Self-Ranging Thumb-sized Multichannel Electrochemical Instrument for Global Wearable Point-of-Care Sensing

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***Abstract*— This paper presents a self-ranging, multichannel, multi-technique electrochemical instrument with the size, power, and performance suitable for wearable applications, such as point-of-care sensing. It comprises a custom analog interface and a commercial low-power microcontroller and hosts two independent readout channels that are capable of dynamically adjusting to a wide range of input currents exhibited by various electrochemical sensors. To evaluate its functionality and versatility, the system was tested with multiple sensors using multiple electrochemical methods and was benchmarked against two commercial electrochemical instruments. While occupying only 8.5 cm^3 and consuming an average active power of 250 mW, the instrument provides nearly 10-bit accuracy over a 115 dB dynamic operational range and matches benchtop instrument results within 1.8%, demonstrating its capability to serve as a universal wearable electrochemical instrument.**

Keywords—electrochemical sensor; point-of-care testing; wearable sensing; Wearable Biomedical Sensors & Systems.

I. INTRODUCTION

The global wearable and portable sensing market is poised to reach 148 million shipments yearly with a projected annual growth of over 35% until 2019 [1]. As a result, there is a surge in markets for point-of-care and "internet of things" sensing systems that are compact and low power. Many biological and environmental tests, such as protein classification, DNA sequencing, air quality analysis and glucose monitoring, already utilize electrochemical sensors because they exhibit a valuable combination of features including robustness, high sensitivity and selectivity [1]. Hence, electrochemical sensing is emerging as a prominent mode for point-of-care applications [2].

To perform comprehensive electrochemical monitoring, the point-of-care instrument should support a wide range of sensor interfaces, which may utilize various methods and exhibit a broad range of response current. For example, Fig. 1 depicts a conceptual electrochemical point-of-care system that measures multiple biological signals such as glucose, lactic acid, and metabolites. Although the electrochemical instrumentation for all of these analytes are structurally similar, each may require different electrochemical methods and can exhibit response currents ranging from pA to mA. In contrast, compact electrochemical instruments are typically tailored to one specific type of sensor. For example, a portable platform with a disposable sensor chip was developed to detect malaria antibodies in remote locations [2], and a unified amperometric-potentiometric glucose sensor has been reported [4]. These devices demonstrate excellent performance for detection of specific electrochemical targets but lack the capacity to adapt to other targets utilizing different sensors. To address the challenges of a universal instrument, a multi-technique electrochemical biosensor platform was developed for wearable applications in [5]. However, this system cannot automatically adapt and requires prior insight into the sensor being tested. Furthermore, real-world applications often demand monitoring multiple variables, which requires instrumentation with more than one channel/sensor.

To address these needs, this paper introduces the first self-adjusting thumb-sized multichannel electrochemical instrument for wearable global point-of-care sensing. As depicted in Fig. 1, our instrument is composed of a compact

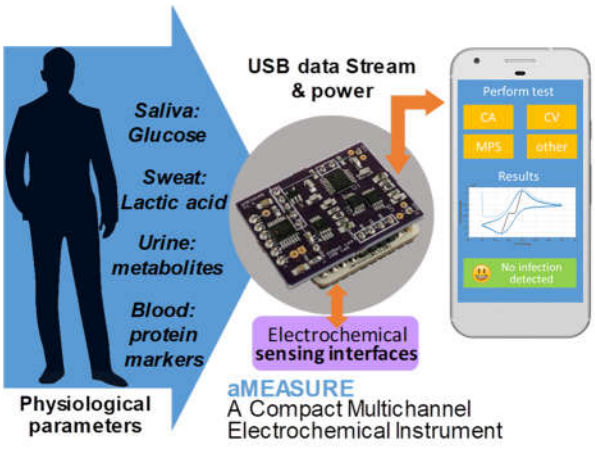

Fig. 1. The compact, versatile aMEASURE2 electrochemical instrument can interface to a wide range of electrochemical sensors and stream measurement results to and receive configuration commands from a USB host.

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commercial microcontroller and a custom analog electrochemical platform (AEP). The AEP contains two independent electrochemical readout channels and is capable of maintaining maximum accuracy by automatically tracking the wide range of electrochemical currents produced by a variety of sensors. The integrated instrumented is called aMEASURE2 because it builds on a prior generation called aMEASURE [6], significantly reducing size while maintaining features and performance. aMEASURE2 is powered by and communicates via a USB port, which permits expanding available readout channels using multiple aMEASURE2 units in a parallel.

