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A novel semiconductor based wireless electrochemical sensing platform for chronic disease management

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ABSTRACT

Electrochemical sensors are very versatile and can be used for a diverse range of biomedical applications. In this paper, a novel fully-integrated wireless electrochemical sensing platform is presented. The platform uses standard semiconductor technology to create a miniaturized integrated bioelectronics system that consists of an electrochemical sensor, potentiostat, signal processing circuitry, wireless power harvesting circuitry, and wireless telemetry unit, all on a single microchip. The platform is orders of magnitude smaller than the state-of-the-art sensing systems and costs a fraction. At 1.4 mm × 1.4 mm size, the sensor costs less than $1 to manufacture. The presented design provides fundamental advantages in decreasing sensor noise and settling time, thus providing superior response compared to existing solutions. System design and implementation details are presented as well as examples for metabolic sensing (glucose, lactate, O_2) applications. The system can have widespread applications in biosensing applications.

1. Introduction

Sensors are an integral part of biomedical monitoring systems, providing critical information about signals of interest. Typical applications include personal health monitoring, patient monitoring in hospitals, and monitoring health progression during treatment (Ozcan and Koydemir, 2018). These sensors are crucial for modern healthcare systems to properly function and address the needs of the growing population and disease patterns. As an example, chronic diseases are now the leading cause of death worldwide, surpassing the infectious diseases (WHO, 2018). In the United States, about half of all adults (117 Million people) suffer from one or more chronic diseases (Ward et al., 2014). Globally, more than 50% of the world's population is affected by at least one chronic disease (> 3.5 Billion people), Fig. 1a. These diseases are not only a huge healthcare challenge; they pose a significant risk to global economy. Their economic burden is estimated to be more than $40 trillion for 2010–2030 period, around 75% of total global GDP in 2010 (World Economic Forum, 2011). Therefore, the need for a carefully designed chronic disease management system has been laid out as one of the most important technological healthcare innovation.

Personal health monitoring and management is the primary method to minimize the burden of chronic disease management and to individualize care and tailor it to each patient (Oldenburg et al., 2015). Effective, safe, and low-cost monitoring of personal health is essential for efficient operation of the modern healthcare system (Reynolds et al., 2018). Important health markers include metabolites (e.g., glucose), proteins (e.g., insulin for diabetes, troponin for cardiovascular), and physiological indicators (e.g., temperature, blood pressure) (Pendley and Lindner, 2017).

Several researchers have presented technologies focused on biomedical sensing applications. Noninvasive sensors are the most attractive solutions as they can be used outside the body and collect data without causing risks and discomfort. For example, optical (e.g., NIR, Raman) and electrical (e.g. Dielectric, Microwave) spectroscopic sensors have gained considerable attention (Strobbia et al., 2018), (Entesari et al., 2017); however, achieving clinical accuracy, size and cost-effectiveness for personal use have been challenging due to many interferents and complexity of biological media (Kim, 2018). Such systems have therefore been able to be used for sensing on purified samples and progress towards in-vivo use requires more developments that are ongoing. Minimally invasive devices like contact lenses, sweat sensors, and saliva sensors have been proposed as alternate techniques (Bandodkar and Wang, 2014). Although these devices are promising, lack of reliable access to the bodily fluids and accuracy in complex media has posed challenges in developing clinical products using these methods (Acciaroli et al., 2018).

Invasive (in-vivo) electrochemical sensing is an attractive choice for critical biomedical applications due to its versatile nature, accurate and

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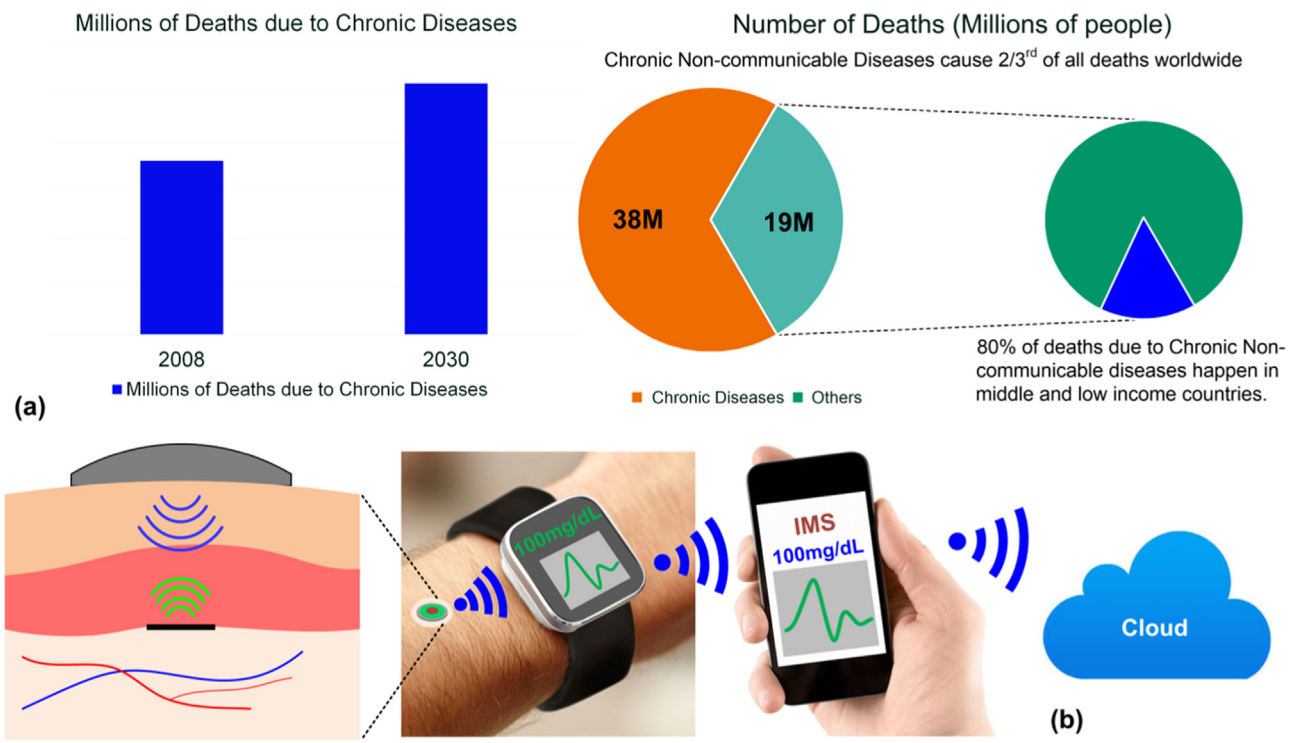

