-potential-CE configuration,  $V_{CE}$  is fixed at a constant potential. The fix-potential-CE configuration is only rarely used with a specially designed electrochemical transducer [27] and is not popular.

The floating-potential-CE configuration is the most popular one and has been widely used [25, 28-32] because it is simple, low cost and low power. In the floating-potential-CE configuration, the potential at CE,  $V_{CE}$ , is floating, and the potentiostat provides controllable potentials to WE and RE. A voltage follower is widely used in this configuration, as shown in Figure 2.4, where  $V_{RE}$  is equal to  $V_{Bias}$ . By changing either  $V_{Bias}$  or  $V_{WE}$ , the voltage between RE and WE is controlled. As a result, the voltage between WE and WE/electrolyte interface changes according to (2.1). Because the amplifier has ultra-low input leakage current, the current at RE is close to zero. The amplifier's output provides current to the CE.

In Figure 2.4, stimulus signals can be applied on either RE or WE to control the  $V_{cell}$ . In an electrochemical transducer array sharing the same electrolyte bulk, a single RE and CE are used, and stimulus signals are applied on multiple WEs [25, 26, 29]. The reason is as follows. Ignoring the electrolyte voltage drop  $iR_s$ , the electrolyte potentiostat  $V_{lyt}=V_{RE}-\Delta V$ . Because only one  $V_{lyt}$  value is allowed for an electrolyte bulk, only one RE is used to control  $V_{lyt}$ . Because CE only provides current needed by WE, only one CE can be used to be shared by multiple WEs. Each WE may need different  $V_{cell}$  value for difference redox reactions, which is controlled by stimulus signals at different WEs.



Figure 2.4. Circuit diagram of a potentiostat for amperometric and impedance sensing. CE, RE, WE are there electrodes of transducer.  $V_{CE}$ ,  $V_{RE}$ , and  $V_{WE}$  are voltages at CE, RE, and WE, respectively. *Z1*, *Z2* are the equivalent transducer impedances between CE and RE; and between RE and WE, respectively. *21*, *Z22*, *Z23* are the equivalent transducer impedance of RE/electrolyte interface, electrolyte between RE and WE, and WE/electrolyte interface respectively.  $\Delta V$ ,  $iR_s$ , and  $V_{cell}$  are voltage drops and their detail definitions can be found in (2.1).

## 2.3.2 Electrochemical readout

In a three-electrode amperometric transducer, current flows in/out of both WE and CE in potentially equal quantities but in opposite directions. Therefore, a current readout block can

be connected to either of these two electrodes. Electrochemical readout is required to sense current but not to affect the voltage at the sensing electrodes (WE or CE). Measuring current at WE has two benefits: a) it is more accurate when the WE redox current  $I_{WE}$  is comparable with RE leakage current  $I_{RE}$  (is usually tens of pA), because CE current  $I_{CE} = I_{WE} - I_{RE}$ ; b) it allows a broader options of high performance current sensing circuit. The reason is as follows. Figure 2.4 shows that WE has a fix voltage  $V_{WE}$  and CE has a floating voltage  $V_{CE}$  *H*igh performance current sensing current sensing electrode. Because of these two benefits, measuring the current at WE is the most popular configurations in amperometric and impedance sensing. To accomplish this current readout, four kinds of electrochemical readout circuits are popular for current sensing at WE.

#### 2.3.2.1 Resistive feedback transimpedance amplifier

A transimpedance amplifier (TIA) with resistor feedback is shown in Figure 2.5. WE is connected to the negative terminal of an operational amplifier (Op-amp). Due to the input 'virtual short' characteristic of the Op-amp,  $V_{WE}$  is equal to the analog ground voltage at the Op-amp's positive terminal. A feedback resistor  $R_f$  converts  $I_{in}$  into voltage.



Figure 2.5. Circuit diagram of a resistive feedback transimpedance amplifier.  $I_{in}$  is the transducer output current,  $C_{in}$  is the total input capacitance,  $R_f$  is the feedback resistance,  $V_{WE}$  is the voltage at WE,  $V_{OUT}$  is the output voltage.

The TIA's output voltage  $V_{OUT}$  is given by

$$V_{OUT} = R_f I_{in} \tag{2.2}$$

The total input referred noise power spectral density (PSD) of the feedback resistor TIA is given by

$$i_N^2 = 2qI_{in} + \frac{4kT}{R_f} + e_{n-op}^2 \left[\frac{1}{R_f^2} + 4\pi f C_{in}^2\right]$$
(2.3)

where *q* is the charge of a single electron,  $I_{in}$  is the input current,  $R_f$  is the feedback resistance,  $C_{in}$  is the input capacitance, *k* is the Boltzmann constant, *T* is the Kelvin temperature,  $2qI_{in}$ represents shot noise,  $e_{n-op}^2$  is the Op-amp input reference noise.

From (2.3), it is known that in order to decrease the input referred noise, the feedback resistor  $R_f$  needs to be large; the total input capacitance at the circuit input node needs to be miniaturized; and the Op-amp input referred noise needs to be miniaturized. It has been shown that this TIA can provide a 4pA noise performance at 10kHz [33]. However, due to chip area constraints, on-chip  $R_f$  cannot be very large and this limits gain. It has been reported that this TIA can only achieve nA sensitivity at 10kHz bandwidth [34]. Although an active feedback structure has been used to decrease the feedback resistor area while achieving pA level sensitivity [35, 36], the total area is still very large and only eight recording channels can be implemented in a 9 mm<sup>2</sup> area in 0.13 µm CMOS technology. In addition, a large off-chip circuit is needed to achieve the bandwidth of 1 MHz [35, 36]. Therefore, the resistance feedback TIA is not suitable for high throughput, large bandwidth, and high sensitivity applications.

## 2.3.2.2 Charge sensitive amplifier

A charge sensitive amplifier (CSA) uses a feedback capacitor to convert current/charge into voltage. The circuit diagram is shown in Figure 2.6 (a). A reset switch  $SW_1$  is controlled

by the clock  $\varphi$  described in Figure 2.6 (b). SW<sub>1</sub> periodically resets the amplifier output voltage  $V_{OUT}$  to prevent saturation. When  $\varphi$  is logical '0', the input current is integrated onto  $C_f$  and  $V_{OUT}$  changes. When  $\varphi$  is logical '1', the CSA functions as a unity buffer and  $V_{OUT}$  is reset to a known constant value.



Figure 2.6. (a). Circuit diagram of charge sensitive amplifier.  $I_{in}$  is the transducer output current,  $C_{in}$  is the total input capacitance,  $C_f$  is the feedback capacitor,  $V_{WE}$  is the voltage at WE,  $V_{OUT}$  is the output voltage. A switch SW<sub>1</sub> is controlled by the clock  $\varphi$  periodically resets the voltage  $V_{OUT}$  to prevent Op-amp output saturation. (b). The clock diagram of the clock  $\varphi$ . SW<sub>1</sub> is closed when  $\mu$  is logic '1'. SW<sub>1</sub> is open when  $\mu$  is logic '0'.  $T_p$  is the clock cycle period. *T* is the integration time on  $C_f$  in a clock cycle.  $T_2$  is the integration end time on  $C_f$  within an integration period.

If  $\varphi$ 's frequency is much higher than the  $I_{in}$ 's frequency,  $I_{in}$  can be approximated as a DC value, for example, as  $I_{DC}$ . At the integration end time  $T_2$  within an integration cycle, the TIA's output  $V_{QUT}$  is given by

$$V_{OUT}(t) = \frac{1}{c_f} \int_0^T I_{DC} dt + V(T_1)$$
  
=  $\frac{1}{c_f} I_{DC} T + V(T_1)$  (2.4)

where *T* is the period of the integration cycle, *t* is time,  $C_f$  is the feedback capacitance,  $I_{DC}$  is an approximated DC value of  $I_{in}$  within an integration period, and  $V(T_l)$  is the known value of  $V_{OUT}$  when  $\varphi$  is logical '1'. Because a capacitor inherently has less noise than a resistor, the CSA's feedback circuit has a better noise performance than the resistive feedback TIA. The charge injection and kT/C noise in the CSA can be eliminated by correlated double sampling (CDS) technology [33, 37]. Note that when CDS technology is used, the Op-amp should be designed to minimized thermal noise rather than flicker noise because CDS technology will double the thermal noise [33]. Better than 10 pA sensitivity can be achieved by CSA [29, 38]. Moreover, a CSA can be used as a circuit block within a high resolution analog-to-digital convertor (ADC) such as a Sigma Delta  $\Sigma \Delta$  ADC and integration ADC. Therefore, many CMOS electrochemical circuits with digitization have used CSA as the electrochemical readout [25, 32, 39-44]. However, CSA cannot achieve very high bandwidth with low noise performance. The reason is as follows: a high frequency input signal requires sampling signal  $\varphi$  to have a very high frequency. Compared to a low frequency  $\varphi$ , a high frequency  $\varphi$  generates larger substrate noise and capacitive coupling noise, and also results in larger error effect due to clock jitter noise. It has been shown that CSA achieves better noise performance in high bandwidth, while resistor feedback TIA achieves better noise performance in high bandwidth [45].

#### 2.3.2.3 Current amplifier with matched double-MOS structure feedback.

A circuit has been report to achieve ultra-low noise performance in a large bandwidth [46]. This circuit achieves 25 pA<sub>rms</sub> input referred noise in a 1 MHz bandwidth. The schematic is shown in Figure 2.7. The transistors  $M_{p2}$  and  $M_{n2}$  have a width-over-length ratio N times larger than that of  $M_{p1}$  and  $M_{n1}$ . The gate source voltages on all these transistors are equal, and  $V_{o2}$  is kept under constant bias equal to  $V_{WE}$ . Hence, any variations in the current passing through  $M_{p1}$  and  $M_{n1}$  would be amplified N times through  $M_{p2}$  and  $M_{n2}$ . The capacitances  $C_1$  and  $C_2$  also hold the same N ratio, maintaining a constant circuit gain at higher frequencies. The low noise is achieved by operating all the feedback transistors in

sub-threshold region to reduce shot noise. This current amplifier is good for high bandwidth and high sensitivity applications. Because the gain response of transistors may not exactly equal to that of capacitors over the bandwidth, the circuit may result in signal distortion. Moreover, this circuit does not have a large input dynamic range because  $V_{01}$  because saturated for a large  $I_{in}$ . Moreover, the current amplifier does not have good area efficiency when implementing a large gain.



Figure 2.7. Circuit diagram of current amplifier with matched double-MOS structure feedback. This figure is adapted from [46]. The node  $V_{o2}$  is kept under constant bias equal to  $V_{WE}$ .

#### 2.3.2.4 Current conveyor

The use of a CMOS current conveyor (CC) in electrochemical instrumentation dates back to 1987 [47]. A CC can be used as a current buffer to both read WE current and apply a voltage bias at the electrode. Many of groups have used CC as the electrochemical readout [47-50]. A schematic of the CC in [49] is shown in Figure 2.8.  $I_{bias}$  converts the bidirectional input current  $I_{in}$  into unidirectional current. Because no capacitor is needed, this CC is compact and has high bandwidth. If  $I_{in}$  is unidirectional,  $I_{bias}$  can be removed to reduce power consumption. If  $I_{bias}$  is removed, OTA1 consumes the majority of the CC power, and because OTA1 does not need to provide large output current, the total power consumption of a CC can be low. Therefore, a CC is suitable for a high throughput, high bandwidth sensor array. The
disadvantage of this circuit is that the next stage directly contributes to the input referred noise.



Figure 2.8. Circuit diagram of current conveyor for electrochemical sensing. This diagram is adapted from ref. [49].

#### 2.3.2.5 Summary of prior work of electrochemical readout

Different electrochemical readouts have been reported for specific applications in electrochemical sensing. However, pushing electrochemical sensor detection limit to single molecule level generates new challenges to the electrochemical readouts that have not been addressed in existing work. A high throughput biosensor array is needed to develop protein biosensor with single molecule detection ability. For such a sensor array, the electrochemical readout needs to simultaneously have pA sensitivity, high bandwidth, low power and small area [51, 52]. The literature review reveals that none of prior work meets these requirements. Therefore, a novel electrochemical readout is needed to push the electrochemical sensor array detection limit towards high throughput single molecule detection.

# 2.3.3 Signal condition and digitization circuit in amperometric and impedance sensing instrumentation

The wearable sensor needs an instrumentation circuit that can digitize the electrochemical readout output signal for further digital signal process and data analysis within the smart system. Furthermore, in impedance mode, a signal condition circuit is

desired to extract the impedance information from the electrochemical readout output before digitization, because redundant signal digitization consumes excess power. Often the signal condition and digitization circuits are inherently integrated with electrochemical readout to achieve low noise, compact size, low power and low cost. This section reviews signal condition and digitization circuits for amperometric and impedance sensing.

#### 2.3.3.1 CMOS digitization circuits for amperometric instrumentation

Sigma-Delta ( $\Sigma\Delta$ ) ADC based instrumentation circuits need an integrator as the first stage. Because CSA is behavior as an integrator, it is used as the electrochemical readout to implement  $\Sigma\Delta$  architecture.  $\Sigma\Delta$  ADC based instrumentation circuits for amperometric sensing should have high resolution, compact size and low power consumption. An  $\Sigma\Delta$  ADC has been reported to achieve compact size by using the sensor's capacitance as the ADC's integration capacitance within the analog front end [40]. As a result, large on-chip capacitors were avoided and thus the circuit area was decreased. Small circuit area allows implementation of high throughput on-chip sensor arrays. Another  $\Sigma\Delta$  ADC based instrumentation circuit has used feedback current modulation to achieve accurate digitally-programmable input current range over six orders of magnitude [44]. 16 channels have been implemented on a  $3 \text{mm} \times$ 3mm chip. However, this circuit requires very slow conversion rate to achieve 100fA sensitivity, and it has low power efficiency for large input currents. Another  $\Sigma\Delta$  ADC based instrumentation uses a semi-synchronous approach to achieve 50-fA sensitivity without significantly reducing conversion rate and consuming only µW-level power [39]. The semi-synchronous approach improves sensitivity by reducing substrate noise at the  $\Sigma\Delta$  ADC modulator output. 42 channels have been implemented on a  $3mm \times 3mm$  chip. However, this circuit suffers from poor power and area efficiency for an input current with large dynamic range. Moreover, this circuit exhibits a slow conversion rate of over 100ms.

In all,  $\Sigma\Delta$  ADC based instrumentation circuits for amperometric sensing can achieve very high sensitivity, compact size and low power consumption. A review of the literature shows that this architecture provides the best sensitivity and the lowest power consumption compared to other ADC-based amperometric instrumentation circuits. All these benefits make  $\Sigma\Delta$  ADC a good candidate for a high sensitivity, high throughput, electrochemical sensor array. However,  $\Sigma\Delta$  ADCs exhibit slow conversion rates and therefore cannot be used in very high bandwidth applications. Furthermore, the reported circuits lose power and area efficiency for large dynamic range input currents.

The integration ADC architecture has been used for amperometric sensing [32, 49, 53, 54]. For this ADC, a charge sensitive amplifier or a current conveyor can be used as the electrochemical readout. Integration ADC architecture achieves high sensitivity in low bandwidth applications. In order to achieve 120dB input dynamic range, the input current has been normalized to a certain range before digitization by an integration ADC [49]. This circuit achieves 46-pA sensitivity consuming over 700  $\mu$ W. To reduce circuit area, the sensor's capacitance has been used to avoid large on-chip capacitors, and 128 channels have been implemented on a chip [55]. In all, for amperometric sensing instrumentation, integration ADC architectures can achieve good sensitivity with compact size and low power consumption. However, the sensitivity and power consumption is not as good as  $\Sigma \Delta$  ADC based instrumentation. Furthermore, for this instrumentation application, integration ADCs

have the same disadvantages as  $\Sigma\Delta$  ADCs: slow conversion rate and reduced power and area efficiency for a large input dynamic range.

Current-to-frequency (*I-F*) ADC based instrumentation circuits have a simple architecture and generate fast conversion rates, but they generally have poor sensitivity. The typically use a CSA or a CC as the electrochemical readout [28, 30]. Although a hybrid ADC has been reported [56] that combines I-F ADC and integration ADC architectures to improve sensitivity and dynamic range, the sensitivity performance and power consumption is still much worse than  $\Sigma\Delta$  ADC based instrumentation.

Table 2.1 summarizes the existing work on CMOS digitization circuits for amperometric instrumentation. The best sensitivity has been achieved by  $\Sigma\Delta$  ADC based instrumentation that also shows ultra-low power consumption and compact size [39]. However, this circuit loses power and area efficiency for an input current with large dynamic range, and it has a slow conversion rate. Although the integration ADC in [49] can measure a large input current with high power efficiency, the sensitivity is much worse than the  $\Sigma\Delta$  ADC in [39]. Overall, this literature review has shown that a circuit with high sensitivity, large input current dynamic range, compact and high input range vs. power factor (RvP) is still an open challenge.