II. aMEASURE2 DESIGN

A wearable electrochemical instrument must possess several key attributes including small size, low power consumption and the versatility to self-adjust to any incumbent sensor. Electrochemical sensing interfaces can be very small, typically mm-cm scale, and the instrumentation should be small enough to match this compact size, ideally no larger than a mobile phone or a wristwatch for portable and wearable point-of-care applications. Electrochemical sensors are inherently low power with typical measurement currents on the order of ~µA. To complement this while maintaining a small footprint, instrumentation should be able to operate with long lifetime from a compact, light-weight battery, and thus power consumption should be in the mW range. Versatility is also a key requirement because the instrumentation circuitry must seamlessly connect a diversity of sensing electrode interfaces to a myriad of host systems. The instrument must also support multiple electrochemical techniques and be able to measure from multiple devices in parallel. Ideally, it could achieve all these features with limited user intervention.

To simultaneously achieve the requirements for size, power, and versatility, we utilized the architecture shown in Fig. 2, which was adapted from our previously reported aMEASURE electrochemical instrument [6]. The goal of this aMEASURE2 iteration was to maintain the features and performance of our first generation design while significantly reducing the size and power consumption, and demonstrating versatility to multiple electrochemical sensors. The AEP is the central block to this design. It provides a platform unto which a compact commercial microcontroller unit and electrochemical sensors can be mounted. The AEP provides the core smart feature of flexible electrochemical sensor interfacing. Within the AEP, a variable gain transimpedance amplifier (VGT) block provides a versatile interface that is able to adapt to any electrochemical sensor response through the digital feedback system shown in Fig. 2. The VGT was designed for low power consumption and high stability. Stability is an important factor in the design because various electrochemical sensors have vast range of double-layer capacitances on their electrodes and may cause stability issues in a not well-compensated VGT. To this end, VGT was designed using CMOS high-speed (GBW: 100 MHz) low-power amplifiers that ensure stability and was then implemented in the 2.5 cm × 3.4 cm PCB shown in Fig. 2.

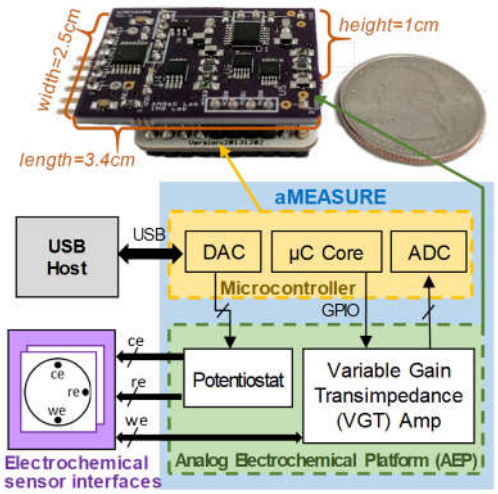

Fig. 2. aMEASURE2 operational block-diagram and size dimensions.

A large contributor to area and power in many wearable instruments are the auxiliary systems, such as ADC/DAC, communication block, and power regulation. To mitigate the impact of these necessary blocks, we selected a commercial microcontroller (ATmega 32U4) with ADC/DAC, USB communication, and power generation blocks built into a single small (2.5 cm × 2.5 cm) and low power board. One downside of this compact microcontroller is that the internal ADC/DAC has only 10bit accuracy. To mitigate this issue, we employed oversampling at 1 kHz and utilized the internal DSP low-pass filter at 10 Hz.

III. INSTRUMENT CHARACTERIZATION

To ensure adequate performance, the signal-to-noise and distortion ratio (SINAD) was assessed by applying an 800 nA peak to peak 1 Hz sinusoidal signal at the VGT input for 1000 seconds. The effective SINAD and effective number of bits (ENOB) was then calculated after performing fast Fourier transform (FFT) and applying a low-pass digital filter at 100 Hz using MATLAB. The results were recorded during a normal aMEASURE2 amperometric procedure. Fig. 3 shows the results of SINAD analysis to be 61 dB, which correlates to effective number of bits (ENOB) of 9.84 bits as an indicator of overall accuracy. The extracted 10 bit accuracy indicates that the VGT can support an input current range from 0.87 nA to 0.5 mA, which is well suited for miniaturized electrochemical sensors. aMEASURE2 occupies a total volume of 8.5 cm^3 roughly the size of a human thumb, and consumes only 250 mW of average power, allowing it to run for 14 hours continuously when powered through the USB of a smartphone with a healthy standard 2300 mAh battery. A brief summary of aMEASURE2 performance metrics are presented in Table 1.