Fig. 1. (a) Scale of chronic health disorders worldwide. (b) The proposed health monitoring system.

fast response, and ability to provide selectivity in complex media. Invasive sensors require to be partially or fully implanted in the body. The resulting foreign body response limits the usefulness of such implants in terms of accuracy, response speed, and longevity. The foreign body response is affected by the size of the device as well as by the damage caused by the insertion process (Wang et al., 2015).

It has been well understood that miniaturization is the key to minimize body's response to the implant as well as to minimize implant friction with the surrounding tissue (Veiseh et al., 2015). This is very important in achieving stable, reliable results required for clinical use (Helton et al., 2011). Currently, commercial electrochemical sensors are designed as transcutaneous devices in which the constant sensor tissue friction shortens the useful sensor life. In addition, the transcutaneous nature poses limitations in terms of warm-up time, skin irritation, effect of pressures during sleep, difficulty of multi-analyte sensing, and cost (Petrie et al., 2017). This has prompted significant research into fully-wireless implantable electrochemical systems. Current fully implantable electrochemical sensors are rather large and require surgical insertion process (Lucisano et al., 2016a, 2016b). This limits their use in terms of implant location, suitable patient population, calibration requirements, warm-up time, and response speed. Although some devices have been proposed to miniaturize the size of the system (Ahmadi and Jullien, 2009), (Croce et al., 2013); they utilize discrete components, requiring significant packaging efforts, making it difficult to achieve extreme miniaturization as well as reliable and scalable manufacturing. Hence, clinical efficacy of these systems has been quite limited. Development of a miniaturized, real-time, sensitive, accurate, low-cost and patient-friendly wireless electrochemical monitoring platform remains of significant interest for many researchers, public health, and commercial organizations (Tricoli et al., 2017).

In this paper, we present a novel integrated wireless electrochemical sensing platform that offers extreme size and cost reduction for accurate electrochemical sensing of analyte (e.g., metabolites, Oxygen, ions, etc.) in the interstitial fluid (ISF). This platform is comprised of a microelectronics device that integrates all components as a monolithic solution without the need for additional bonding or complicated packaging. As an example, we present design of a complementary metal oxide semiconductor (CMOS) based architecture that integrates wireless power harvesting and wireless communication with an electrochemical sensor along with all the required control and processing circuitry on a single microchip that is smaller than a sesame seed. Other than decreasing foreign body response, a fundamental advantage of such design is reduced system noise due to elimination of wiring and enhanced signal-to-noise ratio (SNR) improving sensitivity, accuracy. Additionally, sensor miniaturization results in improved response speed. The proposed design is well suited for sensing multiple analyte using a multiplexed architecture, making it distinct from other discrete designs. Furthermore, the core technology can be used for many sensing applications (e.g., metabolic sensing, protein sensing) by tuning the sensor surface material (e.g., Platinum or Gold) and surface chemistry (e.g., enzyme or aptamer). This technology has the potential to enable widespread use of patient monitoring and timely interventions through sensing fundamental health markers in patients at risk who cannot otherwise afford to use painful or cumbersome devices (e.g., children, elderly).

2. System design

The proposed wireless health monitoring platform consists of several components (Fig. 1b). The core of the system is a novel, integrated, wireless, electrochemical sensor fabricated using CMOS technology. The sensor is wirelessly powered by and wirelessly communicates with a wearable, wireless transmitter. The transmitter communicates the data to a smart reader that analyzes the data and provides feedback to the patient and their care team (e.g., family, physicians) over secure data links. The reader also saves the data in a secure online database for further analysis as well as for long term trend monitoring and for pattern recognition. These components are described in detail here.

2.1. The sensor

The proposed sensor utilizes electrochemical detection as the sensing mechanism due to its versatility, sensitivity and specificity in complex biomedical media such as ISF. In this work, amperometric

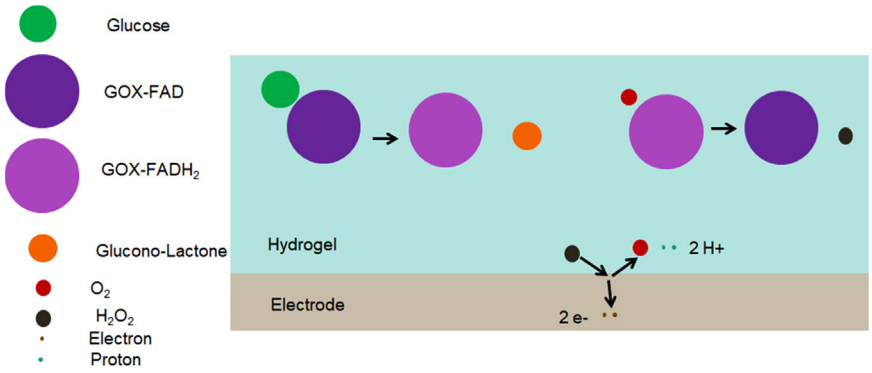

Fig. 2. Enzymatic detection of glucose at platinum working electrode.

electrochemical detection is used as the modality of choice as it is best suited for continuous monitoring based upon surface reactions. However, the platform can be easily used for other sensing modalities (e.g., potentiostatic). In the case of electrochemically active agents such as O_2, direct transduction and hence sensing is possible; however, if the agent of interest is electrochemically inactive (e.g., glucose), detection is made possible through a sensing reaction mediated by an agent specific enzyme incorporated in the surface chemistry. In the particular example of glucose detection, sensing is enabled through a two-step chemical reaction catalyzed by glucose oxidase (GOx) immobilized on an electrochemical sensor comprising of a working electrode (WE), counter electrode (CE), and reference electrode (RE). At WE, glucose and O_2 generate H_2O_2 catalyzed by the GOx (Fig. 2)·H_2O_2 is reduced at the WE leading to a redox current proportional to the glucose concentration. At CE, the most common reaction is thought to be the reduction of O_2.