	Max. Current	Sensitivity	Dynamic Range	Power/Chan.	RvP <sup>1</sup>	Process	ADC structure	
TCAS06 [39]	100 nA	50 fA	126 dB	11 µW	0.033	0.5 µm	Semi-synchronous $\Sigma\Delta$	
TbioCAS07 [44]	0.5 µA	100 fA	140 dB	1300 μW	0.001	0.5 µm	Feedback modulation $\Sigma\Delta$	
TCAS06 [49]	50 µA	46 pA	120 dB	781 μW	0.578	1.2 μm	Current normalization + Integration	
TCAS09 [28]	1 μA	1 nA	60 dB	70 µW	0.026	0.18 µm	Current to frequency	
TbioCAS13 [56]	350nA	24 pA	95 dB	188 μW	0.006	0.35 μm	Current to frequency + Single slope	
Sensors'06 [53]	200 nA	1 pA	116 dB	>130 µW		0.5 μm	Integration	
TCAS'14 [40]	32 µA	~2.8nA	>60dB	25 μW	0.25	2.5 μm	All-CMOS ΣΔ	
JSSC'04[54]	100 nA	10 pA	>100dB	-	-	0.5 µm	Integration	

Table 2.1. Performance summary of CMOS digitization circuits for amperometric instrumentation

<sup>1</sup>RvP (Input range vs. power) factor is defined as input current range (maximum value) divided by readout circuit's maximum consumed current.

2.3.3.2 Impedance extraction principle for electrochemical impedance sensing

For impedance sensing, the signal condition and digitation circuit block extracts impedance information from the electrochemical readout output and digitizes the impedance signals for subsequent digital signal processing and smart system data analysis. This section provides an overview of the impedance extraction principle as realized in CMOS solutions.

In impedance sensing, a small amplitude AC voltage with a known DC voltage offset is used as the stimulus signal. The transducer's impedance causes the response current to change in amplitude and phase, and this change is algebraically related to real and imaginary components of transducer's impedance (or its inverse, admittance). CMOS instrumentation circuits popularly use the frequency response analyzer (FRA) method to extract the real and imaginary components of admittance. Compared to the alternative Fast Fourier Transform (FFT) method, FRA method enables hardware realizations with much more compact area and lower power, and is therefore preferable for single-chip realization of an electrochemical sensor array[41, 57]. The operating principle of the FRA method is shown in Figure 2.9. A known frequency sinusoid stimulus voltage  $Asin(\omega t)$  is applied on the electrochemical transducer. The transducer's response current is defined by  $A'sin(\omega t+\theta)$ , where A' and  $\theta$  are determined by the transducer admittance. By multiplying the response current with two reference signals and then applying low pass filters, two orthogonal components, REAL and IMG, can be extracted, and these signal components are proportional to the real and imaginary components of transducer admittance.



Figure 2.9. FRA method for extracting transducer impedance/admittance. Both phasor domain and time domain signal expressions are given.  $\omega$  is the stimulus signal frequency.  $|Y| \angle \theta$  is the phasor form of the transducer admittance.  $Asin(\omega t)$  is the stimulus voltage for the electrochemical transducer.  $A'sin(\omega t+\theta)$  is the output current of the transducer.  $sin(\omega t)$  and  $cos(\omega t)$  are the reference signals to extract the real part of imaginary part of the signal. LPF is the low pass filer. REAL and IMG are two orthogonal outputs, representing real and imaginary components of impedance/admittance.

For the transducer response current  $A' \angle \theta$  in Figure 2.9, phasor domain analysis gives

$$A' \angle \theta [A'\sin(\omega t + \theta)] = A \angle 0^0 \cdot |Y| \angle \theta$$
(2.6)

where  $A'\sin(\omega t + \theta)$  is the time domain representation of  $A' \angle \theta$ ,  $A' \angle 0$  is the stimulus signal, and  $|Y| \angle \theta$  is the phasor format of the transducer admittance. From (2.6), it can be seen that |Y| = A'/A.

At the output of multiplier 1 (Figure 2.9), we have

$$A'\sin(\omega t + \theta) \cdot \sin(\omega t) = \frac{A'}{\frac{A'}{2}\cos(\theta)} - \frac{AC}{\frac{A'}{2}\cos(2\omega t + \theta)}$$
(2.7)

where DC and AC symbol represent DC component and AC component, respectively.

At the output of multiplier 2, we have

$$A'\sin(\omega t + \theta) \cdot \cos(\omega t) = \frac{A'}{\frac{2}{2}}\sin(\theta) + \frac{A'}{\frac{2}{2}}\sin(2\omega t + \theta)$$
(2.8)

where DC and AC symbol represent the DC component and AC component, respectively.

The low pass filters (LPF) remove the AC components in (2.7) and (2.8), and generate

$$\begin{cases} REAL = \frac{A'}{2}\cos(\theta) \\ IMG = \frac{A'}{2}\sin(\theta) \end{cases}$$
(2.9)

The transducer's conductance  $|Y| \angle \theta$  can be calculated by

$$\begin{cases} |Y| = \frac{A'}{A} = \frac{\sqrt{REAL^2 + IMG^2}}{2A} \\ \theta = \tan^{-1} \frac{REAL}{IMG} \end{cases}$$
(2.10)

2.3.3.3 Prior work of signal condition and digitization circuit for impedance sensing

The FRA method can be implemented directly by using analog multipliers [48, 58]. These circuits only achieve 330 pA sensitivity and occupy huge area and consume large power over 8 mW. Furthermore, they do not have digital outputs.

Targeting high throughput sensor arrays, a compact, low power and high sensitivity lock-in ADC has been proposed to implement FRA method [41]. By combining  $\Sigma\Delta$  ADC techniques with lock-in techniques, this circuit achieves 78 fA sensitivity and 6  $\mu$ W power consumption, and permits over 100 channels integrated within a 3 × 3 mm<sup>2</sup> die. All these benefit make it suitable for high throughput high sensitivity electrochemical sensor arrays. However, this circuit requires slow conversion time to achieve sub-pA sensitivity and is only suitable for low bandwidth applications.

To address the bandwidth limitation of [41], another compact and low power CMOS impedance extraction circuit has been proposed [43]. A multiplying dual-slope ADC structure was used in this circuit. However, compared to the work in [41], this circuit occupies larger area and consumes larger power.

A common limitation to all of the impedance extract circuits above is that they cannot support stimulus frequencies over 100MHz. The analog-multiplier based circuit in [48, 58] can support stimulus frequency below 50 MHz. The lock-in ADC [41], and multiplying dual-slope ADC [43] can only support stimulus frequencies below 10 kHz. To address this issue, a fully-integrated impedance extractor has been reported that can support stimulus frequencies from 20 kHz to 150 MHz by using a downconversion/amplification/upconversion architecture [59]. However, this circuit consumes large power, occupies large area and does not have digital output.

# 2.4 Summary and analysis

The literature review reveals that several performance issues have been addressed by prior work in CMOS instrumentation for amperometric and impedance sensing. However, three challenges still exist associated with our wearable sensor's new performance requirements. Together, these challenges represent critical obstacles to the development of next-generation electrochemical sensor arrays for wearable sensor applications.

- Multi-mode gas sensors provide orthogonal information to improve electrochemical gas array system sensitivity and selectivity [5, 60, 61], and instrumentation circuits are needed to efficiently integrate amperometric and impedance (multi-mode) sensing abilities onto a single chip, with high efficiency in power, size and cost. However, the existing instrumentation circuits do not effectively support amperometric and impedance sensing simultaneously. Details of this challenge and our solutions will be presented in Chapter 3.
- A wearable electrochemical sensing array measures multiple targets in different concentration ranges. These targets concentrations cover a wide range. Take gas

sensing as an example, the target gas concentrations can be from parts per billion (ppb) to tens of percentage. Most electrochemical gas sensors are operated in chronoamperometry mode [62-64]. As a result, the sensing array generates a wide range of DC current outputs. The instrumentation should be able to measure currents from sub-pA level to achieve ultra-high sensitivity of target gases, and also measures large current level at tens  $\mu$ A for some other gases at high concentrations, for example, O<sub>2</sub>. Therefore, power-efficient compact amperometry digitization instrumentation with large dynamic range and sub-pA level sensing ability is desired. However, no chronoamperometry digitization instrumentation of these performance factors. Details of this challenge and our solutions will be presented in Chapter 4.

• For high throughput bio/chemical sensor arrays, the electrochemical readout needs to simultaneously have pA sensitivity, high bandwidth, low power and small area [51, 52]. However, none of prior work meets these requirements. Details of this challenge and our solutions will be presented in Chapter 5.

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# 3. Low Power Multi-mode Electrochemical Sensor Array System for Wearable Health and Safety Monitoring

# 3.1 Motivation and Challenges

Chapter 2 identified the electrochemical method as a preferred sensor technology for wearable sensors because electrochemical sensors are suitable for miniaturization, have ultra-low power consumption, low cost; good selectivity; low detection limit, and can detect broad target gases. The very first step towards electrochemical wearable sensors is to build a personal hazard monitor system with electrochemical sensors for initial evaluation of the system size, function, cost and power.

Exposure to air pollution consistently ranks among the leading global causes of illness and mortality, and explosive gases are an increasing threat to occupational safety as energy demands rise. To improve scientific understanding of the health impacts of personal exposure to these pollutants and effectively protect workers throughout the vast underground mine environment, individual portable/wearable devices are desperately needed. Existing commercial multiple gas detectors are not suitable for broad individual use due to their high cost, large size and/or large power consumption. In addition, the frequent maintenance required by some of these sensors raises their operating cost and lowers their feasibility. As a result, a new portable/wearable system is urgently needed to measure the concentrations of multiple explosive and toxic gases.

This chapter describes a miniaturized electrochemical sensor array for gas sensing. A new resource sharing instrumentation architecture tailored to our novel room temperature

ionic-liquid gas sensor array was utilized to meet the wearable sensor requirement within the constraints of power, area and cost. The architecture also supports multiple electrochemical measurement modes to provide orthogonal data to in-module sensor array algorithms for better prediction accuracy. To expand this personal gas exposure monitoring system to biosensors applications and demonstrate the system response, a malaria electrochemical biosensor was used as an example of biological transducer. Achievements of this project provide a suitable system platform for both further miniaturization toward a wearable bio/chemical hazard monitoring system, and novel instrumentation development for wearable bio/chemical monitoring.

# 3.2 Personal hazard monitoring system design

# 3.2.1 System requirements and design layers

Simultaneously achieving all of the desired features for a personal hazard monitoring system introduces many challenges. To be wearable, the system needs to be miniaturized, light weight, battery powered and either store data, transmit it wirelessly, or both. The system needs to perform measurements intelligently and autonomously, without any external equipment, software, or other support infrastructure. The system must predict mixed gas concentrations accurately and with rapid response while consuming low power for long operation lifetime.

To achieve all these requirements, four design layers were identified for the gas sensing system, namely gas sensors, instrumentation electronics, sensor array processing algorithms and system control. The gas sensor array layer transduces multiple target gas concentrations into electrical signals. The instrumentation electronics layer produces detection-mode dependent stimulus signals and converts gas sensor response signals into a recordable data. The array processing layer executes algorithms designed to identify species and quantify concentrations of target gases within a gas mixture. The system control layer stores system configuration parameters, manages communication, and controls the system to enable autonomous operation. This chapter analyzes all requirements and constraints from a system-level perspective and shows how they can be mapped to component-level decisions within each design layers. All the four layers options are funneled through a filter of the system performance goals to design and implement personal gas exposure monitoring system, as shown in Figure 3.1.



Figure 3.1. All functional layers of sensor system need to be funneled through a performance goals filter to generate a system platform with ideal performance.

#### 3.2.2 Gas sensor array layer

A wearable multi-gas sensor microsystem requires gas sensors to be small, low cost, low maintenance, highly sensitive, highly specific, fast response, and low power. Among gas sensing technologies, electrochemical (EC) sensors are suitable for miniaturization, have ultra-low power consumption, low cost; good selectivity; low detection limit, and can detect

broad target gases [5]. These advantages over other sensor types make them a preferred choice for wearable multi-gas sensor microsystem because electrochemical sensors.

EC gas sensors require the use of an electrolyte, which is an ionically conducting medium that transports charge within electrochemical cells, contacts all electrodes effectively, solubilizes the reactants and products for efficient mass transport, and is chemically and physically stable under all conditions of sensor operation. Traditional electrolytes are classified as liquid electrolytes (aqueous and non-aqueous) and solid electrolytes[65, 66]. Liquid electrolytes have high electrical conductivity but suffer from solvent exhaustion and require periodic electrolyte maintenance. Solid electrolytes overcome this problem but suffer from large power consumption because they must be operated at a high temperature to achieve sufficient ion mobility to sense gases. Room-temperature ionic liquids (RTIL) are novel materials that combine the benefits of both solid and liquid electrolytes. Furthermore, the use of RTILs as electrolytes can eliminate the need for a membrane and thus simplify sensor design. Electrochemical oxidation of NH3, NO2 and SO2 and the electrochemical reduction of O2 have been reported using RTIL gas sensors, and some have shown wide detection limits, high sensitivity and excellent reproducibility [67, 68]. In addition, RTILs are thermally stable to up to 200°C, enabling them to be employed in harsh, high-temperature environments. Therefore, RTIL EC sensors were chosen in our system for multi-gas measurement.

# 3.2.3 Sensor instrumentation layer

To support the goals of a portable/wearable system, the instrumentation electronics

should have low power consumption, small size and low cost. High-resolution instrumentation electronics are needed to maximize detection limits. The instrumentation electronics should provide stimulation signals to EC gas sensor array and extract sensor output information in two EC modes. A three-electrode EC cell potentiostat should be utilized to maximize the DC bias accuracy on each gas sensor. Our experiments have shown that RTIL-based EC sensor requires a long settling time to stabilize the electrode/RTIL interface after the DC bias is applied or changed. Thus, to create an array of sensors tailored to specific gas targets, each element of the array should be biased to a different target-specific voltage and held at that potential constantly. Our experiments have also shown that a large voltage drop can exist between CE and RE. For example, an O<sub>2</sub> sensor with  $V_{WE-RE}$ =1.2V has been observed to generate a voltage difference between RE and CE  $V_{RE-CE}$  close to 1.2V. This phenomenon requires the power supply to be large enough to cover the total voltage drop between CE and WE, over 2.4V for the example O<sub>2</sub> sensor.

# 3.2.4 System control and sensor array processing layer

An autonomous wearable gas sensing system requires an embedded microcontroller ( $\mu$ C). This  $\mu$ C should be power efficient to extend system lifetime. In addition, a  $\mu$ C with built-in analog-to-digital convertor (ADC) is preferred to minimize component count and thus system cost and size. The  $\mu$ C should receive commands from a graphic user interface (GUI) on a PC or smartphone, wirelessly or through a USB port. The  $\mu$ C should also control system operation modes, process sensor array data, generate alerts and send data back to the GUI.

Although our previous work on  $O_2$  and  $CH_4$  IL EC sensors show they have good selectivity, the overall cross-sensitivity of gas sensor array may degrade as unknown mixed gases are present or as the number of mixed gas species increases. To maximize the selectivity and sensitivity of an EC gas sensor array, an array signal processing algorithm should be employed. A sensor array processing algorithm would run on the  $\mu$ C to enable identification and quantification of individual gas concentrations within a mixed-gas environment using sensors with imperfect selectivity. Current methods implemented in hardware only allow detection of a single gas instead of gas mixtures [69]. Thus, our goal is to enable identification and quantification of individual gas concentrations presented simultaneously in a gas mixture. The gas sensor array processing algorithms are under development by another PhD student [70].

# 3.3 Sensor instrumentation design and implementation

#### 3.3.1 Design

#### 3.3.1.1 Architecture

Small component count helps to decrease the system power consumption, size and cost. Sharing circuit components between the two EC modes (amperometric and impedance modes) and among gas sensing channels helps to decrease instrumentation electronic component count. The traditional amperometric and impedance instruments are shown in Figure 3.2. (a) and (b), respectively. In the amperometric instrument, a signal generator (SigGen) generates DC voltage  $V_{RE}$ , a potentiostat applies  $V_{RE}$  at RE, and a current-to-voltage (I/V) convertor measures the sensor current  $I_{in}$ . In the impedance instrument, a SigGen generates a sine waveform voltage  $V_{RE}$ , a potentiostat applies  $V_{RE}$  at the transducer and a readout circuit coverts the response current  $I_{in}$  into real component REAL and imaginary component IMG, by using frequency response analyzer (FRA) method.



Figure 3.2. Traditional instrumentation for (a) amperometric mode and (b) impedance mode.

Both of the circuits in two different modes in Figure 3.2 need a SigGen and a potentiostat. Therefore, these two circuit blocks can be shared between the two modes. Furthermore, the FRA method can be applied after the current is converted into a voltage signal. It means that an I/V convertor can be added into impedance readout as an amplification stage, which improves the circuit's sensitivity. On the other hand, the mixer in Figure 3.2 (b) can be used as gain stage for amperometric instrument by multiplying the sensor response with a DC voltage. The low-pass filter (LPF) in Figure 3.2 (b) can be used in amperometric instrument to remove high frequency noise. As a result, optimized amperometric and impedance instruments are shown in Figure 3.3 (a) and (b). The circuits are optimized so that SigGen, potentiostat, I/V convertor, mixer and LPF can be shared between amperometric and impedance modes.



Figure 3.3. Optimized instrumentation for resource sharing architecture. (a) Amperometric mode instrument and (b) impedance mode instrument.

In a multi-channel recording system, sharing circuit components among target sensing channels can effectively reduce the cost, and power. In the impedance instrument, the SigGen needs to generate a low distortion sine waveform, and can be expensive. For all reading channels, the sine waveform can have the same amplitude, such as 10mV, and the same frequency, such as 1Hz. Different channels only require different DC offsets of the sine signals. Therefore, it reduces cost to share a sine waveform among different channels. The resulting electrochemical instrumentation circuit architecture is illustrated in Figure 3.4. Four gas sensing channels are used to demonstrate this technique. All of the EC sensor elements share one AC generator that provides a sine waveform. The DC generator generates four different DC voltages. The sine signals and DC voltage are summed up for different channels in impedance mode. Current-to-voltage (I/V) convertors and low pass filters (LPFs) are shared between amperometry mode and electrochemical impedance spectroscopy (EIS) mode. To minimize interference between the different sensor array elements, independent potentiostats are provided to control the bias voltage of each of four sensor channels. Similarly, four independent DC bias voltages, Vdc, are applied to four separate working electrodes (WEs) to establish independent WE-to-RE biasing potentials. The potentiostats are kept on to maintain constant sensor bias voltages.