IV. APPLICATION TESTING AND EVALUATION

To evaluate electrochemical functionality, cyclic voltammetry (CV) measurements were conducted and compared to those obtained from a standard commercial

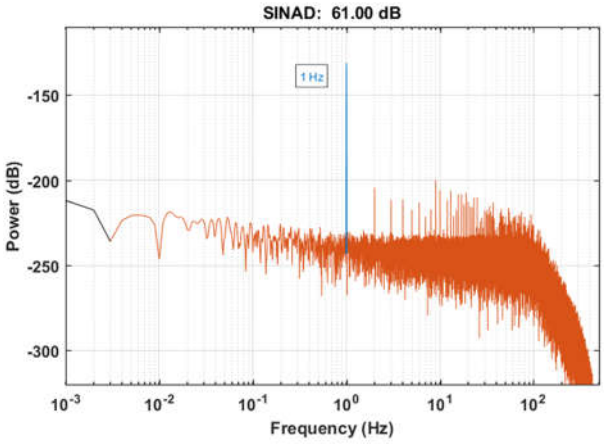

Fig. 3.The FFT results implemented over 1000 seconds of amperometric sinusoidal input current. The results were digitally filtered to get rid of high-frequency noises. Total SINAD indicate that aMEASURE2 has a resolution of ~10 bits.

benchtop electrochemical instrument (CHI-760c). First, a solution with 30 mM potassium ferricyanide, $K_4[Fe(CN)_6]$(0.1M KCl), was tested at scan rates of 50 mV/s, 100 mV/s and 500 mV/s with the CV potential swept from 0 V to 600 mV. Then, similar tests were performed using different solution concentrations (40 mM, 30 mM and 20 mM) at 100 mV/s. Both tests were conducted for 10 cycles, and Fig. 4 plots the results from the 9th CV cycle for both instruments. These results show that aMEASURE2 achieves the desired electrochemical functionality (current increases linearly with concentration and scan rate). Moreover, aMEASURE2 can match the results of the benchmark instrument with a maximum normalized root mean square (RMS) difference of less than 1.8% across all tested concentrations and scan rates.

To test aMEASURE2's adaptability to a completely different sensor platform, amperometric measurements were performed to detect *Plasmodium falciparum* histidine-rich protein-2 (*Pf*HRP2), a biomarker for *P. falciparum* infection, (causing severe malaria), in spiked blood samples [7]. Measurements were conducted using disposable gold tri-electrode electrochemical sensors on PMMA [8]. A sandwich assay format was employed where anti-*Pf*HRP2 capture antibodies were immobilized on the surface of the working electrode via linking with self-assembly thiol groups. Spiked samples and *Pf*HRP2 detection antibodies labelled with horseradish peroxidase were sequentially dispensed on the sensor followed by rinsing in PBS and drying using nitrogen gas. Measurements were carried out by dispensing a substrate of $4AP/H_2O_2$ on the sensor followed by the application of a 0.2V bias potential. As shown in Fig. 5, amperometric signals

Table 1: aMEASURE2 performance metrics

Dimensions	2.5 cm × 3.4 cm × 1 cm
Dynamic range @ 1Hz	115 dB (0.87 nA – 0.5 mA)
SINAD (0.1-100 Hz)	61.00 dB
ENOB (0.1-100 Hz)	9.84 bits
Power Consumption	250 mW at 50.7 mA

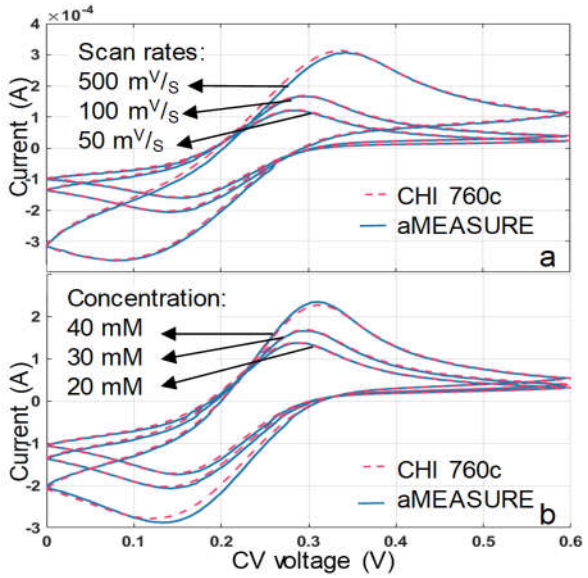

Fig.4. CV measurements for both CHI-760c and aMEASURE2 in a) 30 mM $K_4[Fe(CN)_6]$ with scan-rates of 50 mV/s, 100 mV/s and 500mV/s and b) 40 mM, 30 mM and 20 mM $K_4[Fe(CN)_6]$ at 100 mV/s.