The enzyme is immobilized within a cross-linked protein gel known as hydrogel that is in contact with the solid-state electrochemical sensor. Glucose and oxygen diffuse into the hydrogel and encounter the enzyme, the above reactions occur and the resulting hydrogen peroxide (H_2O_2) is detected by the solid-state sensor.

A CMOS microchip including the sensing electronics serves as the platform for the solid-state sensor with Pt WE and CE and RE. This set of metal electrodes is best suited for any agent whose detection involves H_2O_2 sensing, (e.g., glucose and lactate). To detect proteins using aptamers, gold is the metal of choice for the sensor electrodes. The electrodes are arranged as co-centric rings in an overall area of 500 µm × 500 µm, as shown in Fig. 3a. The electronics is covered by a stack of SiO_2/Si_3N_4 which is included in the standard CMOS fabrication process. In some cases, different insulation materials (e.g., polyimide) can be provided by the CMOS foundry for further insulation. The solid-state sensor outlined is formed by the top Aluminum metal layer in the CMOS process and exposed through the removal of the top insulation layer during the CMOS fabrication process.

2.2. Post-processing and functionalization

The top metal in CMOS process is made up of Aluminum which corrodes in saline environment and hence is not suitable for long term sensing applications. Therefore, it is replaced by more suitable metal (e.g., Pt or Au for WE & CE, and Pt, Au, or Ag/AgCl for RE) through a CMOS-compatible lithographic post-processing (Mujeeb-U-Rahman et al., 2016). Since, it is very difficult to reliably etch noble metals specially Pt, the sensor electrodes are patterned using lift-off. The sensor pattern is selected through lithography (photo/e-beam) depending upon feature size. To guarantee proper adhesion of Pt to the underlying layer (e.g., SiO_2), an intermediate layer of Ti is deposited. Physical vapor deposition (e.g., sputtering, e-beam deposition, or thermal evaporation) is used for deposition of metals. For example, e-beam deposition is used to avoid exposing the sensor electronics to high-energy plasma and for easier lift-off. This is followed by gentle solvent lift-off. An optional step is to perform another lithography followed by Silver deposition, liftoff and Chlorine exposure to create silver based reference electrodes (e.g., Ag/AgCl). However, due to their small size, microelectrodes of noble metals can be used as quasi-reference electrodes, especially when connected to CMOS electronics that reduces current flow through electrodes. Fig. 4a illustrates the processing steps involved in the formation of the solid-state sensor on the CMOS electronics platform. On the left hand side it shows the process steps for Ti/Pt electrodes and on the right hand side for Ag based electrode.

Due to the removal of the passivation layer (SiO_2/Si_3N_4) to define sensor electrodes during CMOS fabrication, a well is formed that encompasses the solid-state sensor, as shown in Fig. 4d. The well is used to retain the surface chemistry layer(s) directly on top of the solid-state sensor. Crosslinking within an immobilization matrix is a suitable technique to keep desired protein (e.g., enzyme) near sensor electrodes. This allows easy functionalization for long-term sensing. For aptamer sensing applications, thiol based chemistry is used to attach the aptamers to suitable electrode (e.g., Au WE). Further protective layers are used to cover enzyme or aptamer chemistry in-vivo.

The CMOS microchip contains a potentiostat and signal-conditioning circuitry, a wireless telemetry system, and a wireless power harvesting unit to eliminate the need for a bulky battery and hence minimize the size and enable monolithic integration. The potentiostat can sample the sensor current as frequently as once every millisecond (1 KSample/s), encodes the sample and transmits the reading as a radio-frequency signal to an external transmitter, where the signals are decoded and recorded. The potentiostat circuitry in the implant is based on an electronic design described in detail elsewhere (Nazari et al., 2014), extended in this case for lower power operation and robust power telemetry and communication. This monolithic system does not require hermetic sealing as the CMOS electronics benefit from water-tight passivation and there is no wiring involved to make system prone to humidity. The implant has been tested for operation of more than one year in-vitro in buffer solution and more than 3 month in-vivo in rats.

2.3. Implant electronics

Fig. 3c shows the block diagram of the electronics design utilized in the implant. An on-chip antenna is implemented using the top metal in the standard CMOS process that facilitates power harvesting and up-link/down-link communication to the external transmitter. Power signal is transmitted from the external transmitter over the 900 MHz carrier signal. This signal is modulated by the downlink signal to send sensor readout command to the implant. The choice of the frequency was based on the optimization of the coil size and the tissue absorption (Gabriel et al., 1996) to achieve maximum power transfer efficiency (Fig. 3b) as well as considering the available ISM bands for medical applications. Sensor readout circuitry includes a potentiostat to