Figure 3.4. Instrumentation architecture for four gas detection channels. In EIS mode,  $\Phi=1$ . In amperometry mode,  $\Phi=0.LPF$  is a low pass filter. REAL and IMG are sensor admittance's real part and imaginary part output, respectively. DC is amperometry mode output.

In the readout portion of Figure 3.4,  $\Phi$  is 1 in EIS mode and all switches except S3 are closed. SigGen generates a 1Hz, 20mVpp sine wave signal to stimulate the gas sensors. This stimulus signal is provided as input to mixers M1 and M2 to produce reference signals for the lock-in technique. Two LPFs are used to extract the real (REAL) and imaginary (IMG) portions of the gas sensor's complex impedance.

Individual gas sensors respond with highest sensitivity to specific portions of the overall complex admittance. For example, we use impedance magnitude |Z| for O<sub>2</sub> and NO<sub>2</sub> and real portion of complex capacitance C<sub>re</sub> for CH<sub>4</sub> and SO<sub>2</sub> to report the highest sensitivity response of these sensors. Both |Z| and C<sub>re</sub> can be readily converted from REAL and IMG outputs of the multi-mode electrochemical instrumentation board (MEIB) by [1]

$$|\mathbf{Z}| = \frac{1}{\sqrt{\mathrm{REAL}^2 + \mathrm{IMG}^2}} \tag{3.1}$$

$$C_{\rm re} = {\rm IMG}/_{\omega} \tag{3.2}$$

where  $\omega$  is the angular frequency.

In amperometry mode,  $\Phi$  is 0 and all switches except S3 are open. The DC generator of

SigGen provides a fixed DC voltage. Mixer M1 functions as a second gain stage to provide additional gain for the measured electrode voltage. Out-of-band noise is removed by an LPF to improve readout resolution.

Although several switches are used in this resource-sharing circuit, they are low cost, take very small area and consume almost no power. Furthermore, the switch control signal  $\Phi$  can readily be generated by the system control layer. Table 3.1 shows that the resource-sharing instrumentation architecture reduces total components count from 12N to (7N+2) for N gas detection channels. As a result, power, cost and size are significantly improved.

Table 3.1. Components count of instrumentation electronics

	DC SigGen	AC SigGen	90° delay	Potentiostat	mixer	LPF	I/V	Total count
a	Ν	Ν	Ν	Ν	3N	3N	2N	12N
b	Ν	1	1	N	2N	2N	Ν	7N+2

N: total number of gas detection channels.

a: without resource-sharing.; b: with resource-sharing.

# 3.3.1.2 Circuit blocks

A resistance feedback transimpedance amplifier (TIA) is good as the I/V convertor, because it is simple and easy to be build. A traditional resistor feedback TIA is shown in Figure 3.5 (a). The voltage at WE is controlled by  $V_{WE}$ . The circuit amplifies the input current  $I_{in}$ .  $V_{out}$  is proportional to  $I_{in}$ , and equal to  $V_{WE}$ - $I_{in}R_{f}$ . Our experiment data shows that our ionic liquid gas sensor can be modeled as a large capacitance Cdl in parallel with a resistance. This large capacitance forms a differentiator with the ideal resistance feedback TIA, which can cause circuit instability. To analyze the circuit stability, the sensor is simply modeled as Cdl. For the circuit in Figure 3.5 (a), we have

$$V_{out} = V_{WE} - R_f C_{dl} \frac{dV_{RE}}{dt}$$
(3.3)

 $V_{RE}$  consists of high frequency noise, which makes the term of  $dV_{RE}/dt$  in (3.3) to be equal to infinite. As a result, the circuit is not stable. To reject this oscillation, two components, resistor R3 and capacitance Cf were used, as shown in Figure 3.5 (b). For the high frequency component of  $V_{RE}$ , Cdl and Cf behavior as zero impedance, and the circuit gain is equal to Rf/R3. As a result, the gain to high frequency input becomes finite and the circuit is stable. Cf forms a low-pass filter with Rf to further improve the circuit stability by reducing high frequency gain. Our sensor's response current  $I_{in}$  is no more than 10  $\mu$ A. For a 1 k $\Omega$  R3, the maximum voltage drop at R3 is no more than 10mV, which is negligible. As a result, the voltage at WE is not affected by R3.



Figure 3.5. Schematic of current-to-voltage convertor. (a) Traditional resistor feedback TIA. (b) Adapted resistor feedback TIA for ionic liquid sensor with improved stability. WE is the working electrode.  $V_{RE}$  is the voltage at RE. The sensor is simplified as a capacitance Cdl for stability analysis.

For an electrochemical transducer with large capacitance, potentiostat may have oscillation [71]. To reject any possible oscillation, a circuit reported in [72] was used. The schematic is redrawn in Figure 3.6. R1, C1 and R2 change the phase response to make the circuit to be stable. Theoretical analysis can be found in [71]. A large voltage drop can exist

between CE and RE. Counting in the voltage drop between RE and WE, the voltage headroom between WE and CE can be large. Take our ionic liquid  $O_2$  sensor as an example,  $V_{RE} - V_{WE} = 1.2$  V, and  $V_{CE} - V_{RE}$  is between 1.2 V and 1.6 V. As a result,  $V_{CE} - V_{WE}$  can be as large as 2.8 V. If  $V_{WE} = 0.9$  V,  $V_{CE}$  can be as high as 3.7 V.  $V_{CE}$  can be larger than 3.7 V for other target sensing. To cover this range, a 5V supply and a rail-to-rail amplifier was used in potentiostats.



Figure 3.6. Schematic of potentiostat.

#### 3.3.2 Implementation

I/V convertor and potentiostat are two circuit blocks directly interfacing transducers. They are critical to the instrumentation functionality, such as stability, and noise performance. These blocks were constructed using low-power commercial analog components in surface mount packages to minimize power and size. Other circuit blocks, such as sine waveform generator and mixer, do not have strict requirements. Hence, these blocks were implemented by Labview for rapid prototyping. AD8619 has four channels of low-noise, low cost, low power (micro-watt), rail-to-rail-input/output CMOS amplifiers. It also has very low input leakage current (<1 pA), is unity gain stable, has large current drive ability (7mA) and has surface amount package available. All these features make AD8619 being one of the excellent candidates for amplifiers of MEIB. Therefore, AD8619 was chosen as the amplifier chip. TLV5620 is a 4 channel 8-bit digital-to-analog convertor chip, which consumes low power,

and can be controlled by microcontroller ( $\mu$ C) through I<sup>2</sup>C bus. Therefore, it was chosen as the DC voltage generator. The final implementation of the multi-mode electrochemical instrumentation is shown in Figure 3.7.



Figure 3.7. Diagram of the implemented multi-mode electrochemical instrumentation. The "AC" circuit block represents the sine waveform generator.

Commercial low-power temperature sensor (AD22103) and humidity sensor (HIH5030) were included on the MEIB to monitor the ambient environment and permit compensation of secondary sensitivities of the gas sensor. All the electronics parts are assembled to a plastic circuit board (PCB), which was designed by Protel 99 SE. The signals at wires between WE and R3 are very sensitive to noise, which is introduced by parasitic capacitance. To reduce the associated parasitic capacitance, these wires are very short on the PCB. To shield environmental noises from these wires, they are also surrounded by grounded trace. The photo of the sensor board is shown in Figure 3.8.



Figure 3.8. The photo of the sensor board. 1. OTA1. 2. OTA2, 3. Rf of the four I/V convertors, 4. Unity buffer at the output of I/V convertor. 5. Vwe generation circuit for all four channels. 6. Temperature sensor. 7 Humidity sensor.

# 3.4 System integration

An low-cost, ultra-low-power, and small MSP430 Launchpad (Texas Instruments)  $\mu$ C board was utilized to control system operation, perform environmental compensation, and execute gas sensor array processing algorithms. The  $\mu$ C MSP430G2553 has eight built-in 10-bit ADC channels to support all sensor inputs without additional ADC hardware on the MEIB. The  $\mu$ C can also control the DC bias voltages on sensors by controlling the DAC chip TLV5620. The connection map between the sensor board and  $\mu$ C board is shown in Table 3.2. P2.1, P2.2, and P2.3 are reserved for controlling a triple color LED to generate alert. Because of the limit connector numbers of the commercial Launchpad, three gas channels of the sensor boards are connected to the  $\mu$ C. For the next generation, an undergraduate student is designing a customized  $\mu$ C board to fully access the four gas channels and reduction of power and size.

A 2×2 IL EC sensor array board, the  $\mu$ C board and the sensor board are connected by SIP connectors for system integration. These three boards can be easily replaced and serviced

independently, thereby decreasing maintenance cost. A prototype of personal gas exposure monitoring system integrating these components was implemented to demonstrate a small and light-weight device for personal health monitoring, as shown in Figure 3.9.

μC I/O port	Sensor board port	Description
P1.0	Gas channel #1 output	P1.0 is a ADC port
P1.5	Gas channel #3 output	P1.5 is a ADC port
P1.3	Gas channel #4 ouput	P1.2 is a ADC port
P1.6	Temperature output	P1.6 is a ADC port
P1.7	Humidity output	P1.7 is a ADC port
P2.0	DAC enable	P2.0 enables the DAC chip TLV5620
P1.4	I <sup>2</sup> C clock	P1.4 provides I <sup>2</sup> C clock to TLV5620
P1.2	I <sup>2</sup> C MOSI	P1.2 provides I <sup>2</sup> C data to TLV5620
P2.1	-	Reserved for a triple color LED
P2.2	-	Reserved for a triple color LED
P2.3	-	Reserved for a triple color LED

Table 3.2. Connection map between the sensor board and  $\mu C$  board



Figure 3.9. A prototype personal gas exposure monitoring system with a 4-element RTIL electrochemical sensor array, an MEIB for electrochemical voltage bias and sensor readout, and a  $\mu$ C board for system control and signal processing algorithms to predict multi-gas concentrations.

# 3.5 Results

# 3.5.1 Instrumentation characterization

The MEIB instrumentation was characterized in amperometry mode and EIS mode,

separately. In amperometry mode, the MEIB was set at a small gain and the input current generator (Keithley 6430) was swept from -20µA to 20µA in steps of 10nA to determine the maximum current input range. As shown in Figure 3.10 (a), the effective input current magnitude ranges bidirectionally from 1µA to 20µA with an output error ratio below 0.5%. Input current lower than 1µA can be achieved by selecting a larger gain. To characterize the current detection limit, the MEIB was set at the largest gain and the input current generator (Keithley 6430) was swept from -10nA to 10nA in steps of 0.01nA. Test data, regression line and output error are plotted in Figure 3.10 (b). With detection limit defined as three times the regression line standard error divided by the regression line slope, results show the current detection limit is 0.34nA. Therefore, the MEIB instrumentation can measure currents from 0.34nA to 20µA bidirectionally in amperometry mode by setting the gain to different values. The dynamic range at the largest MEIB gain setting is 29.4dB. A 5-bit ADC is sufficient to cover this dynamic range.



Figure 3.10. Amperometric mode instrumentation output range and output errors as a function of input currents. (a) Input current was varied from  $-20\mu$ A to  $20\mu$ A in steps of 10nA at; (b) Input current was varied from -10nA to 10nA in steps of 0.01nA.

The MEIB instrumentation was also characterized in EIS mode. A simplified Randles

cell model commonly used for EC instrumentation characterization [28, 56, 73] was adopted to construct a sensor emulation circuit. Although a more accurate model might be needed for interface characterization, this simplified model is sufficient for our instrumentation testing. Figure 3.11 shows the Randles model, where  $R_{et1}$  and  $R_{et2}$  represent charge-transfer resistances,  $C_{d11}$  and  $C_{d12}$  represent double-layer capacitances,  $R_{s1}$  and  $R_{s2}$  denote solution resistances and RE, CE, WE denote electrode terminals. Based on our prior IL EC gas sensor measurements,  $R_{et1}$  and  $R_{et2}$  were set to  $10M\Omega$ ,  $C_{d11}$  and  $C_{d12}$  were set to  $1\mu$ F, and  $R_{s1}$  and  $R_{s2}$ were set to  $10\Omega$ . Thus, |Z| is equal to 159kohm at 1Hz. The EIS stimulation signal amplitude was set at 10mV and frequencies around the nominal EIS operation frequency of 1Hz were tested. Figure 3.11 (bottom) plots the measured MEIB instrumentation impedance amplitude output vs. frequency. Error ratio defined as the difference between tested impedance values and the ideal impedance spectrum divided by ideal impedance, is also plotted in Figure 3.11 (top) and show the MEIB circuit output matches the ideal data very well with the largest output error ratio less than 1%.



Figure 3.11. EIS mode MEIB instrumentation output for a 10mV stimulation signal at frequencies of 0.1Hz, 0.3Hz, 0.5Hz, 0.8Hz, 1Hz, 1.5Hz and 2Hz to cover our EC sensors 'nominal operation frequency of 1Hz. Lower plot: impedance spectrum comparison between ideal curve and test data; Upper plot: output error ratio extracted from lower plot, where output error ratio is defined as output error divided by ideal impedance.

#### 3.5.2 Gas sensor experiments

To characterize the response of the personal gas exposure monitoring system, the sensor array was connected to the custom MEIB and tested. Our IL sensors demonstrate good response to  $O_2$ ,  $CH_4$ ,  $SO_2$  and  $H_2$  by our collaborators. Due to safety regulations in our research laboratory,  $O_2$  was chosen as an example target gas to validate the system response to IL gas sensors. The resulting MEIB outputs in AC impedance and constant-potential amperometry mode are shown in Figure 3.12 along with the corresponding calibration curves. The long settling time when concentrations are changed is not due to  $O_2$  sensor response time but rather to the limitations of the gas chamber that requires at least 5 minutes stabilize to a new gas concentration. Response time on the order of 10 sec have been reported for the IL gas sensor [74].System and sensor performance parameters measured from the prototype system are summarized in Table 3.3, including a maximum response resolution of 0.01 vol% in amperometry mode and 0.06 vol% in AC impedance mode for the example  $O_2$  target gas.



Figure 3.12. (a) MEIB outputs for sensor array with  $O_2$  concentration from 1% to 20% using (top) chronoamperometry mode and (bottom) AC impedance mode. (b)  $O_2$  calibration curves for data in (a). The chronoamperometry  $O_2$  response shows good linearity with an R-squared value of 0.98.

System					
Dimension (w/o	2.6inch×2inch×1inch				
battery)					
Weight (w/o battery)	1.6 Oz				
Power	120 mW				
Electronics cost (w/o	\$22				
battery)					
Detection modes	Amperometry				
	Impedance				
	spectroscopy				
Monitored gases	$CH_4O_2SO_2/H_2$				
channels					
O <sub>2</sub> response:	Sensitivity:				
amperometry mode	6.5mV/%				
	Resolution <sup>1</sup> : 0.01%				
O <sub>2</sub> response: AC	Sensitivity:				
impedance mode	1.36kohm/%				
@20% O <sub>2</sub>	Resolution <sup>1</sup> : 0.06%				

Table 3.3. System performance

<sup>1</sup> resolution =system output noise divided by system sensitivity

### 3.5.3 Malaria sensor experiment

To expand this personal gas exposure monitoring system to biosensors applications and demonstrate the system response, a three-electrode malaria electrochemical transducer [75] was used as an example of biological transducer. This malaria transduce requires the voltage between WE and RE to be set at -0.2V. Malaria concentrations were set at values from 16 ng/mL to 1024 ng/mL. The system transient response is shown in Figure 3.13 (a). A plateau region exists at the first tens of seconds of the response curve for 1024 ng/ml. The reason is that a step voltage was applied between WE and RE to generate desired -0.2V from 0V when the system starts up. This step voltage generates a large charging current. As time goes, this charging current reduces rapidly so that this plateau region disappears. The responses of 16ng/mL and 32 ng/mL are overlapped, showing that the system detection limit cannot be lower than 32 ng/mL. All the response current at 147 s for different malaria concentrations in

Figure 3.13 (a) was extracted to plot the Figure 3.13 (b). Figure 3.13 (b) shows that the malaria transducer has reduced response for larger malaria concentrations, meeting the results published in [75]. The reason is that at large malaria concentrations like 1024 ng/mL, most of the WE are covered by analyzed targets, which results in smaller active WE area to grab targets at higher concentrations. Therefore, the sensitivity is reduced for large malaria concentration. All the results demonstrate that the system can be a good platform for malaria sensing.



Figure 3.13. (a) System transient response to different malaria concentrations, and (b) corresponding extracted dataset showing the relation between system output at 147s and malaria concentrations.

Figure 3.13 (cont'd)



# 3.6 Conclusion

The development of a wearable, low-cost, low-power, multi-analyte sensor array system, from concept to prototype has been reported. Application-critical system performance requirements were mapped to component-level decisions within each design layer. RTILs electrochemical gas sensor was used due to the low power consumption, small size, high sensitivity, good selectivity, and low cost. A prototype system was constructed using a plug-in custom miniaturized RTIL sensor array, a custom multi-mode electrochemical sensor instrumentation board, and a commercial low power microcontroller board. New resource-sharing instrumentation architecture effectively decreases power, cost and size. The prototype system achieves critical system-level performance goals including high resolution gas measurements and low power consumption. The malaria experiments show the personal gas exposure monitoring system can work well for malaria sensing application. It was demonstrated that this personal hazard monitoring system is a suitable platform for further miniaturization toward a wearable bio/chemical hazard monitoring system.