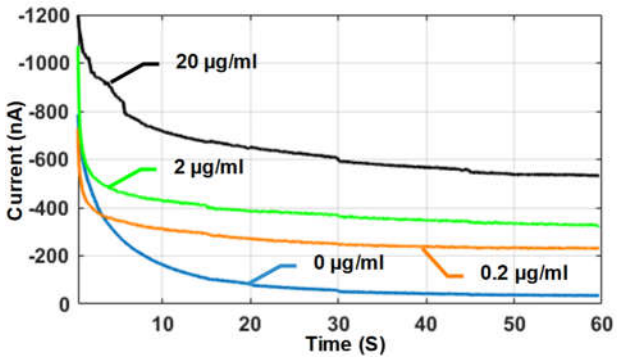

Fig. 5. Amperometric signals of blood spiked with different concentrations of PfHRP2 obtained using aMEASURE2.

were clearly distinguishable at four tested concentrations with relatively smooth response profiles and minimal noise. The results of this experiment were obtained by recording the electrochemical current for 60 seconds as shown on Fig. 5, and extracting the average current in the last 5 seconds of the experiment, as shown in Fig. 6. It should be noted that the experiments shown in Fig. 3 using a potassium ferricyanide solution and Fig. 5 detecting *Pf*HRP2 are conducted with the same aMEASURE2 device without the need for calibration or any electrical preparation despite the fact that the potassium ferricyanide conducts a maximum amperometric current of 300 µA while the *Pf*HRP2 conducts a minimum amperometric current of 20 nA.

To further test aMEASURE2's versatility and potential for wearable sensing, amperometric measurements of xanthine oxidase (XOx), a potential biomarker for urinary tract infection [9], were performed in spiked PBS samples. The tests were conducted using flexible screen-printed electrodes on a textile substrate. Carbon ink was used for the working and counter electrodes and silver/silver chloride was used for

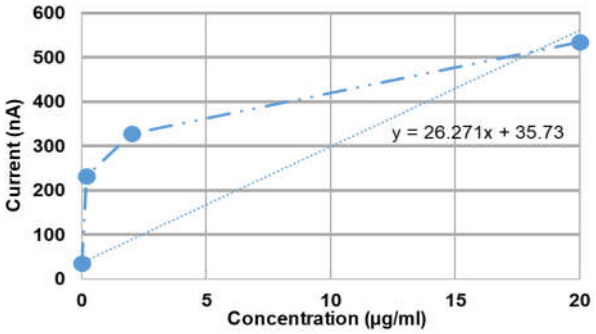

Fig. 6. Calibration curve for PfHRP2 detection obtained by extracting the average amperometric current in the last 5 seconds of each measurement.

the reference electrode. The working electrode was functionalized with hypoxanthine, which is oxidized by XOx to generate xanthine and hydrogen peroxidase. This reaction results in an electrochemical current proportional to the XOx concentration that was read by aMEASURE2. A comparative test was conducted using aMEASURE2 and a GeneFluidics Helios multichannel electrochemical workstation. The infection level may vary based on the infection type, but one of the greatest mean infectious concentrations is for Escherichia coli and was reported to be ~10000 U/L [9]. As shown in Fig. 7, the results acquired by aMEASURE2 and the Helios electrochemical instrument are comparable with a maximum standard deviation of 10 nA at the highest concentration. The slight mismatch observed may be attributed to the single-use nature of screen-printed carbon electrodes, which required the comparative tests to be conducted on different sensors.