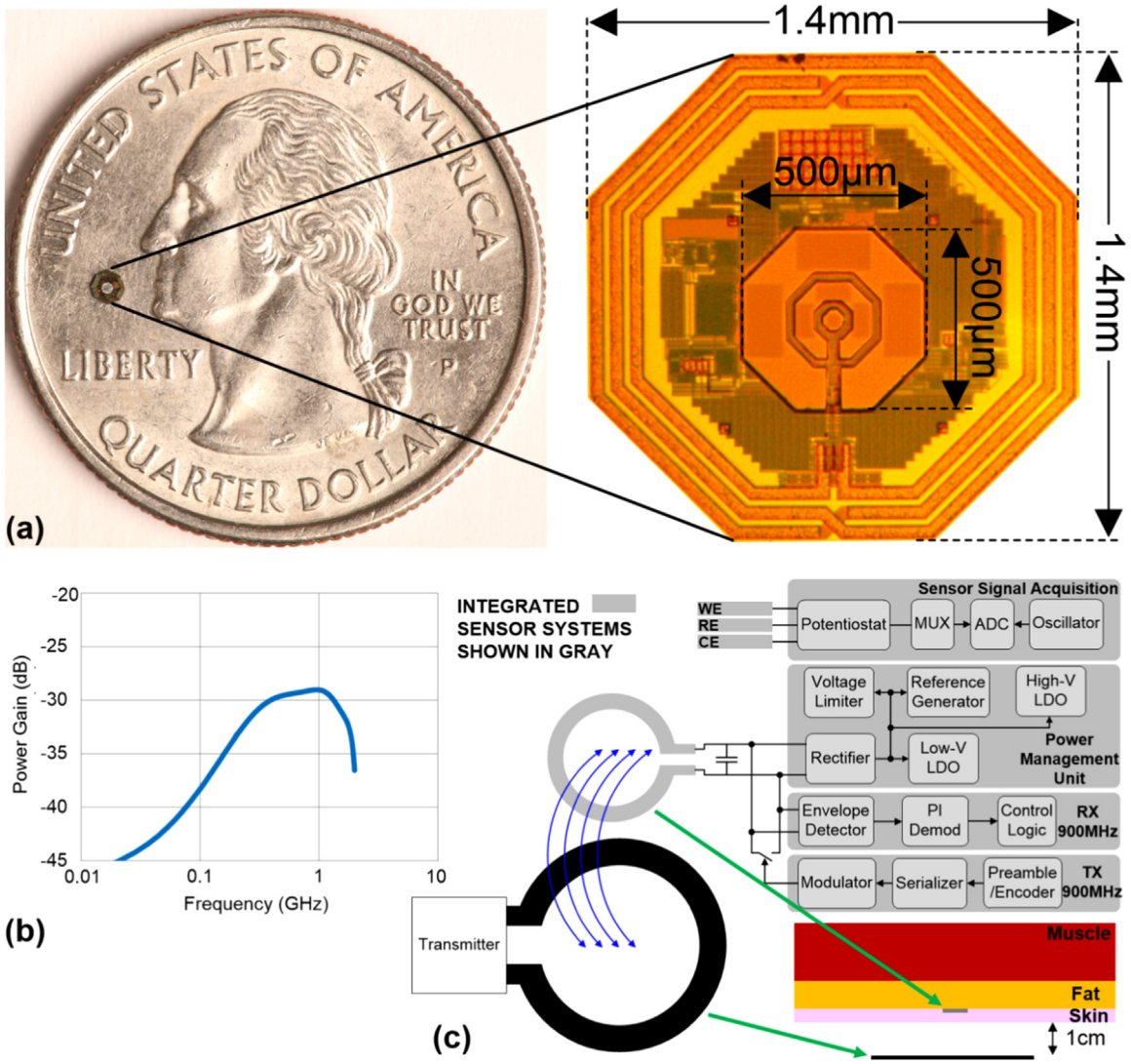

Fig. 3. (a) The Integrated Wireless Sensing Platform (b) Frequency vs. Power Gain for wireless link design (c) Design of electronic components of Wireless sensing platform.

maintain the required redox potential between the working and reference electrode while supplying current through the counter electrode using a feedback amplifier to cover sensor currents from glucose detection in clinically relevant 0–20 mM range. The potentiostat is followed by an ADC which digitizes the sensor current with quantization sensitivity of 200 pA (under the overall sensor noise floor). The digital data is encoded and transmitted to the external reader via backscattering of the power signal (Nikitin and Rao, 2006), thus enabling ultra-low-power operation.

2.4. Surface chemistry

Sensor surface is coated with suitable chemistry to make it selective and sensitive to the analyte of interest. For metabolic sensing, oxidoreductase enzymes are immobilized close to sensor surface using an immobilization matrix. Additional layers are mostly required for an optimal response. For example, GOx based sensing requires sufficient O_2 to complete the reaction (Yu, 2008). Since concentration of O_2 in the ISF is lower than glucose, sensor current will be limited by O_2 rather than glucose. To mitigate this problem a glucose-limiting membrane (e.g., Polyurethane i.e., PU) is utilized which is permeable to O_2 and reduces glucose diffusion. The PU coating decreases the current range of the sensor and increases linearity. This membrane can also act as a suitable material to protect the device.

Conventionally, it is considered that only the WE should be coated with functionalization layer. This becomes more and more challenging as the devices are shrunk and electrodes become smaller and smaller. In this work, we demonstrated that for amperometric sensing with a suitable potentiostat, the WE is polarized at the correct potential to detect the surface reaction. Hence, all 3 sensor electrodes can be simultaneously functionalized with a simpler and scalable process and yet the sensor function isn't affected negatively.

The proposed platform is very versatile due to the availability of a wide variety of surface chemistry to detect a host of analyte that are of interest for different applications such as lactate, creatinine, cholesterol, Uric acid and Urea. Furthermore, by changing the sensor material (e.g., gold rather than platinum) the system can be used for sensing other biomarkers such as proteins through aptamer-based surface modification. This is important for cardiovascular applications by enabling measurement of important cardiovascular health markers like troponin.