# 4. Power Efficient Amperometric Readout with High Sensitivity and Large Dynamic Range for Wearable Sensor Arrays

# 4.1 Motivation

Chapter 3 reports the development of a, low-cost, low-power, multi-analyte intelligent sensor array system toward wearable sensors. New resource-sharing instrumentation architecture effectively integrates amperometric and impedance modes into one circuit, and decreases power, cost and size. The circuit achieves nA-level sensitivity (minimum detectable current) and tens of mW power. This chapter identifies that a new CMOS circuit with sub-pA sensitivity, high dynamic range, and high power efficiency is needed for wearable sensor arrays.

Many electrochemical sensors are operated in chronoamperometry mode [62, 64]. This electrochemical mode can measure targets including  $O_2$ ,  $H_2$ , and toxic compounds such as CO, NO<sub>x</sub>, SO<sub>2</sub>, etc. The versatility of this technology suggests that an array of electrochemical sensors can simultaneously measure concentration of multiple analyte targets in a wearable device, to protect human health. However, a wearable system that operates many electrochemical sensors in tandem requires the design of instrumentation electronics to simultaneously meet demanding cost, power, area, sensitivity and other performance goals. In particular, each target gas is present in a different range of possible concentrations: toxic gases can be harmful at concentrations as low as parts per billion (ppb) while some atmospheric gases of interest, such as  $O_2$ , are present in concentrations ten million times larger. As a result, a sensor array can generate a wide range of DC current outputs, and thus

the instrumentation electronics should be able to measure currents at sub-pA level (to achieve high sensitivity for scarce target gases), at the  $\mu$ A level (for large concentration atmospheric gases) and all ranges in between [76]. Therefore, power-efficient, compact, amperometric instrumentation with wide dynamic range and a sub-pA limit of detection is desired.

The low cost, size, and power consumption of modern CMOS technology enables development of suitable instrumentation circuitry for such a wearable sensing device, and noise performance would be dramatically improved by integrating sensors directly with the CMOS instrumentation. Substantial research effort has focused on CMOS instrumentations of multi-channel chronoamperometry sensor arrays. Different structures were developed for this purpose, including a sigma-delta ( $\Sigma \Delta$ ) analog-to-digital convertor (ADC) [39, 44], integration ADC [49], current-to-frequency ADC [28], and hybrid ADC topology [56]. However, these circuits were not built to simultaneously accommodate tight area, power, and dynamic range constraints, which are required by wearable amperometric sensing arrays. As a result, a new amperometric instrumentation approach for wearable sensor arrays is urgently needed.

This chapter reports a novel power efficient CMOS amperometric readout with 100fA sensitivity and very high dynamic range for wearable sensor arrays. This new amperometric readout can be used in the wearable system architecture presented in chapter 3, to develop next generation of wearable sensors with better performance factors. Compared to the system in Chapter 3, the new system will have more compact size, lower power consumption, higher hazard target detection limit, longer lifetime and larger target detection concentration range.

# 4.2 Approach and circuit concept

Chronoamperometry involves biasing an electrochemical sensor to a constant potential and measuring the steady-state current response, which correlates with the reactive surface area of the electrode as well as the reaction rates of compounds present in the electrolyte solution. If the electrochemical reaction is not limited by mass transportation, the steady-state response current will ideally be proportional to the analyte concentration [23]. The sensor bias potential is specific to the target gas and is important to the amperometric sensor selectivity. Therefore, the circuit needs to set a controllable voltage at the sensing electrode.

Analog circuitry implementing this interrogation protocol should be compact and low-power to improve the system's portability and longevity, and the impact of this requirement is amplified when developing high-density sensor arrays. A miniaturized amperometric sensor array with small electrodes and a ppb-level detection limit requires instrumentation with sub-pA sensitivity. Elements in a gas sensor array can generate current levels ranging from sub-pA to several tens of  $\mu$ A depending on the target concentration range. Such a wide current span requires the readout circuit to have a large dynamic range.

In array sensing, ADC can be integrated at the chip level, at the column level or at the pixel level. In the chip level approach, the ADC is shared by all the sensor elements and is thus required to have very high speed. In the column level approach, the ADC is shared by all the sensor elements in one column and thus has the similar speed requirement as in the chip level approach. In the pixel level approach, every sensor element is assigned to one in-pixel ADC, which is not required to be high speed. As a result, slow-speed but high-precision
low-power ADC, such as  $\Sigma\Delta$  ADC and integration ADC can be used to improve the overall performance. Large column bus capacitance is isolated from the in-pixel ADC and results in better noise performance [77]. Analysis shows that pixel-level ADC should achieve the highest signal-to-noise ratio (SNR) and the lowest power consumption [78]. In addition, in-pixel ADC solution is good for scalability because the same pixel circuit design and layout can be used for a wide range of sensor sizes and less performance restriction to the ADC allowing to use more advanced CMOS process [78]. Lastly, in-pixel ADC solution has low crosstalk noise ideally. In a multiple-channel system, the main crosstalk noises source are the multiplexer's finite turn-off resistance and the parasitic coupling in multiplexer's MOS transistors [20]. In-pixel digitization allows using shifter to transmit the in-pixel ADC output out of chip in series. As a result, multiplexer is not needed and low crosstalk noise is expected. Therefore, in-pixel ADC is used as the solution for the target applications. Ideal in-pixel ADC readout architecture of an amperometric sensing array is shown in Figure 4.1. Each sensor element is driven by a DC potential from the bias potentiostat, and has the maximum response to a specific target. Every in-pixel ADC has a shifter to transmit the ADC output out of the chip. This chapter focuses on the design of the in-pixel ADC.



Figure 4.1. The in-pixel ADC readout architecture for an amperometric sensor array.

## 4.2.1 Analysis of in-pixel ADC structures

Existing in-pixel ADCs for amperometric sensing applications [13-17] that use incremental first-order  $\Sigma\Delta$  structures tend to have the best sensitivity (fA range) of any class of ADC while remaining compact and consuming as little as a few  $\mu$ W of power. This ADC structure combines the benefits of integration and  $\Sigma\Delta$  ADCs and achieves superior performance for instrumentation and measurement applications, namely high absolute accuracy and excellent linearity with small area and power costs [79]. Although such ADCs are not fast, environmental conditions do not change rapidly for most applications, making lower-bandwidth circuits attractive. Unfortunately, traditional  $\Sigma\Delta$  ADCs require reference current supplies larger than their input (measured) current, which dominates the system's power budget when input magnitudes exceed a few µA [76]. Another limitation of conventional current-mode  $\Sigma \Delta$  ADCs is that, to accommodate a large input range, a multiple-bit current-mode digital-to-analog converter (DAC) is needed as a reference. This reference current DAC can occupy a large chip area and have high power consumption, limiting the number of readout channels. These limitations motivated our design of a circuit block for prescaling the input current by a programmable attenuation factor, improving power

efficiency for larger input currents. This scaling factor provides the user with a means to select a current range appropriate to the sensing target. To conserve chip area, an ADC design using this technique can share the same reference current generator between multiple input current ranges.

## 4.2.2 Current scaling approach and circuit concept

A digital modulation scheme was chosen for prescaling the input current. An alternative analog method employing current mirrors is feasible, but it suffers power and precision problems due to device mismatch and occupies large area to achieve large scaling ratio [44]. In contrast, digital modulation can be simply implemented by a single compact CMOS switch, allowing for precise control of device ratios, low area overhead, and low power. A digital modulation circuit is also much easier to reconfigure at runtime.

By modulating the input current  $I_{in}$  with a square wave having a precisely controlled duty cycle of 1/*M*, the average current seen by the ADC input can be reduced to  $I_{in}/M$ . This reduces the  $\Sigma\Delta$  ADC reference current requirement by a factor of *M*. The input current range can be reprogrammed by changing the duty cycle of the modulating pulse train. Figure 4.2 illustrates this digitally modulated input current concept.



Figure 4.2. Concept of the input modulated  $\Sigma\Delta$  ADC for amperometric sensor arrays. The

Figure 4.2 (cont'd) modulation factor M is defined as the reciprocal of the modulation signal's duty cycle.

## 4.3 Circuit block design

#### 4.3.1 ΣΔ ADC

A semi-synchronous incremental  $\Sigma\Delta$  design was chosen as the basis of our input-modulated  $\Sigma\Delta$  ADC because it has been demonstrated to be very compact and achieve fA sensitivity with only  $\mu$ W power per channel [39]. Figure 4.3 (a) shows the block-level schematic for the base ADC design. The circuit uses an integrator and a hysteretic comparator to produce two 1-bit pulse-width-modulation (PWM) digital pulses, D and D\*, that modulate two reference currents, I<sub>refP</sub> and I<sub>refN</sub>. I<sub>refP</sub> and I<sub>refN</sub> inherently suffer from mismatch, requiring post-fabrication calibration and reducing measurement resolution [80]. However, notice that amperometric sensors typically measure current in only one direction, depending on whether oxidation or reduction of the target compound(s) is being recorded. Thus, only one reference current is necessary to complete the negative feedback path required by the  $\Sigma\Delta$  algorithm. This feature allows only one reference current to be employed, resolving the mismatch issue. In addition, an improvement in noise performance is expected because only one reference current source contributes to noise. The resulting simplified  $\Sigma\Delta$  ADC schematic shown in Figure 4.3 (b) contains only a reference current sink I<sub>ref</sub>. This circuit measures a sensor cell with current flowing out of the sensor. For cells with the opposite current direction, a single current source I<sub>ref</sub> controlled by the  $\Sigma\Delta$  modulator output *D* can be used for measurement.



Figure 4.3. Schematic of (a) the semi-synchronous incremental  $\Sigma\Delta$  ADC from [13] and (b) a simplified design for the target application.  $I_{in}$ ' is the input current,  $f_s$  is sampling clock. D and D\* are two inversed phase signals.  $I_{refP}$ ,  $I_{refN}$  and  $I_{ref}$  are reference currents, modulated by D or D\*. RST is a reset clock to reset the integrator and counter.

To simplify analysis of the circuit's behavior, assume that the comparator in Figure 4.3 (b) has no hysteresis. The new incremental  $\Sigma \Delta$  ADC is then governed by the transfer function

$$\overline{I_{in}'} = \frac{\int_0^{T_t} I_{in}'(t)dt}{T_t} = \frac{I_{ref}T_s \sum_{i=1}^N D_i^*}{T_t} = \frac{I_{ref} \sum_{i=1}^N D_i^*}{N}$$
(4.1)

where  $I'_{in}$  is the input current of the  $\Sigma\Delta$  ADC,  $\overline{I'_{in}}$  is the average value of  $I'_{in}$  over the integration time  $T_t$ , t is time,  $T_s$  is the sampling clock period and equal to  $1/f_s$ ,  $D_i^*$  is the value of D\* at time index i, and N is the total number of pulses in a conversion cycle of the ADC and equal to  $T_t/T_s$ .

# 4.3.2 Input modulation stage

A switch controlled by the modulation signal was chosen to implement the input modulation stage because it is simple, compact and consumes almost no static power. As shown in Figure 4.2, the input DC current is modulated by a square wave with a pulse width of  $T_p$  and a period of  $T_m$ . The modulated current can be expressed as a Fourier series as

$$\begin{cases} I'_{in}(t) = I_{in} \sum_{k=-\infty}^{\infty} a_k e^{jk\omega_m t}, k = 0, 1, 2, \cdots \\ a_k = \frac{\sin \frac{k\omega_m T_p}{2}}{k\pi}, k \neq 0 \\ a_0 = \frac{T_p}{T_m} = \frac{1}{M} \end{cases}$$
(4.2)

where  $\omega_m$  is the modulation signal's angular frequency and is equal to  $2\pi/T_m$ .

From (4.1) and (4.2),  $\overline{I'_{in}}$  can be represented as

$$\overline{I'_{in}} = \frac{\int_{0}^{T_{t}} I'_{in}(t)dt}{T_{t}} = \frac{I_{in}}{M} + I_{in} \sum_{k=-\infty}^{\infty} \frac{(\int_{0}^{T_{t}} a_{k}e^{jk\omega_{m}t}dt)}{T_{t}}$$
(4.3)

On the right side of the equation, the first term is the desired one and represents that input I<sub>in</sub> is prescaled by a factor of 1/M; the second term is undesired and represents harmonic distortion due to modulation. To make the second term zero,  $T_t$  needs to be an integer multiple of  $T_m$ . To simplify the implementation of the clocking circuit,  $T_p$  was set equal to  $T_s$ , the ADC's sampling period. As a result,  $T_m = MT_s$ , and  $T_t = LMT_s = NT_s$ . where L, M, N are integers. The resulting modulation signal is shown in Figure 4.4.



Figure 4.4. Control clocks for the input modulation stage and their relation to the ADC sampling clock. The conversion cycle of the incremental  $\Sigma \Delta$  ADC is  $T_t$ . The modulation signal's cycle is  $T_m$ . L and M are integers.

## 4.3.3 Current buffer and biasing potentiostat

A chronoamperometric sensor can be a two-electrode system or three-electrode system. In both systems, sensor output current can be measured from the sensor's working electrode (WE), which must be held at a constant bias to stabilize the output current. The output settling time can be as much as several hours after a new potential is applied [5, 81], necessitating a current buffer to maintain a constant electrode bias when the modulation switch disconnects the sensor from the circuit input. A current conveyor is a small, very low-power choice of current buffer circuit [82]. A current conveyor illustrated with a two-electrode system in Figure 4.5 (a) was used. Here the WE voltage is controlled by  $V_{WE}$ . A current mirror is used in the current conveyor to isolate WE from the input modulation stage. OTA2's transistors are operated in the sub-threshold region, yielding sub- $\mu$ A current consumption. As a result, the power efficiency of the circuit is good for large input currents. When the input current is small compared to the current consumed by the current conveyor, the current conveyor and input modulator may be disabled to save power, leaving only the simplified  $\Sigma \Delta$  ADC.

A three-electrode electrochemical sensor contains an additional counter electrode (CE). These sensors require an additional biasing potentiostat to control the potential difference  $V_{cell}$  between the working and reference electrodes and to provide current to the CE [23, 26]. Because WE voltage is controlled by  $V_{WE}$  in Figure 4.5 (a), only RE voltage needs to be controlled. Voltage followers are widely used as for such a purpose, especially for electrochemical sensor array applications [25, 26]. The schematic of a voltage follower in a three-electrode system is shown as opamp1 in Figure 4.5 (b). The biasing potentiostat opamp1 holds the RE voltage at  $V_{RE}$ . WE voltage is set by the current readout circuit, as it is in Figure 4.5 (a). A large voltage drop can exist between CE and RE. Counting in the voltage drop between RE and WE, the voltage headroom between WE and CE can be large. Take our ionic liquid O<sub>2</sub> sensor as an example,  $V_{RE} - V_{WE} = 1.2V$ , and  $V_{CE} - V_{RE}$  is between 1.2V and

1.6V. As a result,  $V_{CE} - V_{WE}$  can be as large as 2.8V. If  $V_{WE} = 1.5$ V,  $V_{CE}$  can be as high as 4.3V.  $V_{CE}$  can be larger than 4.3V for other target sensing. In modern CMOS technology, supply voltage is generally no more than 5V for low power consumption. It suggests to use wide output swing amplifier to be opamp1. On the other hand, opamp1 needs to have large current drive ability to provide current needed by the electrochemical cell. The electrochemical cell requires a large charging current when the circuit startups due to the large double layer capacitor.



Figure 4.5. (a) Simplified schematic of the current readout circuit, including the current conveyor, and its connection to the input modulation stage and  $\Sigma\Delta$  ADC. (b) Schematic of the biasing potentiostat circuit in a three-electrode system.  $I_{in}$  is the sensor output current, and  $I_{in}$ ' is the modulated current. Reference electrode (RE), working electrode (WE) and counter electrode (CE) are the electrodes of the sensor.

## 4.3.4 Circuit block integration

Combining all the design choices discussed above, a block diagram of the complete input modulated  $\Sigma\Delta$  ADC is shown in Figure 4.6. The readout channel consists of a current conveyor, modulation, and simplified  $\Sigma\Delta$  ADC stages. An additional/optional biasing potentiostat for three-electrode sensors is also shown. A capacitor array C<sub>f</sub> was chosen as the integrator feedback capacitance to provide programmable integration gain. This circuit can readout electrochemical sensors in which current flows unidirectionally out of the working electrode. For sensors that draw current into the WE, a current conveyor with an NMOS current mirror may be used instead, or a bidirectional current conveyor [83] could be used for sensors that need to measure both oxidation and reduction reactions.



Figure 4.6. Simplified blocks of the input modulated  $\Sigma\Delta$  ADC for three-electrode electrochemical sensors. Switch SW is controlled by the modulation signal in Figure 4.3.  $f_s$  is the sampling frequency.  $I_{in}$  is the sensor output DC current and  $I_{in}$  is the modulated current.