CONCLUSION

This paper presented the design and characterization of a compact, adaptive, multichannel electrochemical instrument name aMEASURE2. This system occupies a volume of only 8.5 cm^3 and consumes only 250 mW of average power. To demonstrate the versatile, autonomous, and high-accuracy operation of aMEASURE2, tests were conducted using industry-standard electrochemical instruments and aMEASURE2. Comparative tests using potassium ferricyanide solutions and xanthine oxidase indicate that aMEASURE2 results match very well with commercial electrochemical instruments, with a reported standard deviation of 1.8%. Device accuracy was evaluated by extracting aMEASURE2 minimum precision to be ~1nA with a signal-to-noise and distortion of 61 dB through fast Fourier transform analysis with an ideal sinusoidal input current. Tests conducted on custom-made electrochemical sensors for measurements of xanthine oxidase and *Plasmodium falciparum* histidine-rich protein-2 demonstrate aMEASURE2's versatility in interfacing a wide variety of electrochemical sensors. During these tests, an amperometric current range between 300 µA and 20 nA was observed which

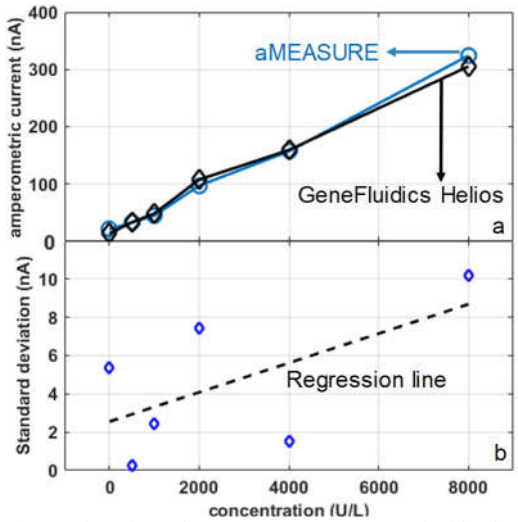

Fig. 7. a) XOx detection using aMEASURE2 compared with a benchmark GeneFluidics Helios electrochemical instrument; b) standard deviation between Helios and aMEASURE at each measured concentration.

demonstrates the wide dynamic range operation and self-calibration of this device.

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REFERENCES

[1] S. Imani, P. P. Mercier, A. J. Bandodkar, J. Kim, and J. Wang, "Wearable Chemical Sensors: Opportunities and Challenges," *Int. Symp. Circuits Syst.*, pp. 1122–1125, 2016.

[2] D. Zhang and Q. Liu, "Biosensors and bioelectronics on smartphone for portable biochemical detection," *Biosens. Bioelectron.*, vol. 75, pp. 273–284, 2016.

[3] P. B. Lin, Tung-Yi and Parsenjad, Sina and Tu, Linlin and Pfeiffer, Trey T and Mason, Andrew J and Xing, Guoliang and Lillehoj, "Finger-powered microfluidic electrochemical assay for point-of-care testing," in *Nano/Micro Engineered and Molecular Systems (NEMS), 2017 IEEE 12th International Conference on*, 2017, pp. 313--317.

[4] K. S. Sohn *et al.*, "A unified potentiostat for electrochemical glucose sensors," *Trans. Electr. Electron. Mater.*, vol. 14, no. 5, pp. 273–277, 2013.

[5] A. Sun, A. G. Venkatesh, and D. A. Hall, "A Multi-Technique Reconfigurable Electrochemical Biosensor: Enabling Personal Health Monitoring in Mobile Devices," *IEEE Trans. Biomed. Circuits Syst.*, pp. 1–10, 2016.

[6] S. Parsnejad, Y. Hu, H. Wan, E. Ashoori, and A. J. Mason, "Wide dynamic range multi-channel electrochemical instrument for in-field measurements," in *2016 IEEE SENSORS*, 2016, pp. 1–3.

[7] S. Parsnejad, T. Lin, Y. Hu, H. Wan, E. Ashoori, P. Lillehoj, A. Mason, "Compact , Adaptive , Multichannel Electrochemical Instrument for Point-of-Care Sensing," in *Healthcare Innovation Point-Of-Care Technologies Conference (HI-POCT), 2016 IEEE,* Nov 2016.

[8] P. B. Lillehoj, M.-C. Huang, N. Truong, and C.-M. Ho, "Rapid electrochemical detection on a mobile phone.," *Lab Chip*, vol. 13, no. 15, pp. 2950–5, 2013.

[9] P. Ciragil, E. B. Kurutas, and M. Miraloglu, "New markers: Urine xanthine oxidase and myeloperoxidase in the early detection of urinary tract infection," *Dis. Markers*, vol. 2014, 2014.