3. Sensor design considerations

After an initial electrical potential (E) is applied to the electrochemical sensor, total sensor current is given by the sum of polarization

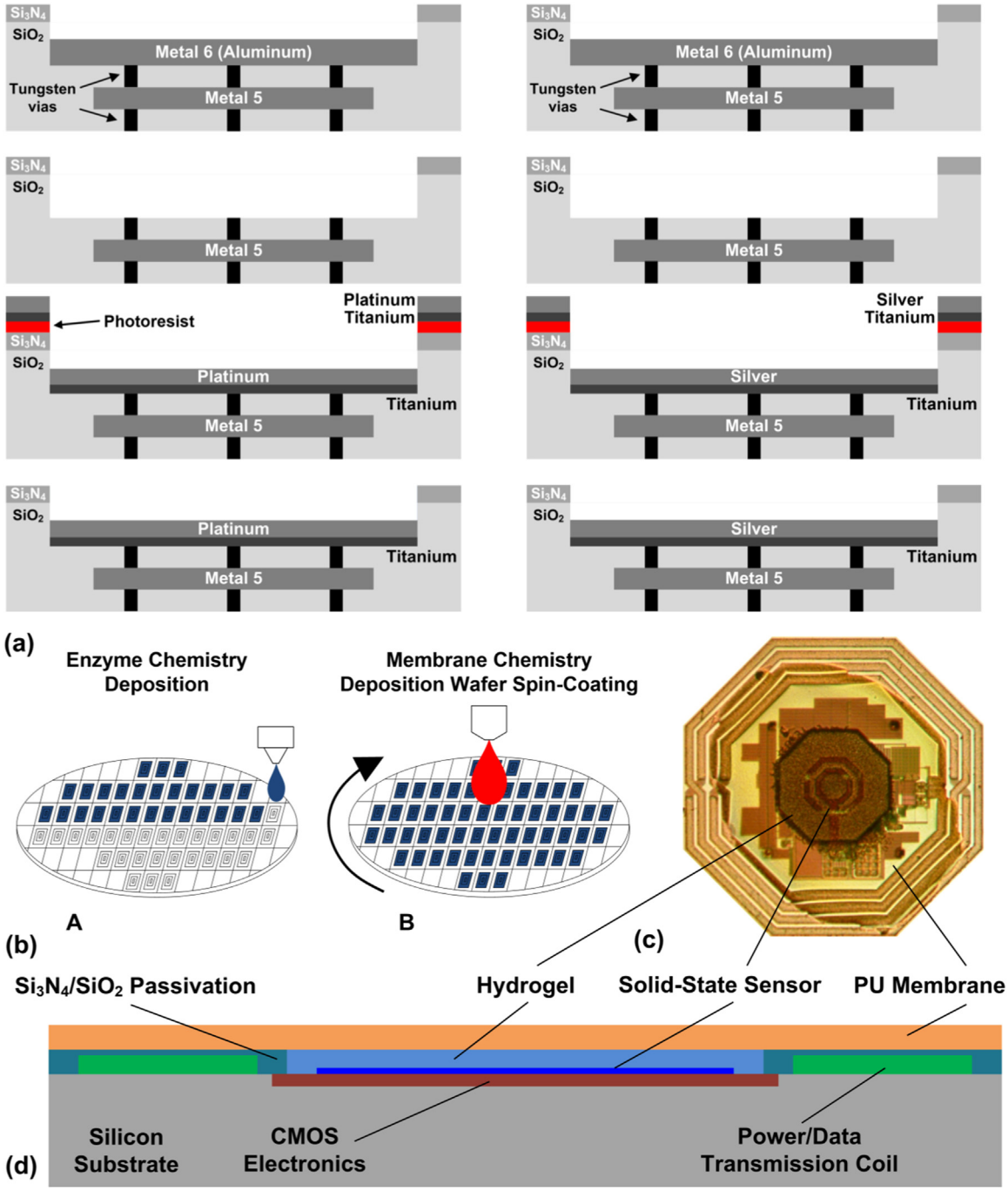

Fig. 4. (a) Postprocessing steps to create the solid-state sensor on the CMOS electronics (b) Functionalization of integrated electrochemical sensing platform, (c) Sensor coated with GOx hydrogel and PU membrane, (d) Functionalized sensor.

and faradaic currents (Bard and Faulkner, 2000)

$$\mathbf{i} = \mathbf{i_p} + \mathbf{i_F} = \frac{E}{R}\exp\left(\frac{-t}{RC}\right) + \left(nFADc\frac{1}{\sqrt{D\pi t}} + nFDcL_e\right) \quad (1)$$

Here, R and C represent the resistance and capacitance of charging path. For faradic current contribution, n is the number of electrons to reduce/oxidize one molecule of analyte, F is the Faraday constant (96485 C/mol), A is the area of the electrode, c is the bulk concentration of the analyte, D is the diffusion coefficient, t is time in seconds, L_e is edge length (for rectangular electrode, sum of all sides is the edge length). The time-dependent term dominates the response initially and subsequently diminishes as time grows. In steady state, current is limited by the diffusion characteristics at electrode-electrolyte interface and becomes independent of time.

The steady-state current after the application of cell voltage represents the equilibrium redox current. The 'time constant' to achieve this steady-state is important as it dictates the settling speed of the sensor after an abrupt voltage change. Constant potential amperometry to measure analyte concentration is possible after the time-dependent terms in Eq. (1) subsides and steady-state is reached at which time the sensor current is linearly proportional to analyte concentration. For small electrodes, the polarization term diminishes quite rapidly as the capacitor value is sufficiently small. Therefore, this 'settling time' can be defined as the time it takes the $\frac{1}{\sqrt{t}}$ term in Eq. (1) to drop to less than 10% of the total current. Rearranging faradaic current from Eq. (1),

$$t_s = \frac{81 \quad (A/ \quad L_e)^2}{\pi D} \tag{2}$$

Here, t_s is the sensor settling time. Hence, settling time has a square dependence on ratio of electrode area to that of diffusion length. The smaller the electrode is, the shorter the settling time will be and vice versa. Miniaturization is therefore beneficial in this regard (faster response). This is especially of importance when sensor is energized intermittently for readings and is not powered continuously.

The redox current given by Eq. (2) is a good measure of the concentration of redox specie near electrode surface, within the limits of noise processes. Sensor size has a direct impact on noise and hence on sensitivity and reliability of electrochemical measurements. Since current is the quantity of interest for amperometric sensors, current noise is the parameter of interest in this analysis. For electrochemical current sensors, noise is inversely proportional to electrode area in a linear manner, while the steady state signal is proportional to edge length, resulting in SNR improvement with miniaturization of sensor electrodes - until sized ultramicroelectrodes (e.g., 1 μm x 1 μm) where other noise sources start to dominate (Morgan and Weber, 1984). Therefore, sensor miniaturization improves SNR for amperometric measurements resulting in enhanced sensor accuracy, especially in the lower end of detection range (e.g., in hypoglycemia).