# 4.4 Transistor level circuit implementation

# 4.4.1 ΣΔ ADC

OTA1 in the integrator in Figure 4.6 was implemented as a folded-cascode amplifier, as shown in Fig 4.7 (a), because it achieves a good tradeoff between noise, output range, chip area, and power performance. PMOS input transistors with large area were used to reduce the flicker noise. The 1pF capacitor C<sub>c</sub> was used to improve the circuit stability.  $M_{p7}$  and  $M_{p8}$  comprise the output stage, providing large current drive capability. A class AB output stage may be used to replace these two transistors for better power efficiency. The voltage  $V_{BIAS}$  sets the output stage bias current. For small input currents, the output stage can be disabled to maximize power efficiency by setting  $V_{BIAS}$  to  $V_{dd}$  and setting the multiplexer to bypass this stage. The current drive capability of the OTA1 was set to cover sensor outputs up to 10  $\mu$ A to meet application goals. This OTA1 consumes very low power because the bias current is very low.  $M_{pb1}$  consumes only 1  $\mu$ A.  $M_{p3}$  and  $M_{p4}$  consume 500 nA. All the transistor sizes

are listed in Table 4.1.  $M_{p1}$  and  $M_{p2}$  were set at large area to reduce flicker noise.  $M_{p7}$  and  $M_{p8}$  were set at large area to reduce the overdrive voltage (voltage between transistor's drain and source) so that the V<sub>o</sub>'s output swing can be large. Reducing threshold voltage can further reduce the output swing, and is achieved by shorting bulk and source terminals of  $M_{p8}$ .



Figure 4.7. Schematic of the sub-circuits of the  $\Sigma\Delta$  modulator: (a) the OTA used by the integrator, and (b) the hysteretic comparator.

Transistor	Size	Transistor	Size	Transistor	Size
	(μm/μm)		(µm/µm)		(µm/µm)
M <sub>pb1</sub>	4.2/2.4	M <sub>p3</sub> , M <sub>p4</sub>	2.1/2.4	M <sub>n3</sub> , M <sub>n4</sub>	4.2/1.2
M <sub>p1</sub> , M <sub>p2</sub>	16.8/1.2	M <sub>p5</sub> , M <sub>p6</sub>	4.2/1.2	M <sub>n1</sub> , M <sub>n2</sub>	8.4/2.4
M <sub>p7</sub> , M <sub>p8</sub>	16.8/0.6				

Table 4.1. Transistor sizes of OTA used by the integrator.

A hysteretic comparator is needed by the semi-synchronous  $\Sigma\Delta$  ADC to reduce the substrate noise interference and improve converter linearity [39]. A schematic of the comparator is shown in Figure 4.7 (b). The comparator consists of preamplification (preamp) and decision stages. The preamp stage enhances the comparator's sensitivity by providing a large gain and isolating the input from switching noise in the decision stage [84]. The decision stage is a positive feedback circuit, generating hysteretic output. The two hysteresis levels can be programmed by V<sub>biasP</sub> and V<sub>biasN</sub>. These two voltages also control the

comparator's dynamic power by setting the switching current of a current starved inverter formed by  $M_{n3}$ ,  $M_{n4}$ ,  $M_{p4}$  and  $M_{p5}$ .

A counter is needed to act as a low-pass and decimation filter in an incremental  $\Sigma\Delta$  ADC. This counter needs to be highly compact and power efficient for a wearable sensor array. To reduce area cost, the counter output needs to be serially transferred off-chip to simplify system-level interconnects. To implement this counter, an area and power-efficient counter/shifter design [80] was chosen that saves area by sharing the counter hardware with the serialization shifter and saves power by using current starved inverters.

The reference current source  $I_{ref}$  in Figure 4.6 needs to have low power, area, and noise. The schematic for the implemented current generator is shown in Figure 4.8.  $M_{n1}$  and  $M_{n2}$  form a cascoded stage to generate a precise reference current.  $V_{b1}$  controls the value of  $I_{ref}$  and is generated by a low-power current splitting circuit [85]. This current splitting circuit can generate pA range currents while maintaining very low area because it does not require any capacitors or resistors [86]. The integrator input is virtually connected to analog ground by OTA1 in Figure 4.6. To increase the switching speed and reduce switching noise,  $M_{n4}$  was used to set  $M_{n2}$ 's drain at analog ground when  $M_{n3}$  is turned off. To permit tuning of input current range of other performance parameters,  $I_{ref}$  was implemented as a programmable current array with a maximum value of 500 nA.



Figure 4.8. Schematic of the reference current generator  $I_{ref}$  in Figure 4.6.

4.4.2 Input modulation stage, current buffer and biasing potentiostat

The input modulation stage is simply a CMOS switch and is therefore very small and low power. Switching noise is minimized by using a transmission gate structure, minimum size transistors and dummy transistors. Although the on-resistance of this switch can form a low-pass filter with the current conveyor's output capacitance [87, 88], the sensor output frequency is very low (almost DC) and this filter has negligible effect on the input signal.

In the current conveyor in Figure 4.6, OTA2's output is connected to the gate of transistor  $M_f$ . Therefore, no output stage is needed, and OTA2 can be very low power and compact. OTA2 used the same design as OTA1 in Figure 4.6 (a), without the output stage. The current mirror was implemented with a cascoded structure to improve accuracy, and the mirror ratio was set at 1 to maximize accuracy and minimize the area. To set the output node voltage to analog ground when the input modulation stage is turned off, a transistor like  $M_{n4}$  in Figure 4.8 was included in the current mirror design.

The analysis in Section 4.3.3 encloses that the biasing potentiostat amplifier needs to have large current drive ability as well as large output range. A rail-to-rail amplifier present in [89] meet the requirements very well. Therefore, this amplifier was used as the biasing potentiostat amplifier in Figure 4.6.

# 4.5 Theoretical analysis

# 4.5.1 Transfer function

The modulated input current at the ADC stage  $I_{in}$  in Figure 4.6 can be expressed as

$$I_{in}(t) = \begin{cases} I_{in}, \ n \cdot M \cdot T_s \le t < n \cdot M \cdot T_s + T_s \\ 0, \ else \end{cases}$$
(4.4)

where n = 0, 1, 2, ...L-1;  $T_s$  is the sampling clock period, and M is the modulation factor as in Figure 3.

Substituting (4.4) into (4.1), the transfer function of the input modulated  $\Sigma\Delta$  ADC is given by

$$I_{in} = \frac{I_{ref}}{L} \sum_{i=1}^{N} D_i^* \tag{4.5}$$

where *L* is the total number of '1' pulses in the modulation waveform, as defined by Figure 4.4. Because (4.5) is independent of the sampling clock cycle  $T_s$  and the integrator feedback capacitance  $C_{f_s}$  no precise clock or capacitor components are needed to operate the input modulated  $\Sigma \Delta$  ADC.

# 4.5.2 Power analysis

If we define  $\alpha$  as the average duty cycle of D<sup>\*</sup> such that  $0 \le \alpha \le 1$ , then (for a constant input) the summation in (4.5) becomes

$$\sum_{i=1}^{N} D_i^* = \alpha N \le N \tag{4.6}$$

Since  $N = L \times M$ , substituting (4.6) to (4.5), yields

$$I_{in} = \frac{I_{ref}}{L} \alpha N = I_{ref} \times \alpha M \le I_{ref} \times M \xrightarrow{\text{thus}}$$

$$I_{ref} = \frac{I_{in}}{\alpha M} \ge \frac{I_{in}}{M} \tag{4.7}$$

When  $\alpha = 1$ ,  $I_{ref} = I_{in}/M$ ; setting M = 1 produces the  $I_{in}$  to  $I_{ref}$  relationship of an unmodulated  $\Sigma \Delta$  ADC. Thus (4.7) shows that the input modulated  $\Sigma \Delta$  ADC scales down the required magnitude of the reference current  $I_{ref}$  by a factor of M for a given  $I_{in}$ . This also shows that the input modulated ADC can expand maximum input current by a factor of M; in other words it can improve the input current range by  $20\log_{10}(M)$  dB.

To evaluate power improvement, the power consumption of the input modulated ADC was compared to that of an unmodulated ADC. Both versions use the same unmodulated simplified semi-synchronous  $\Sigma\Delta$  ADC core as in Figure 4.3(b), with the same integrator, comparator, D flip-flop and counter, but with different reference current values. The modulated version adds input modulation and current conveyor stages. Since the biasing potentiostat stage would be the same for both versions, it was omitted from this analysis. Because the digital components in both versions are largely the same and their power consumption will change negligibly with sensor input current, we can assume that, excluding the reference current  $I_{ref}$ , both versions consume the same  $\Sigma\Delta$  ADC core current  $I_a$ . If the input current  $I_{in}$  is DC, then the unmodulated ADC reference current  $I_{ref\_um}$  must obey  $I_{ref\_um} \ge I_{in}$  from (4.7). The minimum power  $P_{um}$  of the unmodulated ADC is therefore

$$P_{um} = [min(I_{ref\_um}) + I_a]V_{dd}$$
$$= (I_{in} + I_a)V_{dd}$$
(4.8)

which shows that  $P_{um}$  directly increases with  $I_{in}$  when  $I_{in} \gg I_a$ . (4.7) gives  $\alpha I_{ref_m} \ge I_{in}/M$ . Similarly, the minimum power  $P_m$  of the modulated ADC is given by

$$P_{\rm m} = \left[\min\left(I_{\rm ref_m}\right) + \overline{I_{\rm in}} + I_{\rm a} + I_{\rm cc}\right] V_{\rm dd} \xrightarrow{\overline{I_{\rm in}}^{\prime} = {}^{\rm lin}/_{\rm M}} P_{m} = \left[2I_{in}/M + I_{a} + I_{cc}\right] V_{dd} \qquad (4.9)$$

where  $I_{cc}$  is the current dissipated by the current conveyor,  $\overline{I_{ln}}$  is the average current flowing through the input modulation stage, and  $I_{ref_m}$  is the unmodulated ADC reference current. The simplified form of (4.9) is obtained by noticing that (4.3) gives  $\overline{I_{ln}} = I_{ln}/M$  and (4.7) gives  $\min(I_{ref_m}) = I_{ln}/M$ .

Defining a power improvement factor as  $\eta_{\Delta} = (P_{um} - P_m)$ , we have

$$\eta_{\Delta} = (P_{um} - P_m) = \left[ \left( 1 - \frac{2}{M} \right) I_{in} - I_{cc} \right]$$
(4.10)

When input currents are small, M=1 and  $\eta_A$  is negative indicating the modulated version requires more power. However, the difference is small in value because  $I_{in}$  is small. Furthermore, when M=1 the current conveyor and input modulator can be powered off to reduce power consumption. On the other hand, when  $I_{in}$  is large enough that M > 2 and  $I_{in}$  >  $I_{cc}$ , then  $\eta_A$  is positive and the modulated version starts to save power. For example, if M=32 and  $I_{cc} = 1\mu A$  (which is readily achievable by operating transistors in the subthreshold region), then  $\eta_A$  > 0 for any  $I_{in} \ge 1.07 \mu A$ . As  $I_{in}$  gets larger, M is increased and the input modulated ADC can achieve significantly lower power consumption than the unmodulated ADC.

## 4.5.3 Input modulation effect on resolution and signal range

This section analyzes the effect of input modulation on the ADC performance. The ideal least significant bit (LSB) resolution of the input current  $I_{inLSB}$  can be estimated by substituting  $\sum_{i=1}^{N} D_i^* = 1$  into (4.5), and the maximum input current  $I_{inMAX}$  can be estimated by substituting  $\sum_{i=1}^{N} D_i^* = N$  into (4.5). These substitutions yield

$$\begin{cases} I_{inLSB} = \frac{1}{L} I_{ref} \\ I_{inMAX} = M I_{ref} \end{cases}$$
(4.11)

where *L*, *M*, and *N* are defined in Figure 4.4. For a fixed  $I_{ref}$ , larger *L* corresponds to a smaller LSB value and the maximum input current is proportional to the modulation factor *M*. In practice these ideal parameters are limited by circuit constraints.  $I_{inMAX}$  is limited by the drive current ability of OTA1 in Figure 4.5.  $I_{inLSB}$  is limited by noise effects discussed below.

Output saturation in the  $\Sigma\Delta$  ADC's integrator can cause large errors. Therefore, it is important to calculate the integrator output swing. The largest integrator output swing happens when the input current is equal to  $I_{inMAX}$  in (4.11) and the input modulation stage is on. Defining the hysteresis level as  $\Delta$ , the maximum output swing,  $V_{range}$ , is

$$\left|V_{range}\right| \le \Delta + \frac{I_{inMAX}T_s}{C_f} = \Delta + \frac{MI_{ref}T_s}{C_f}$$
(4.12)

where  $C_f$  is the integrator's feedback capacitance,  $T_s$  is the modulation signal pulse width. (4.12) shows that the integrator's output range can limit the maximum input current. To mitigate this effect, large  $C_f$  and small  $T_s$  were used to reduce the integrator output swing for large input current.

## 4.5.4 Noise analysis and performance limitations

The finite gain of OTA1 in the integrator weakens the ADC's noise shaping performance in a similar manner to the traditional incremental  $\Sigma\Delta$  ADC [90]. This section studies other major noise sources associated with the input modulated  $\Sigma\Delta$  ADC.

#### 4.5.4.1 Current conveyor

The current conveyor is one of the major contributors to the input referred noise of the

ADC because it is the first stage of the circuit. The current conveyor's noise model in Figure 4.9 shows the transconductance and dimension of  $M_{p1}$  and  $M_{p2}$  are equal. A similar structure for OTA2 and  $M_f$  has been reported [56]. The loop gain formed by OTA2 and  $M_f$  greatly reduces  $M_f$ 's contribution to the input referred current noise [56]. Adding noise from  $M_{p1}$  and  $M_{p2}$ , the input referred current noise of the current conveyor is

$$i_{ineq}^{2} = (2\pi f)^{2} C_{in}^{2} e_{n}^{2} + \frac{16kTg_{m_{p}}}{3} + \frac{2K_{fp}g_{m_{p}}^{2}}{C_{ox}W_{p}L_{pf}}$$
(4.13)

where the second and third terms are the thermal noise and flicker noise of  $M_{p1}$  and  $M_{p2}$ , f is the frequency, k is the Boltzmann constant, T is the operating temperature in Kelvin,  $g_{m_p}$  is the transconductance of  $M_{p1}$  and  $M_{p2}$ ,  $K_{fp}$  is a process-dependent constant, and  $C_{ox}$  is the gate oxide capacitance per unit area.  $g_{m_p}$  can be expressed as  $\sqrt{2\mu_p C_{ox} I_{in} W_p / L_p}$ , where  $\mu_p$  is the hole mobility. Substituting  $g_{m_p}$ 's expression into (4.13) yields

$$i_{ineq}^{2} = (2\pi f)^{2} C_{in}^{2} e_{n}^{2} + \frac{\frac{16kT}{\mu_{p} C_{ox} I_{in} W_{p} / L_{p}}{3} + \frac{4K_{fp} \mu_{p} I_{in}}{L_{p}^{2} f}$$
(4.14)

Therefore, to reduce the input referred current noise contribution from the conveyor,  $e_n$ ,  $W_p/L_p$  was set to be small and  $L_p$  was set to be large. Small  $C_{in}$  can be achieved by reducing biosensor capacitance and parasitic capacitance. Monolithic integration can effectively reduce  $C_{in}$  by decreasing the parasitic capacitance [35].



Figure 4.9. Noise model of the current conveyor and input modulation switch SW.  $C_{in}$  is the total capacitance at WE, including sensor capacitance, wiring capacitance and parasitic capacitance.  $e_n^2$  is the OTA1's input referred voltage noise,  $I_{n1}^2$  and  $I_{n2}^2$  are the current noise of transistors of M<sub>p1</sub> and M<sub>p2</sub>,  $W_p$  and  $L_p$  are the dimension of transistor M<sub>p1</sub> and M<sub>p2</sub>.

## 4.5.4.2 Input modulation stage

The noise analysis of the input modulation stage can be simplified by modeling the modulator as an NMOS switch SW, as shown in Figure 4.9. The modulation switch contributes to both static and dynamic noise. The static noise refers to the noise components  $I_{n3}^2$  generated by the turn-on resistance of the switch [87, 88, 91]. Because transistor SW forms a cascode with device  $M_{p2}$  when it is on, its static noise contribution is negligible. The dynamic noise refers to the error caused by charge injection and clock feedthrough. Small transistors were used to reduce this noise source. A complementary structure with dummy transistors was also used to further reduce the charge injection noise.

Jitter in the modulation signal can cause output errors. Assuming the average pulse width of the modulation signal is  $T_s$ , and the pulse jitter for the *j*th pulse is  $\Delta T_s(j)$  yields

$$I_{in} \cdot (L \cdot T_s + \sum_{j=1}^{L} \Delta T_s(j)) = I_{ref} T_s \sum_{i=1}^{N} D_i^*$$
(4.15)

The second term on the left of (4.15) represents the error due to clock jitter. If  $\Delta T_s(j)$  follows a Gaussian distribution, this clock jitter noise is rejected by the summation operation

(to a first order). Large L, i.e. sampling for a longer time, was thus used to provide better jitter noise rejection.

## 4.5.4.3 $\Sigma\Delta$ modulator

OTA1's finite gain, slew rate, and bandwidth limit the input modulated  $\Sigma\Delta$  ADC's performance in the same way they do with a conventional  $\Sigma\Delta$  ADC. The finite gain of OTA1 causes integrator leakage and weakens the noise shaping performance [90]. The slew rate and bandwidth limit the integrator's settling time and increase the output error [90].