4. Results

4.1. In-vitro testing

Hydrogen peroxide is generated during enzymatic detection of several important metabolites e.g. glucose, lactate when using oxidoreductase enzyme (e.g., GOx). Therefore, the bare (non-coated) sensor was tested in-vitro in phosphate buffer solution (PBS) spiked with hydrogen peroxide (Fig. 5a, Fig. 5b). The variation in peroxide response was characterized by determination of the coefficient of variation (CV) between different readings from different sensors. Typical value of CV was 3.12%, indicating small variation within a batch (e.g., n = 6) of sensors. Furthermore, reversible response demonstrates the stability of the sensor (Fig. 5a).

After functionalization with GOx, in-vitro experiments were performed to test the quality of the CMOS electronics and feasibility of surface chemistry for stable glucose sensing as an example of enzymatic sensing. Measured noise in this case was slightly lower than peroxide measurements. This can be attributed to less impedance variations after stable solid-state surface coating as compared to bare surface.

Fig. 5c demonstrates the in-vitro glucose response of the functionalized wireless sensors after GOx coating. Fig. 5d shows the stability of hydrogel when stored at room temperature over one year and used to measure glucose concentration in-vitro over this time period. As seen in Fig. 5c, the functionalized sensor with GOx response to glucose concentration is not linear due to the sensing limitation to Oxygen concentration. Deposition of the PU membrane over the GOx hydrogel results in an overall linear response to glucose by limiting the diffusion of the glucose to the sensor surface and balancing the glucose-oxygen ratio. This is demonstrated in Fig. 5e. As expected, this linearization in response comes at the cost of overall signal reduction compared to the sensor with only GOx hydrogel as the glucose concentration is limited. Fig. 5f shows the linearity of the PU coated sensor with $R^2 > 0.99$ for a linear fit.

Experimental testing also demonstrated extremely low levels of noise from the integrated system. The cumulative noise level depicted as variations in sensor readings in a given solution. For typical H_2O_2 measurements, variance level (for n = 100 readings) was calculated to be (2.5 ± 1) % of average value (e.g., SD of 250 pA for current reading of 15.4 nA). Sensors had an SNR of 23.8 with a SD of 5.2. Some sensors (almost 1 out of 10 sensors) demonstrated an SNR as high as 72, possibly due to a significantly cleaner surface compared to other sensors. Time-domain sensor current was modeled using Cottrell equation (Eq. (1)) and the fit was used to calculate settling time for multiple (n = 6) sensors. Settling times for bare electrode, electrode with hydrogel only, and electrode with hydrogel and PU coating were found to be 37.94 ± 9.63 s, 37.16 ± 16.57 s, and 89.24 ± 55.02 s, respectively (Table I in Supplementary section).

The sensitivity and measurement resolution of the system was also calculated. Given the average system noise floor as 0.25 nA and reliability constraints (SNR of 3), the detection limit is 0.75 nA and resolution limit is 0.25 nA. System sensitivity after PU coating is more than 3.6 nA/mM (for more detail refer to Table I in Supplemental section), translating to detection limit of 0.2 mM and sensing resolution of 0.07 mM.

4.2. In-vivo testing

After in-vitro validation, in-vivo studies were performed to test the efficacy of the wireless sensing platform under BTS Research IACUC protocols (NIH assurance number A4519-01). A total of 4 individual sensors were implanted in 2 nondiabetic Sprague Dawley rats, two sensors for each rat. Results from this study included verification of (i) electronic circuitry reliability and telemetry performance in-vivo; (ii) sensor mechanical robustness including long-term maintenance of hermeticity; (iii) immobilized enzyme life for 1 week; (vi) stability of the electrochemical detector structure; and (vii) acceptability and tolerance of the animals to the implanted device. The sensor was able to track glucose changes in-vivo following intraperitoneal glucose tolerance tests. At concentrations above 200 mg/dl, sensor demonstrated saturation effects typical for GOx based sensors. This indicates the need for better PU coating for future experiments. A typical in-vivo excursion curve is shown in Fig. 6a.

To quantify clinical accuracy of the sensor, Clarke error grid analysis was performed. First the sensor readings were calibrated using the in-vitro data from the sensor prior to implantation to estimate the ISF glucose level, as shown in Fig. 6b. A second order approximation was utilized in this analysis. The sensor saturation at high glucose concentrations (> 200 mg/dL) was due to imperfect PU coating used in these sensors. Better PU coatings (e.g., as shown in Fig. 5f) were developed after these limitations were observed. Fig. 6c demonstrates the sensor reading compared with the blood glucose concentration measured by a glucometer. As seen, more than 80% of the readings are in region A where the sensor data is within 20% of the reference measurement. Less than 20% of the sensor readings fall in region B which is outside of 20% of the reference measurement but would not lead to inappropriate treatment. No reading was observed in regions C, D, and E.

One sensor in each animal responded to glucose changes, while one sensor in each animal did not respond or failed to communicate with the transmitter. Upon extraction the sensors that did not function were found lodged in muscle tissue rather than subcutaneous tissue. This prompted the development of implantation apparatus and techniques for more precise implantation in subcutaneous tissue; ongoing investigations of which will be communicated in future publications.

Compared to in-vitro readings, the signal current in-vivo for comparable glucose concentration (~4 mM) was measured as 12.2 ± 2.2 nA, noise was calculated as at 0.68 ± 0.15 nA, and hence SNR was calculated as 18.5 ± 4.72.

We performed in-vivo toxicity in a different set of mice (n = 3) using clinical chemistry of blood before and after implantation and removal of multiple (n = 2–3) sensors per mice. No adverse effect was observed in any mice.

4.3. Additional applications

We have focused on glucose due to the scale of diabetes problem; however, the proposed sensor can be utilized for a host of other

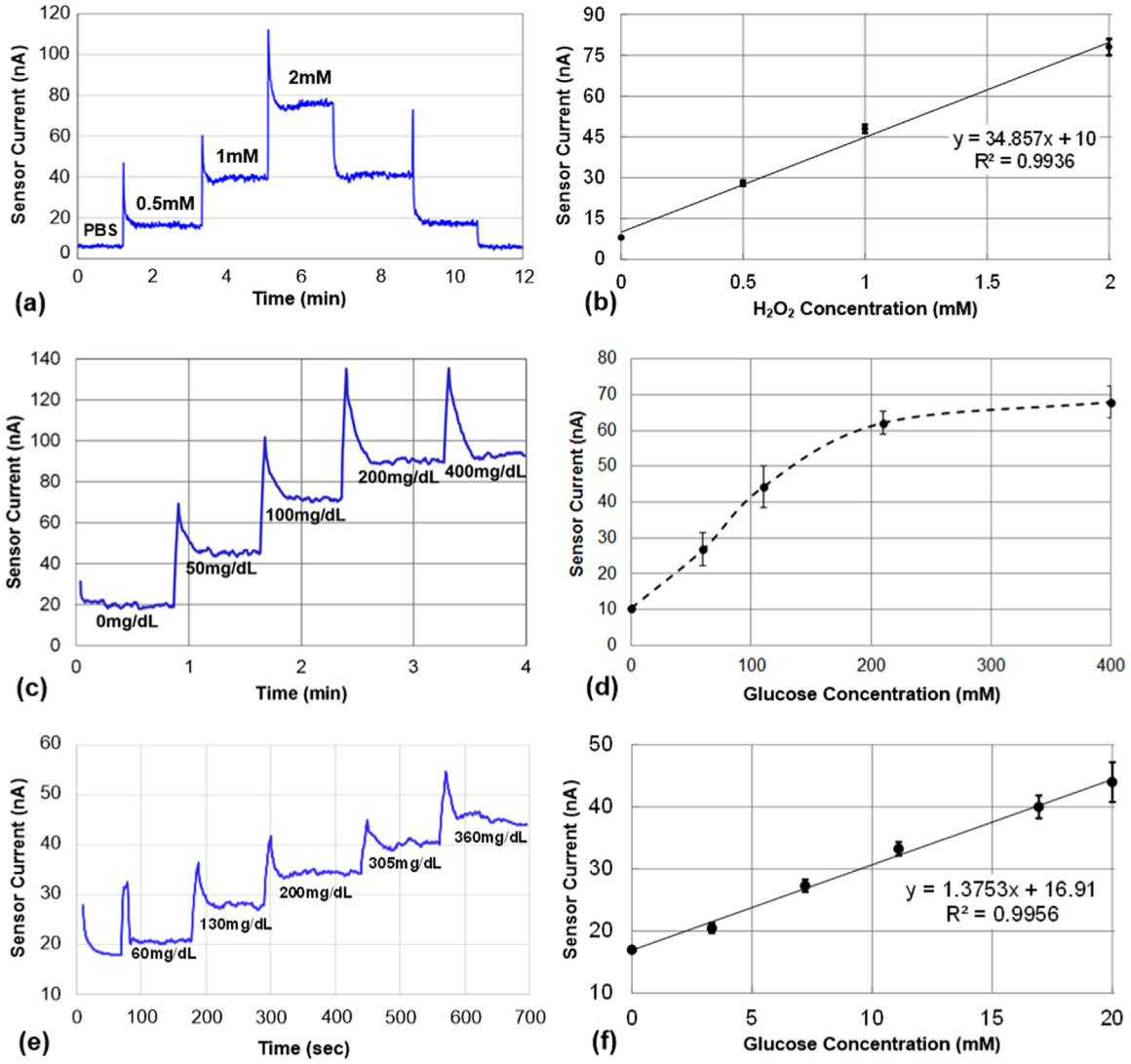

Fig. 5. (a), (b) In-vitro characterization of the wireless sensor in H_2O_2 solution in PBS, (c) In-Vitro Response of GOx Hydrogel Coated Sensors (d) Response variations over first 360 days, (e) Improvement in sensor linearity by using multiple PU coatings In-Vitro Response, (f) calibration curve.

applications by adjusting the surface chemistry. As an example, lactate oxidase was immobilized to sense the concentration of lactate in a spiked buffer solution (Fig. 6e). Similarly, O_2 can be sensed without requiring any enzymatic coating, as shown in Fig. 6d.

5. Discussion

In this work, we have demonstrated in-vivo operation of world's first fully-integrated (single-chip) wireless electrochemical sensor. The proposed sensor is fabricated by lithographic processing of standard CMOS electronics without the need for any external components or special packaging. This means biosensors can be manufactured using the same scalable technology as is used to create commercial electronics, thus enabling extremely low-cost, high-yield and reliable manufacturing that can address the need of the large patient population suffering from chronic diseases.

The proposed sensor provides exceptional performance in terms of size, accuracy, and response speed. The size of the sensor is significantly smaller than the state-of-the-art electrochemical sensing products and other published devices (Table III in Supplementary section). Its overall accuracy is comparable to existing solutions at high concentrations while superior in low concentrations. The proposed sensor demonstrates settling times of few 10's of seconds. This minimizes the warm-up time together with the small size which minimizes the disruption of local microvascular environment after implantation as demonstrated in the in-vivo experiments where accurate sensor readings could be taken shortly (~10 min) after sensor implantation, as compared to few hours for competitor devices. The CMOS wafer for 180 nm process costs around $1000 and contains more than 15,000 sensors. The remaining fabrication processes (Post-processing, chemical coatings, dicing, sterilization) all are done at wafer level at cost comparable to that of the CMOS process, resulting in a total cost of $2000 for 15,000 sensors. Therefore, each sensor will cost less than $1 when manufactured in volume. Furthermore, due to its size and wireless nature, the system exhibits minimal foreign body response, hence the potential for longer term use with minimal calibration. Moreover, automation of the post-processing and functionalization methods will eliminate the need for calibration as has been achieved by other implantable biosensors.