The noise model of the integrator in the input modulated ADC is shown in Figure 4.10. The input referred noise of OTA1 is  $e_{n_{int}}^2$ , and the total admittance at the integrator's input node is  $Y_M$ .  $Y_M$  includes the admittance looking into the input modulation stage and parasitic capacitance at OTA's negative input terminal. Referring to the noise analysis of the integrator in [33] and using the total integration time  $T_t = LMT_s$ , the input referred current noise of OTA1 during integration is derived as

$$I_{ni\_int}^{2} = e_{en\_int}^{2} \left( \frac{Y_{M}}{T_{t}s} (1 - e^{-T_{t}s}) \right)^{2} M$$
$$= e_{en\_int}^{2} \left( \frac{Y_{M}}{L\sqrt{M}T_{s}s} (1 - e^{-T_{t}s}) \right)^{2}$$
(4.16)

where  $e_{n_{int}}^{2}$  is OTA1's voltage noise; *s* is the Laplace variable, and  $T_{t}$  is the total integration time in one ADC conversion cycle. The factor of *M* is due to the input modulation.



Figure 4.10. The noise model of the integrator and reference current.

When the input modulation stage is on, the impedance looking into the input modulation stage is a very large resistance, formed by the cascoded transistors  $M_{p2}$  and  $M_{p4}$ , in parallel with the very small drain capacitance of transistor SW. When the input modulation stage is off, this impedance is very large because the modulation switch is off. In either case, the impedance looking into the modulation stage is very large, and the admittance  $Y_M$  is very small. On the other hand, an incremental  $\Sigma\Delta$  ADC generally uses very large  $T_t$  to achieve a very high resolution, meaning that L and M are large. As a result, the equivalent input referred current noise of OTA2 is negligible.

The reference current noise is dominated by  $M_{n1}$  in Figure 4.8. This noise is modulated by the 1-bit output D\* of the  $\Sigma\Delta$  modulator, which can be modeled by a multiplicative factor of  $\sum_{i=1}^{N} D_{i}^{*}/N$ . The equivalent input referred current noise of the reference current is

$$I_{ni\_ref}^{2} = \left(\frac{8kTg_{m\_n}}{3} + \frac{K_{fn}g_{m\_n}^{2}}{C_{ox}W_{n}L_{n}f}\right) \times \frac{\sum_{i=1}^{N}D_{i}^{*}}{N}M$$
(4.17)

where  $g_{m_n}$  is the transconductance of  $M_{n1}$  in Figure 4.8,  $W_n$  and  $L_n$  are  $M_{n1}$ 's size, and  $K_{fn}$  is the NMOS flicker noise constant.  $g_{m_n}$  can be expressed as  $\sqrt{2\mu_n C_{ox} I_{ref} W_n / L_n}$ , where  $\mu_n$ is the electron mobility Substituting  $g_{m_n}$ 's expression and (4.5) into (4.17) yields

$$i_{ni\_ref}^{2} = \left(\frac{\frac{8kT}{\sqrt{\frac{2\mu_{n}C_{ox}W_{n}}{L_{n}}}}{3\sqrt{I_{ref}}} + \frac{2K_{fn}\mu_{n}}{Ln^{2}f}\right)I_{in}$$
(4.18)

To reduce the reference current contribution to input referred current noise,  $W_n/L_n$  was set to be small, and  $L_n$  was set to be large.

# 4.6 Experimental results

The input modulated  $\Sigma \Delta$  ADC was fabricated in 0.5 µm CMOS, and the chip photograph is shown in Figure 4.11. The biasing potentiostat was added for testing three-electrode sensors, and the output buffers are only needed for chip testing purposes. Omitting these elements, the active area of the readout circuit is 0.157mm<sup>2</sup>, allowing integration of over 57 readout channels on a 3×3 mm<sup>2</sup> chip area. Including the biasing potentiostat, the active area of the circuit is 0.219mm<sup>2</sup>, allowing over 41 channels on a 3×3 mm<sup>2</sup> chip. To produce control clocks and acquire the ADC output results, a digital hardware block was implemented in a Spartan 3E FPGA. A Faraday cage was used during testing to suppress 60-Hz line and other environmental noise. The whole chip was powered by a low-noise 5V regulator. Battery was used as the regulator input to provide a low-noise supply voltage.



Figure 4.11. Chip photograph of the input modulated instrument.

# 4.6.1 Electrical characterization

To characterize the circuit performance, a GPIB-controlled high resolution current source (model 6430 SourceMeter, Keithley Instruments) was used to generate input currents.

Labview (National Instruments) programs the current source through General Purpose Interface Bus (GPIB) port. GPIB is a bus interface in IEEE standard that connects instruments to PC for automation test. For all measurements, the number of pulses in a conversion cycle, *N* as defined in Figure 4.4, was set at  $10^5$ . When the sampling frequency is 100 kHz, the ADC conversion time is 1 s, which is an integer multiple of 60 Hz power-line frequency. As a result, the line frequency is suppressed by the counter's summation operation [79]. The hysteresis level of the comparator was set at 100mV. First, the input modulation was turned on by setting the modulation factor *M* at 8, 16 and 32 to study *M*'s effect on current ranges. The reference current  $I_{ref}$  was set at 70nA and 500nA to study how the input current ranges are affected by  $I_{ref}$  at a fixed value of *M*. The normalized ADC output curves for different  $I_{ref}$  and *M* are shown in Figure 4.12, which shows that larger *M* and  $I_{ref}$  shift the ADC response curve toward larger input current ranges.



Figure 4.12. The normalized digitized output of the input modulation  $\Sigma\Delta$  ADC for different input currents when input modulation is on. *M* is set at 8, 16, and 32.

Next, to test measurement of small currents, the input modulation was turned off by setting M to 1. The sampling frequency was kept at 100 kHz and N was kept at 10<sup>5</sup>. Figure 4.13 shows the ADC outputs for low input currents, normalized to the ADC output full range.

Without input modulation, the ADC can measure currents from 3 nA to 493 nA. With a fixed  $I_{ref}$ , the modulation technique expands the ADC maximum input current to 16  $\mu$ A, and thereby improves the input current range by 30 dB without significant power increase. If desired, the maximum input current could be further expanded by increasing the output current drive of OTA1 so that *M* can go beyond 32. Figure 4.13 shows that a sensitivity (minimum linear response) as low as 100 fA can be achieved. As a result, the cross-scale dynamic range of the circuit is 164 dB.



Figure 4.13. The normalized digitized output of the input modulation  $\Sigma\Delta$  ADC for different input currents when input modulation is turned off by setting *M* at 1.

Using the data from Figure 4.12, the linearity and accuracy of circuit were quantified by the integral nonlinearity (INL) and differential nonlinearity (DNL) parameters, as shown in Figure 4.14. Both parameters are defined in dB as errors divided by full range of the input current. When *M* is 32, the largest DNL is -46.8 dB and the largest INL is -40.52 dB, corresponding to 6.7 bit error. When *M* is 1, the largest DNL is -47.96 dB and the largest INL is -47.79 dB, corresponding to 8 bit error. The compensation steps used for the semi-synchronous  $\Sigma \Delta$  ADC [39] can reduce the nonlinearity errors. Simulation reveals that the current conveyor's current mirror can limits the INL and DNL performance. The statistics of the largest INL and DNL for M = 4, 8, 16, 25, 32 indicate that the median INL and DNL are -46.0 dB and -40.0 dB, respectively; and the standard deviations of INL and DNL over all choices of M are 3.1dB and 2.1 dB. This shows that the INL and DNL do not depend substantially on the choice of M.



Figure 4.14. Measured integral nonlinearity (INL) and differential nonlinearity (DNL) for (a) a modulation factor M = 32 and (b) M = 1.  $I_{ref}$  was set at 500nA for both measurements.

Table 4.2 illustrates the comparison between this work and other amperometric sensor instrumentation circuits. For a fair comparison, all the data is for electrochemical readout circuits. The biasing potentiostat's power consumption is omitted. Among the surveyed designs, this work achieves the largest dynamic range, the second best sensitivity and second best input range vs. power (RvP) factor. Compared to the semi-synchronous  $\Sigma\Delta$  ADC with no input modulation and no optimization, the reported circuit has 10-time better RvP factor and 160-time larger current range, with very small change of sensitivity.

	Max. Current	Sensitivity	Dynamic Range	Power/Chan.	RvP <sup>1</sup>	Process	ADC structure
TCAS I '06	100 nA	50 fA	126 dB	11 μW	0.033	0.5 µm	Semi-synchronous sigma-delta
[39]							
TbioCAS'07	0.5 μΑ	100 fA	140 dB	1300 μW	0.001	0.5 µm	Feedback modulation sigma-delta
[44]							
TCAS I '06	50 µA	46 pA	120 dB	781 µW	0.578	1.2 μm	Integration
[49]							
TbioCAS'13	350nA	24 pA	95 dB	188 µW	0.006	0.35 µm	Current to frequency + Single slope
[56]							
This work	16 µA	100 fA	164dB	241 μW	0.331	0.5 μm	Input modulation sigma-delta

Table 4.2. Comparison between this work and other published instrumentations for chronoamperometric sensor arrays

<sup>1</sup>RvP (Input range vs. power) factor is defined as input current range (maximum value) divided by readout circuit's maximum consumed current. <sup>2</sup>For fair comparison of other reported circuit without potentiostats, the biasing potentiostat's power consumption is omitted.

## 4.6.2 Electrochemical experiments

Many electrochemical sensors are in liquid phase. To validate the circuit functionality for general electrochemical interface, the circuit was experimentally validated in a potassium ferricyanide ( $K_4$ [Fe(CN)<sub>6</sub>]) solution, a standard system for electrochemical experiments. The solution was prepared by diluting  $K_4$ [Fe(CN)<sub>6</sub>] with a 0.1M KCL buffer. A three-electrode electrochemical system was built using electrodes from CH Instruments, Inc. The voltage between WE and RE was set at 0.39 V. To validate the circuit response when the input modulation stage is on, the  $K_4[Fe(CN)_6]$  concentrations were set at proper values to generate  $\mu$ A level currents. The input modulation factor M was set at 32 and the reference current  $I_{ref}$ was set at 500 nA. The transient ADC responses for 15 mM, 20 mM, 25 mM and 30 mM K<sub>4</sub>[Fe(CN)<sub>6</sub>] solutions were recorded and converted back to input current. The measurement results are shown in Figure 4.15(a). The current output for the 30 mM solution reaches the full range of the ADC during the first several seconds, and then settles off to a plateau. The measured WE voltage remains stable because the current conveyor can support a much larger input current than the following ADC stage. The currents at steady-state electrochemical conditions (at t = 200 s) for different solution concentrations were extracted to plot the calibration curve in Figure 4.15 (b), which shows very good linearity, with an  $R^2$  fit error of 0.995.



Figure 4.15. Measured ADC response to a potassium ferricyanide  $(K_4[Fe(CN)_6])$  solution. (a) ADC transient response, and (b) corresponding calibration curve.

The three-electrode ionic liquid gas sensor array [5] was used to validate the gas sensing response of the circuit. MCQ gas blender 100 (MCQ Instruments) was used to automatically set and change the gas concentrations. Our gas sensor array shows good response to CH<sub>4</sub>, SO<sub>2</sub>, NO<sub>2</sub> and O<sub>2</sub>. Following safety regulations at Michigan State University, our own research lab is not allowed to have toxic and explosive gases. Therefore, oxygen was used as an example gas to validate the circuit functionality with a electrochemical gas sensor. An input modulated circuit with NMOS-current-mirror current conveyor was used to measure current flowing into WE. The modulation factor *M* was set at 8. The voltage between WE and RE was set at -1.23 V. The oxygen concentrations were changed every 30 s. The oxygen concentration values and the transient ADC responses are shown in Figure 4.16(a). The corresponding calibration curve is shown in Figure 4.16(b), and shows good linearity with a R<sup>2</sup> value of 0.9986.



Figure 4.16. Measured ADC response to ionic liquid  $O_2$  sensor. (a) ADC transient response, and (b) corresponding calibration curve.

# 4.7 Conclusion

This chapter reports an input current modulated  $\Sigma \Delta$  ADC for wearable amperometric sensor arrays. By modulating the input current before digitization with a semi-synchronous incremental  $\Sigma \Delta$  ADC, large dynamic range is achieved with very good power efficiency and sub-pA sensitivity. Comprehensive analysis of performance limitations was applied to guide the circuit design. Fabricated in 0.5 µm CMOS, the circuit's compact size allows over 57 readout channels on a 3×3 mm<sup>2</sup> chip. Compared to an unmodulated  $\Sigma \Delta$  ADC, by setting the current modulation factor at 32, the measured input current range of the circuit can be improved by 30 dB without a significant increase in power and area. The input modulated  $\Sigma \Delta$ ADC was measured to achieve 100 fA sensitivity and 164 dB cross-scale dynamic range with high power efficiency. Experiments in a potassium ferricyanide solution and with an electrochemical gas sensor validate the circuit's feasibility for electrochemical sensing applications.

# 5. Ultra-compact Micro-watt CMOS Current Sensing Circuit with Pico-ampere Sensitivity for High-throughput Electrochemical Biosensor Arrays

Chapter 4 presents a CMOS amperometric circuit addressing challenges of electrochemical sensor arrays by simultaneously achieving wide dynamic range, fA-sensitivity, high power efficiency and compact size. This circuit targets to chemical/biological sensors generating very low frequency signal (<1Hz) and requiring less than 100-channel integration on one chip. In biological studies such as cell membrane and DNA, circuit allowing higher density (over 100 channels) array and higher bandwidth (> 10 kHz) is required. This chapter presents a new current sensing circuit for these applications.

# 5.1 Introduction

Electrochemical biosensors can identify biological hazard molecules and have superior performance in power, sensitivity, cost, selectivity and size. Therefore, electrochemical biosensors are important for wearable sensors in human health monitoring applications. However, challenges exist during electrochemical biosensor development. These challenges can be clarified by using ion channel study as an example. Ion channel is mostly studied within membrane protein in a living cell, which has a very limited lifetime, generally less than 1 hour. In addition, the biological interface formation have a very low yield, around 30% based on empirical evidence [51]. In contrast, the traditional electrochemical study takes an extensive amount of time to obtain very limited information, but more data needs to be collected for the research. Similar challenges exist for DNA sequencing. New solutions, such as an automatic high-throughput artificial cell membrane array [52] and an automatic nano-patch-clamp integrated system [34, 92], have been proposed to address these issues to permit rapid parallel measurement. An automatic high-throughput artificial cell membrane array is shown in Figure 5.1. Planar bilayer lipid membrane (pBLM) is a kind of artificial cell membrane used to study ion channel. The biological activities turn on or off the ion channel, which acts as gate and regulate ions passing through the pBLM. This ion flows correspond to ion current pulses, which is measured by sensing electrode. In each microfluidic channel, the liquid flow is pumped into the channel to automatically form many pBLMs.



Figure 5.1. An automatic high-throughput artificial cell membrane array. (a) Microchamber structure with two sensing electrodes of working electrode (WE) and reference electrode (RE). Planar bilayer lipid membrane (pBLM) is a kind of artificial cell membrane to study. (b) Microfluidic channel structure with a shared RE and many microchambers. (c) Concept view of the high-throughput array microsystem. A high-sensitivity current sensing CMOS chip is integrated under the microfluidic channels.

These high-throughput solutions require a current sensing circuit having pico-ampere sensitivity, micro-watt power consumption, ultra-compact size and >10 kHz bandwidth to

allow parallel measurement for a high density array [51, 82]. The literature contains numerous examples of CMOS electrochemical current readouts for multi-channel measurement [39, 43, 56, 76]. However, these circuits mainly target to low-frequency current measurement. Although CMOS instruments have been built for ion channel current study achieving pA-sensitivity over 10 kHz bandwidth recording [34, 35, 38], these circuits consume very large power and area, and are not suitable for high-density on-chip biosensor array applications. This chapter reports a new CMOS instrument, which address existing challenges for biosensor array development and push the CMOS performance limits for high-density on-chip biosensor arrays. This work provides a platform permitting rapid parallel measurement in high-density biosensor array, and enabling rapid development of new electrochemical biosensors for wearable health monitoring.

# 5.2 Instrumentation requirements and analysis of current readouts

## 5.2.1 Instrumentation requirements

The critical performance factors of a CMOS circuit for biosensor array include sensitivity, current range, bandwidth, power and area. In this paper, the sensitivity is defined as the minimum detectable current, the same as in [39, 44]. The current specifications on sensitivity, bandwidth and for electrochemical biosensor study are listed in Table 5.1. Generally, an electrochemical biosensor array needs the circuit to achieve pA sensitivity in 10 kHz bandwidth. The input current range should be over 10 nA.

Application	Current level	Bandwidth	Ref.
Single ion channel recording	Tens of pA	1-10 kHz	[38]
DNA sequencing using nanopore	Tens of pA	10 kHz	[38, 93, 94]
Whole-cell patch clamp	Low nA	5-10kHz	[34]
Most biochemical applications	Low pAs to low nAs	1 Hz to 1 kHz	[25]

Table 5.1. Current specifications on sensitivity, bandwidth and current range for electrochemical biosensor study

On-chip high-density electrochemical biosensor array requires the circuit to be very compact. Compact circuit size allows high-density recording channels to be integrated in a tiny chip. Compact size also reduces chip cost. Because many on-chip biosensors are disposable, cheap chip can reduce biosensor development cost and unit cost. To implement over 400 channels on a 5 mm  $\times$  5 mm die, the circuit area per channel must be less than 0.063 mm<sup>2</sup>.

On-chip high-density electrochemical biosensor arrays also require that the chip consumes very low power per channel. The chip can act as a heater to affect the on-chip sensor/bio-interface temperature. Changes in temperature can affect the biosensor and bio-interface's biological activities and biosensor sensitivity. A heat flux of 80 mW/mm<sup>2</sup> can cause damage to biological tissue [95]. For circuit area per channel of 0.063 mm<sup>2</sup>, the power consumption per channel must be less than 50  $\mu$ W. In summary, a high-density on-chip biosensor array requires the circuit to achieve pA sensitivity, over 10 kHz bandwidth, nA range, small area and micro-watt power.

# 5.2.2 Analysis of Current Readouts

To measure pA level small current, the electrochemical current readout needs to have very low noise, and very large amplification gain. The current readout also needs to hold the current sensing electrode at a configurable potential for electrochemical sensing [61]. The current readout needs to measure bidirectional current to because different targets can generate different current directions.

Chapter 2 presents comparisons of traditional current readouts. Current conveyor (CC) function likes a current buffer, which isolates the electrochemical sensor from following stages. CC holds sensing electrode voltage at a constant value and provides output current linearly proportional to input current. CC can be as simple as an OTA and one transistor, and do not need any capacitor or resistor [53]. Hence, CC is very compact and can consume power down to micro watt. In addition, as a continuous time (CT) solution, CC does not inject charges to electrode-electrolyte interface and affect redox reactions. These features make CC an attracting solution for high-density on-chip electrochemical biosensor array. The performance comparison between TIAs and CC for target applications is summarized in Table 5.2. Because CC's unique advantages over TIAs, CC is chosen as a starting point to build the instrument for the target applications.

Circuit	Pros	Cons
Res.	Simple; Bidirectional; No	Large area, Large gain variation
feedback	interference to redox reactions	
TIA		
Switched-	Bidirectional; Medium area;	Switching noise and noise folding;
cap. TIA	Low noise	Large gain variation; Interference to
		redox reactions.
Current	Very small area; Low power;	Large noise
conveyor	No interference to redox	Low gain
	reactions;	

Table 5.2. Performance comparison of traditional current readouts for target applications

Many CC topologies have been built for electrochemical sensing but are not good for the target applications. The circuit in [53] can only measure one directional current and the

bandwidth is less than 1Hz. The circuit in [49] shows large noise and needs a high-resolution current-to-digital convertor, which occupies large area and additional power. The design in [83] requires lots of transistors and chopper clocks. Many transistors can occupy much area. The chopper clock requires many clock-wire routing and isolation shielding between analog and digital signals, which can occupy much area. The current mirror structure only provides low amplification gain and therefore the circuit requires a high-resolution current-to-digital convertor, which occupies large area and additional power. In this thesis, the disadvantages of CC are addressed by a new CC topology and new system architecture. This chapter presents a new CC design, providing accurate gain and sufficient noise and bandwidth with small transistor counters. New shared-segment interleaved two-stage architecture provides large current gain without requiring large area and power.

# 5.3 Instrumentation architecture design

This work uses a new compact CC topology to address the existing current readouts' problems, as shown in Figure 5.2. The voltage at current sensing electrode WE is set at  $V_{WE}$  by the OTA1. A highly precise current mirror is used to provide gain of A, which has ultra-low gain variation among difference recording channels. To achieve large current gain, two-stage architecture is used to provide high gain of  $A^2$ . The current sources  $I_{11,12,21,22}$  are used for bidirectional current sensing. From  $I_{in} < I_b$  ( $I_{11}$ ),  $I_{o1} > -I_b$  ( $I_{21}$ ) and  $I_{o1} = AI_{in}$ , we have the ideal range of  $I_{in}$  is ( $-I_b$ ,  $I_b$ ). Assuming that A = 10, for nA level input range, the current source consumes very low power (nA current). The operational transconductance amplifiers (OTAs) consume very low power because they are connected to transistor gates, which do not

require large drive current. As a CT solution, this circuit does not inject charges to electrode-electrolyte interface and affect redox reactions. Any voltage change at  $V_{o1}$  can change current mirror output current and hereby change the current gain of the circuit. Therefore, to obtain constant gain,  $V_{o1}$  is held at a DC voltage by the following stages.



Figure 5.2. Simplified circuit block of a two-stage current conveyor for bidirectional current sensing with current gain of  $A^2$ . WE is the current sensing electrode.  $I_{in}$  is the input current,  $I_{o2}$  is the circuit output current.  $I_b$  is the bias current.

Sharing circuit resources in multi-channel recording instrumentation can effectively reduce the circuit area and power consumption. Figure 5.3 (a) shows an example of two-channel recording circuit, utilizing the current readout in Figure 5.2. Because OTA's positive terminals are connected to the same voltage  $V_{WE}$ , a shared-segment OTA can be used [96]. As shown in Figure 5.3 (b), the OTAs are separated into two segments: a shared segment and pixel segments. The shared segment is connected to the same bias voltage  $V_{WE}$ .



Figure 5.3. Block diagram of two-channel current readouts with (a) conventional OTA, and (b) with shared-segment OTA

To reduce the circuit area and power in a multi-channel recording system, the second stage in Figure 5.3 can be shared by using a multiplexer in interleaved architecture. Combining the shared segment OTA concept and the two-stage structure, the circuit architecture is shown in Figure 5.4. This architecture is designed for  $N \cdot M$  recording channels. The recording channels are divided into N clusters. Each cluster consists of M recording channels. The first stage is named as pixel amplifier, locally reading sensor current. The second stage is named as gain amplifier, providing additional current gain. In each cluster, the OTAs share one common segment. The pixel amplifiers in one cluster share one gain amplifier though a multiplexer. The N OTAs in the gain amplifier stage also share the same segment. All the gain amplifier outputs are bundled to a single multiplexer and then connected to a signal processing stage, which filters the noise and then digitize the signal.


Figure 5.4. Block diagram of 2-stage, shared-segment-OTA architecture for  $N \cdot M$  recording channels.

# 5.4 Circuit block design and implementation

## 5.4.1 Current conveyor feedback element

The input current range of the circuit directly depends on current source values in Figure 5.2, and is affected by the current source mismatch. Defining the deviation of current ratio between  $I_{11}$  and  $I_{12}$  from current gain *A* as  $\Delta A$ , and the deviation is  $\Delta B$ , as shown in Figure 5.5, we have

$$\begin{cases} I_{o1} = (A + \Delta A)I_b - A(I_b - I_{in}) = \Delta AI_b + AI_{in} \\ I_{o2} = AI_{o1} - \Delta BI_b = (A\Delta A - \Delta B)I_b + A^2I_{in} \\ -(I_b + \Delta AI_b/A) < I_{in} < I_b \end{cases}$$
(5.1)

Therefore, deviation  $\Delta A$  and  $\Delta B$  generates large output current offset and can reduce

input current range largely. Precision current mirrors and the current sources are needed for small offset and large current range.



Figure 5.5. Analysis of current source mismatching effect on circuit performance.

To provide precise current ratio, cascoded structure is used. The schematic of the pixel amplifier is shown in Figure 5.6.  $M_{n(1,2,3)}$  and  $M_{An(1,2,3)}$  form current sources. Transistor  $M_{p(1,2,3)}$  and  $M_{Ap(1,2,3)}$  form a current mirror to provide accurate current ratio, *A*.  $M_{p(n)3, Ap(An)3}$  are operated in deep linear region to reduce noise, functioning equally to degeneration resistance. They are more compact than resistors in CMOS process.  $C_L$  is used to improve circuit stability. Noise analysis and optimized transistor sizes are in section 5.5.



Figure 5.6. Schematic of the pixel amplifier.  $C_{in}$  is the total capacitance including parasitic capacitance and sensor capacitance.

## 5.4.2 Shared-segment OTA

Shared-segment OTA topology is demonstrated to have good stability, bandwidth, and isolation between recording channels [96]. This topology is used as starting point to build the OTA1 in Figure 5.6. Analysis of a similar structure for OTA1 and M<sub>f</sub> shows that high open loop gain of OTA1 can largely suppress the noise contribution of transistor M<sub>f</sub>[56]. Large OTA's output impedance can achieve large gain. Compared to original topology, two transistors of M<sub>pN3,nN3</sub>, as shown in Figure 5.7, are added to improve output impedance. If assuming the transconductance and output impedance of M<sub>pN3,nN3</sub> are equal to  $g_{m,N3}$  and  $r_{o,N3}$ , respectively, the output gain is improved by  $g_{m,N3} \times r_{o,N3}$ . In the shared segment, the negative feedback loop, formed by M<sub>pb1</sub>, M<sub>ps1</sub>, M<sub>ns3</sub>, regulates V<sub>c</sub> for good isolation between pixel segments [96]. For the target biosensor applications, OTA noise performance is very importance. Design optimization for noise performance and transistor sizes are in Section 5.5.



Figure 5.7. Schematic of shared-structure OTA in N recording channels.

## 5.4.3 Multiplexer

The multiplexer needs to have low on-resistance for small voltage drop. The multiplexer also needs to

provide DC bias to inactive pixel amplifiers' output for short settling time of turning the pixel amplifier to active. Figure 5.8 (a) takes two recording channels as an example and shows the multiplexer's switch positions when pixel amplifier #1 is active. Single-pole double-throw switches are used to set the inactive pixel amplifier's output at a DC bias. Transmission gates with large W/L transistors in Figure 5.8 (b) are used as switches to reduce the switching-on resistance.



Figure 5.8. The schematic of (a) multiplexer for two recording channels, and (b) the switches.  $\Phi$  and  $\overline{\Phi}$  are two inverting digital controlling signals.

## 5.4.4 Self-test Current Pulse Generator

In ion channel current study, biosensors need to be integrated on chip to minimize the parasitic and connection capacitance to achieve good noise performance [35]. Before biosensors are fabricated on chip, an on-chip module is needed to generate ion channel currents to characterize circuit performance and self-test circuit functions. The ion channel currents are current pulses with pico-ampere amplitude  $I_{amp}$  and  $\leq 1$  ms pulse width  $I_{width}$ . A current splitter array can generate femtoampere current but cannot generate bidirectional current pulses [85]. To resolve this problem, a compact solution is used and shown in Figure 5.9 (a). A capacitor is connected to pixel amplifier input, the voltage of which is  $V_{WE}$ . Voltage pulses  $V_{in}$  is applied on the capacitor to generate current pulses  $I_{in}$ , as shown in Figure 5.9 (b). Assuming the  $V_{in}$  slope at rising/falling time is SL, we have  $I_{amp} = C \times SL$ .



Figure 5.9. (a) The schematic and (b) waveforms of the current pulse generator.

#### 5.4.5 Signal Processing Stage

The signal processing stage in Figure 5.4 needs to digitize the gain amplifier output current for further digital signal processing and data storage. Because sensor current is greatly amplified before reaching to this stage, ultra-low noise is not required.

Discrete chips can be used as this block for short development time. Most discrete low-cost low power analog-to-digital convertor (ADC) needs a voltage input. Therefore, a current-to-voltage (I/V) convertor is needed. The resistance feedback TIA does not require additional controlling signals and can provide additional gain to improve input current sensitivity. Because the biosensor current is amplified by on-chip two-stage circuit, the TIA's feedback resistance is not required to be large. Therefore, a discrete resistance feedback TIA and ADC are used as the signal processing stage. A feedback resistor array is used for different current gains and ranges. An optional feedback capacitor is used to improve the circuit's noise performance.

# 5.5 Noise analysis

As the first stage, the pixel amplifier dominates circuit contributions to input referred noise. Noise analysis can help reducing noise by identifying major noise sources and optimizing component sizes. To simplify the noise analysis, resistors  $R_{p,n,Ap,An}$  are used to

replace the  $M_{p3,n3,Ap3,An3}$  in Figure 5.7 with equivalent resistance, as shown in Figure 5.10 (a). The difference between noise contributions of resistor and transistor is that the transistor has additional noise components of flicker noise. This difference is ignorable when using large transistor area to reject the flicker noise. The current ratio *A* is used as resistance ratio to have equal voltage drop on the  $R_{Ap}$  and  $R_p$ . As a result, the source terminal voltages of  $M_{p2}$  and  $M_{Ap2}$  are equal. The same resistor ratio is also applied to  $R_{An}$  and  $R_n$ .



Figure 5.10. Equivalent circuit of pixel amplifier for noise analysis. (a) Resistors are used to substitute transistors in linear region; (b) non-dominated noise source components are removed to simply noise analysis.

A similar structure for OTA1 and  $M_f$  is reported and the analysis shows the loop gain formed by OTA1 and  $M_f$  greatly reduces  $M_f$ 's contribution to the input referred current noise [56]. Transistors  $M_{p1,n1,Ap1,An1}$  have negligible noise contribution as cascode transistors [97]. Ignoring these negligible noise sources, the input referred current noise of the pixel amplifier

$$i_{ineq}^{2} = (2\pi f)^{2} C_{in}^{2} e_{n}^{2} + I_{n,M_{n2}}^{2} + i_{n,AR_{n}}^{2} + I_{n,M_{p2}}^{2} + i_{n,AR_{p}}^{2} + \frac{1}{A^{2}} (I_{n,M_{An2}}^{2} + i_{n,R_{n}}^{2} + I_{n,M_{p2}}^{2} + i_{n,AR_{p}}^{2} + i_{n,A$$

where *f* is the frequency,  $C_{in}$  is the total capacitance including parasitic capacitance and ion-channel sensor capacitance,  $e_n$  is the input referred noise of OTA1,  $i_{n,(x)}$  represents the current noise of component *x*. (5.2) shows that the current noises of the transistors  $M_{n2,p2}$  and the resistors  $R_{An,Ap}$  dominate the input referred noise. As a result, the Figure 5.10 (a) can be simplified into Figure 5.10 (b) for noise analysis by removing the non-significance current sources.

The relation expression of input referred current noise and transistor sizes needs to be found to determine transistor dimensions for optimized noise performance. Because very large sizes are used, flicker noises are very small. To simplify noise analysis, only thermal noise is considered. The voltage noise of  $M_{n2}$  is expressed as [98]

$$V_{n,M_{n2}}^2 = 8kT/3g_{m,M_{n2}} \tag{5.3}$$

where  $g_{m,M_{n2}}$  is the transconductance of  $M_{n2}$ , k is the Boltzmann constant, and T is the operating temperature in Kelvin. Considering the regeneration resistor effect, the  $M_{n2}$ 's current noise is

$$I_{n,M_{n2}}^2 = V_{n,M_{n2}}^2 \left(\frac{g_{m,M_{n2}}}{1 + g_{m,M_{n2}}AR_n}\right)^2 = \left(\frac{8kT}{3(1 + g_{m,M_{n2}}AR_n)}\right)^2$$
(5.4)

For a fix  $I_b$  value,  $g_{m,M_{n2}}$  is equal to  $\sqrt{2\mu_n C_{ox} I_b W_n/L_n}$ , where  $\mu_n$  is the hole mobility,  $C_{ox}$  is the gate oxide capacitance per unit area,  $W_n$  and  $L_n$  are the transistor size.  $M_{p2}$  noise contribution follows a similar equation as (5.4). Therefore, to reduce input referred current noise contribution of  $M_{p2}$  and  $M_{n2}$ , the transistor lengths were set at a very large value, and the W/L values were set at very small value. Large transistor length of  $M_{p2}$  and  $M_{n2}$  also provide accurate current gain A by improving transistor matching. The current noise of resistance *R* is equal to  $4kT/R^2$ . To reduce resistor's current noise contribution, the resistance should be large. (5.3) shows that large R<sub>n</sub> and R<sub>p</sub> reduce the M<sub>n2</sub> and M<sub>p2</sub>'s noise contributions.

The OTA noise analysis is similar to a traditional folded cascoded OTA. The OTA noise was reduced by using large input PMOS transistors operated in sub-threshold region. By optimizing component dimensions by running circuit simulations and following noise analysis conclusions, the transistors sizes of the pixel amplifier are determined and summarized in Table 5.3. *R* was set at 137 k $\Omega$  to achieve good tradeoff between noise and area.

Transistor	Size (µm)	Transistor	Size (µm)			
M <sub>p2,p3</sub>	3/24	M <sub>An1</sub>	2.1*10/12			
M <sub>p1</sub>	4.2/12	M <sub>An2,An3</sub>	1.5*10/48			
M <sub>n1</sub>	2.1/12	M <sub>ps1,p11</sub>	4.2*40/1.2			
M <sub>n2,n3</sub>	1.5/48	M <sub>ns2,n12</sub>	8.4/2.4			
M <sub>Ap3,Ap2</sub>	3*10/24	M <sub>p12,ps2</sub>	2.1/2.4			
M <sub>Ap1</sub>	4.2*10/12					

Table 5.3. Transistor sizes of pixel amplifier

## 5.6 Results

To evaluate the circuit concept and performance, N was set 1 and M was set at 4 in Figure 5.4. The circuit is implemented using AMI 0.5 µm CMOS technology. The pixel amplifier is used as gain amplifier to reduce the development time. Figure 5.11 shows the chip photo of the 2-stage circuit for 4 channels recording. The active area per channel is only 0.06 mm<sup>2</sup>, allowing over 400 channels implemented on 25 mm<sup>2</sup> chip area. Key analog signal traces on the 4-layter board are surrounded by grounded traces to provide good noise shielding of 60-Hz line and other environmental noise. A Faraday cage is used to provide additional noise suppression. The chip is powered by an ultra-low noise 3.3 V voltage regulator. A data acquisition card (NI USB-6259, National Instruments) is used for data digitization. Labview (National Instruments) is used to configure the circuit and display, record, and store test results.



Figure 5.11. Chip photo of the design, showing the active area per channel is  $0.06 \text{ mm}^2$ , allowing over 400 channels implemented on a  $25 \text{mm}^2$  chip.

## 5.6.1 Electrical characterization

To characterize the pixel amplifier's input current range, a Keithley 6430 ultra-low noise current generator was used to generate different DC input currents. Large feedback resistance  $R_{\rm f}$  of the I/V convertor in the signal processing stage can limit input currents. To evaluate the  $R_{\rm f}$  effect on input current range,  $R_{\rm f}$  was set at 1 M $\Omega$  and 10 M $\Omega$ . The input current ranges for these two resistance values are shown in Figure 5.12. When  $R_{\rm f} = 10$  M $\Omega$ , the input current range, the output voltage reaches the supply rails of 0 V or 3.3 V, which limits the input range. When  $R_{\rm f} = 1$  M $\Omega$ , the input current range is -110~80 nA with output error less than 1%. Larger  $R_{\rm f}$  value produces smaller error by providing larger gain but produces smaller input current range.

reach 0 V. Currents more than 80 nA is out of range of pixel amplifier because the output voltage is less than the I/V maximum output voltage of 3.3 V.



Figure 5.12. DC response test result of pixel amplifier when (a)  $R_f = 10 \text{ M}\Omega$  and (b)  $R_f = 1 \text{ M}\Omega$ .

To characterize the pixel amplifier's AC response, ETabor Electronics waveform generator was used to generate a sinusoid voltage. This sinusoid voltage was applied at a resistor to generate input sinusoid current with power of  $S_{power}$ . The frequency was set from 50 Hz to 19 kHz, and the corresponding channel's output power  $R_{power}$  was recorded by Agilent 4395A spectrum analyzer. The circuit circuit's bandwidth response plot is obtained by  $R_{power}/R_f^2$ , and shown in Figure 5.13 (a). The pixel amplifier has a low-frequency gain of 19.7 dB (9.7×) and a bandwidth of 11.5 kHz. During AC response test, another channel's response power  $R_{crosstalk}$  was recorded. Crosstalk is defined as  $R_{crosstalk}/R_{power}$ . The crosstalk test result and corresponding fitting curve are shown in Figure 5.13 (b), demonstrating the crosstalk is -38.2 dB at 10 kHz.



Figure 5.13. AC response test results of pixel amplifier and the corresponding fitting curves: (a) gain response results, and (b) crosstalk response results. The asterisk markers represent test data, and the dashed line represents the fitting line.

To demonstrate the transient response of the two-stage circuit, the self-test current pulse generator generated a current pulse with amplitude  $I_{amp}$ =105 pA and pulse width  $I_{width}$  =1 ms, as defined in Figure 5.9. A low-pass filter (LPF) with cut-off frequency at 11.5 kHz was used to post-process the data in Matlab. The circuit response output is shown in Figure 5.14. Large  $R_f$  provides good noise performance. To characterize the noise response of the two-stage circuit,  $R_f$  was set at 100 M $\Omega$ , input current was set at zero and the transient response was recorded. The same LPF in Matlab was used to post-process the data. The RMS noise is defined by dividing the peak-to-peak value of the output by 8 (98% confidence interval) and then by circuit gain [93]. The measured RMS noise is 7.2 pA<sub>rms</sub> in 11.5 kHz bandwidth. The circuit performance is summarized and compared to other work in Table 5.4. The reported circuit has superior performance in power and area. All other performance factors meet the biosensor array requirements.



Figure 5.14. Transient current response of the two-stage circuit when  $I_{amp} = 105$  pA and  $I_{width} = 1$  ms.

	This	Ref.	Ref.	Ref.	Ref.	Ref.
	work	[34]	[38]	[35]	[53]	[39]
Power/chan.	21	300	1500	5000	130	11.4
(µW)						
Area/chan.	0.06	0.81	0.28	0.4	-	0.09
$(mm^2)$						
BW. (Hz)	11.5k	10k	10k	1M	<1	< 0.1
Noise over	7.2p	5p	2.4p	61p	<1p	<50f
BW. (A <sub>rms</sub> )						
Max.	-110,	±20	-12,	>18	200	±100
current (nA)	90		13			
Process	0.5	0.5	0.5	0.13	0.5	0.5
(µm)						

Table 5.4. Comparisons to previous work on electrochemical biosensors current readouts

#### 5.6.2 Electrochemical experiments

Cyclic voltammetry (CV) is an electrochemical method, widely used in electrochemical biosensor development. This method applies a triangle stimulation voltage at the biosensor and records the response current to study the electrochemical reactions. Potassium ferricyanide ( $K_4$ [Fe(CN)<sub>6</sub>]) solution is a standard system for electrochemical experiments.

100  $\mu$ M K<sub>4</sub>[Fe(CN)<sub>6</sub>] with a 0.1M KCL buffer solution was used to validate the circuit performance with electrochemical interface. The CV test platform is shown in Figure 5.15. A three-electrode electrochemical system was setup by using a 211  $\mu$ m × 214  $\mu$ m gold microelectrode as WE, a Ag-AgCl electrode (CHI Instruments, Inc.) as reference electrode (RE), and a Pt electrode (CHI Instruments, Inc.) as counter electrode (CE). An off-chip, discrete control amplifier was used to drive the RE and CE. The voltage between RE and WE swept from -0.5 V to 0 V at different scan rates, including 10, 20, 30, 40 mV/s. A zero-phase, low pass FIR filter was used to post-process the data in Matlab. Figure 5.16 (a) shows that the reduction and oxidation current peaks are at -0.186 V and -0.25 V, respectively. The 64 mV peak potential difference is very close to the theoretical value of 59 mV for a fully reversible, single-electron redox process [23]. Figure 5.16 (b) shows the linear relation between oxidation peak current and square root of scan rate, with R-square error of 0.98. The oxidation peak current is defined as the current at -0.25 V subtracting charging current.



Figure 5.15. CV test setup.



Figure 5.16. (a). CV test result of 100  $\mu$ M K<sub>4</sub>[Fe(CN)<sub>6</sub>] solution at different scan rates using a 0.045 mm<sup>2</sup> gold electrode, and (b) corresponding relation between oxidation peak current and scan rate. In (b), the asterisk

## 5.6.3 Biological experiments

To demonstrate the circuit's function as a biological interface with pico-sensitivity, cell membrane impedance was measured during whole-cell patch clamp experiments. Cell membranes can be modeled as a resistor in parallel with a capacitor, and membrane resistance and capacitance can be readily measured using the whole-cell configuration of patch clamp electrophysiology [99]. Changes in passive membrane properties, such as membrane resistance and capacitance, can be interpreted as an indicator of important cellular events such as maturation, morphological changes, alterations in ion channel expression responsible for determining cellular excitability, and changes in cell health [100-102]. Given the close relationship with cellular physiology, measurement of passive membrane properties can be utilized in a variety of biomedical applications including toxin detection and drug screening [92].

The setup of whole-cell patch clamp experiments is shown in Figure 5.17. Cells are placed in an external solution, which provides cell living environment. A sharp-tip pipette is

used to create cell patch. The pipette has an internal solution, which maintains cell life after cell patch is created. For this study we cultured primary cortical neurons isolated from embryonic rats onto plastic coverslips (Thermanox) according to the supplier's protocol (Life Technologies). The external solution was an oxygenated physiological saline solution containing (in mM) 126 NaCl, 2.5 KCl, 1.25 NaH<sub>2</sub>PO<sub>4</sub>, 2 CaCl<sub>2</sub> 2H<sub>2</sub>O, 2 MgSO<sub>4</sub> 7H<sub>2</sub>O, 26 NaHCO<sub>3</sub>, and 10 Glucose. Borosilicate glass pipettes were fabricated with a pipette puller (Sutter Instruments) and filled with internal solution (in mM) of 135 K Gluconate, 7 NaCl, 10 HEPES, 2 MgCl<sub>2</sub>, 2 Na<sub>2</sub>ATP, and 0.3 Na<sub>2</sub>GTP. Once the pipette was properly affixed to the patch clamp micromanipulator (Narishige), primary cortical neurons were approached, sealed, and recorded using the new circuit introduced for this study.



Figure 5.17. Whole-cell patch clamp test setup.

To measure the cell membrane impedance, 100 Hz voltage pulses  $V_{st}$  were applied at the external solution electrode. The pipette electrode voltage is set at  $V_{WE}$  by the reported circuit. The response current pulses during the key test procedures were recorded and shown in Figure 5.18. The monitored resistance is calculated from  $V_{pp}/I_{pp}$ , where  $V_{pp}$  and  $I_{pp}$  are the peak-to-peak value of voltage pulse and current pulse, respectively.  $V_{pp}$  was set at 160 mV for the measurements in Figure 5.18 (a)-(c).  $V_{pp}$  was reduced to 70 mV and offset was set at -35 mV for the measurements in Figure 5.18 (d)-(f) to mitigate the potential for overstimulation and excitotoxicity. The spikes in Figure 5.18 (b) shows capacitive transients in response to

voltage pulses upon contact between the electrode and cell membrane [99]. Figure 5.18 (c)-(f) shows a reduction in capacitive transient amplitude that is proportional to the reduced voltage pulse applied, and also shows offset current due to stimulation voltage offset. In Figure 5.18 (c), negative pressure in the pipette pulls the cell membrane toward the pipette tip, and causes smaller ion current path between the cell membrane and pipette tip. As a result, response current amplitude reduces. In Figure 5.18 (d), with present of the same negative pressure, cell membrane is closer to pipette tip towards sealing, causing smaller current amplitude. In Figure 5.18 (e), the cell membrane is firmly sealed by pipette, which results in very small current. To accurately measure the gigaseal resistance, a low-pass filter with cut-off frequency at 1 kHz in Matlab was used to post-process the data. After gigaseal formation, the membrane patch inside the pipette tip was broken while leave the seal resistance intact. The breakthrough enables larger current passing though the membrane impedance, as shown in Figure 18 (f). As a result, the membrane impedance is recorded. The calculated resistance for all the test procedures meets to theoretical values very well, as listed in Table 5.5. Our results, which demonstrate successful measurement of passive membrane properties through patch clamp electrophysiology, have broad potential applications for sensors which identify changes in cell health, excitability, and membrane integrity in response to varying environmental conditions.



Figure 5.18. Pipette locations to the cell and current response to voltage pulses (a) when pipette is in external solution; (b) when pipette is touching cell; (c) when negative pressure is applied in the pipette (shown as wide arrow); (d) when the same negative pressure is held and the sealing is being formed; (e) when gigaseal is formed; (f) when a suction is applied at the pipette to break the cell.

Experiment procedures	Resistance			
Experiment procedures	Tested	Theoretical		
Figure 5.18 (a), pipette in external solution	14.4 M $\Omega$ (pipette resistance)	10-15 M $\Omega$ (empirical value)		
Figure 5.18 (b), pipette touching cell	19.6 ΜΩ	17.3-21.6 MΩ [94, 99, 103]		
Figure 5.18 (c), applying negative pressure at pipette	160.3 ΜΩ	Beginning to approach 1 GΩ during sealing [99]		
Figure 5.18 (d), cell seal is forming	652.4 ΜΩ	Further approaching 1 GΩ during sealing [99]		
Figure 5.18 (e), cell is sealed	1.4 G $\Omega$ (seal resistance)	>1 GΩ [99]		
Figure 18 (f), sealed cell is broken	139.4 M $\Omega$ (membrane resistance)	~100-200 MΩ [102]		

Table 5.5. Recorded resistance vs. theoretical values for whole-cell experiments procedures

# 5.7 Conclusion

This chapter presents a new CMOS instrument for electrochemical biosensor arrays. New current readout and new shared-segment interleaved system architecture significantly reduce the circuit power and area without compromising other circuit factor requirements. Noise analysis was presented for design optimizations. Circuit characterization results show that circuit achieves pA-level sensitivity, over 1kHz bandwidth, nV level input range with micro-watt power consumption and ultra-compact size, allowing over 400 recording channels integrated on one chip. CV experiments in a potassium ferricyanide solution and patch-clamp whole-cell experiments validate the circuit's feasibility for electrochemical biosensor applications.

# 6. Summary and Future Work

### 6.1 Summary

This dissertation presents new microelectronic instruments from board level to chip level to address the existing challenges of wearable electrochemical sensor array development for human health monitoring of chemical and biological hazards. Firstly, fundamentals of electrochemical sensor are introduced. A comprehensive literature study is done to find existing challenges of CMOS electrochemical circuits for wearable sensors. A unique multi-mode resource-sharing instrumentation circuit tailored to room-temperature ionic liquids (RTIL) transducer arrays was developed to effectively integrate amperometric and impedance sensing abilities with reduced size, cost, and power. This circuit enables miniaturized RTIL sensor development to address traditional electrochemical transducer challenges, and provides orthogonal data to sensor array algorithms to improve sensor sensitivity and selectivity. An input modulation  $\Sigma\Delta$  ADC was designed to simultaneously achieve over 160-dB dynamic range, fA sensitivity with very high power efficiency and compact size. This work enables the development of wearable amperometric sensor array with very wide detection concentration range and high detection limit. An ultra-compact, micro-watt power, pA-sensitivity current sensing circuit was developed, allowing over 400 channels to be integrated on a single chip. Compared to other circuits for high-throughput biosensor array, this circuit demonstrates superior performance in terms of power and area. This work enables high-sensitivity high-throughput biosensor array development for biological study.

## 6.2 Contributions

This dissertation bridges the gap between the electrochemical world and microelectronics world by inventing new electrical systems and circuits for electrochemical sensors in the detection of chemical and biological hazardous targets. These innovations include contributions in threefold:

• Designed a **unique** multi-mode resource-sharing instrumentation circuit tailored to ionic liquid electrochemical sensors that effectively integrate amperometric and impedance sensing abilities (multi-mode) with reduced size, cost, and power

The ionic liquid (IL) gas sensing technology shows many promising features for wearable sensors in detection of gas hazards. In this work, unique multi-mode instrumentation architecture was designed, being tailored for the novel ionic liquid gas sensing technology. The multi-mode operation provides orthogonal data to sensor array algorithms to enhance sensing selectivity and sensitivity. By sharing hardware resources among operation modes and four detection channels, the new architecture reduces electronics component counts by over 38%. Using this circuit, a personal hazard monitoring system was built, having unique features such as low power consumption (milli-watt), low cost (\$22), small size and light weight (1.6 oz). This work paves a path which leads the unique RTIL sensor technology to wearable sensors. This work also provides a suitable platform for further miniaturization toward a wearable bio/chemical hazard monitoring system.

• Developed the *first-ever* CMOS chronoamperometry readout circuit that *simultaneously* achieves an over 160 dB dynamic range, micro-watt power and fA

## sensitivity.

This work developed a new CMOS chronoamperometry readout circuit that simultaneously achieves wide dynamic range (164 dB), high power efficiency, very low power consumption ( $\mu$ W per channel) and 100fA sensitivity. Compared to the state-of-the-art chronoamperometry circuits, this work achieves the largest dynamic range, and competitive sensitivity (only 50 fA difference) with very high power efficiency. This circuit enables researchers to develop a high-sensitivity wearable electrochemical sensor array, which measures a wide range of hazardous targets in a wide range of concentrations with a very long lifetime.

• Developed a new CMOS current sensing circuit that has **superior** power and size over other circuits for high-throughput biosensor arrays

A new CMOS instrument was designed to address existing challenges for high-density on-chip biosensor arrays. By using a new current readout and two-stage shared-segment interleaved architecture, the circuit achieves pA-level sensitivity, over 10 kHz bandwidth, nV-level input range with micro-watt power consumption and ultra-compact size. Compared to other circuits for high-density on-chip biosensor arrays, the reported circuit has superior performance in power and area. This new circuit enables researchers to build a high-throughput (over 400 channels) on-chip biosensor array, which can be used to address the disadvantages of traditional ion channel and DNA study methods in terms of extremely slow analysis time, low yield, and large human labor. This circuit can also enable development of new biosensor arrays, which can measure diverse biological hazardous targets in very low concentrations.

## 6.3 Future work

This research has established the foundations for wearable sensors in human health monitoring. The following suggestions are made for future work.

#### • Build a lab-on-CMOS system using the presented new circuits

Chapter 4 and Chapter 5 present two new circuits. The lab-on-CMOS technologies in [52, 104] need to be used to integrate on-chip electrodes and microfluidic channels directly with the circuit chip to build a high-throughput on-chip recording system. Integrating electrodes directly on the surface of the chip can largely improve the noise performance and hence the sensing detection limit. Integrating multiple microfluidic channels on the chip enables rapid parallel measurement, which is a powerful tool to address the disadvantages of the traditional biosensor development and biological study in slow analysis time, low yield, and large human labor.

• Incorporate the presented new ICs in the developed personal hazard monitoring system

The portable personal hazard monitoring system in chapter 3 uses discrete electronics parts to demonstrate the system function, power, size and cost. The new integrated circuits in Chapter 4 and Chapter 5 need to be incorporated into this system to implement wearable sensors for reduced size, power consumption and cost and improved sensitivity.

## • Develop electrochemical instrumentation supporting more electrochemical modes

Chapter 3 integrates amperometry and impedance modes of electrochemical method into one single instrument to provide orthogonal information from one sensor. Integrating other electrochemical modes such as coulometry into the instrument can enable the system to response to more analyte targets. In addition, multiple-mode data provides higher independent dimensions of sensor data to sensor array algorithm, and can probably improve the concentration prediction accuracy of the algorithm. In addition, the orthogonal Signal Correction (OSC) algorithm was reported to address sensor drift issues[105]. Higher independent dimensions of sensor data may also improve the OSC algorithm performance.

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