Safety is also an important requirement for the proposed implantable sensor. The benign toxicity results obtained were expected as the sensor is relatively small and uses standard enzymatic chemistry that has been verified to be safe in FDA approved products. Furthermore, no severe body reaction was observed at implantation site, further indicating the safe nature of the device.

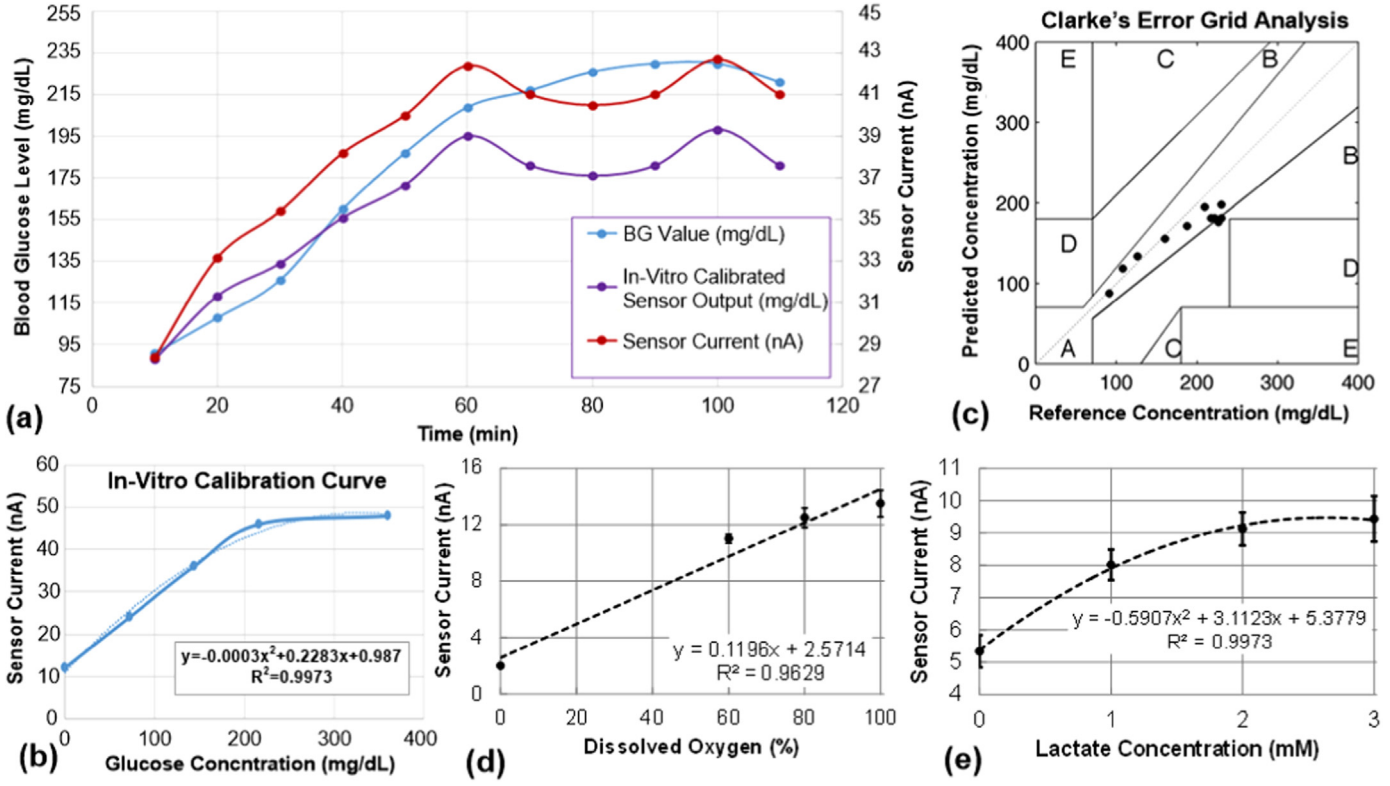

Fig. 6. (a) Glucose excursion curve in a rat indicating the proposed sensor closely tracking the blood glucose level which is measured from tail vein blood using a Contour glucose sensor. (b) Calibration curve of the implanted sensor as measured in-vitro(c) Clarke error grid with single point calibration (d) O_2 measurement using the proposed device (e) Lactate measurement results.

6. Conclusion

This work presents first fully-integrated integrated (single-chip) wireless electrochemical sensor design that is fundamentally scalable and higher yield design compared to other designs.

A comparison with state of the art (table III in Supplementary section) demonstrates the fundamental advantages of the system including (i) more than 250 × reduction in electrochemical sensor size compared to next smallest electrochemical sensor (Dexcom G6), (ii) more than 500 × reduction compared to smallest wireless CGM (Eversense from Senseonics), (iii) on-chip integrated potentiostat minimizing contact capacitance and noise, (iv) more than 30 × lower warm-up time as compared to existing products, (v) improvement in sensor accuracy (as quantified using MARD) in hypoglycemia compared to other products, (vi) better MARD compared to existing implantable wireless electrochemical sensors (e.g., iCGM from Glysens), (vii) and fundamental cost improvements due to scalable manufacturing process. The system demonstrates excellent stability (as demonstrated by relatively small sensor variance and high SNR) and high interference rejection (Fig. I in Supplementary data section), both of which make it a suitable candidate for further investigations for clinical use.

This work demonstrates feasibility of in-vivo sensing with study duration (1 week) comparable to existing wireless electrochemical products. It has been demonstrated by other researchers that an improvement in chemistry stack (e.g., incorporating hydrophilic polymers on the PU layer) can provide long-term performance (> 30 days) for miniaturized electrochemical sensors, albeit wired (Yu et al., 2008). The in-vivo experiments revealed the need for optimized polyurethane coating that can provide enhanced linearity to minimize saturation effects. Such coatings have been tested in-vitro and require further testing. Furthermore, testing in larger mammals (e.g., pigs) is required before human feasibility study can be performed. Thus, improvement in sensor chemistry (e.g., optimization of polyurethane coating, use of hydrophilic biocompatible coating) and in-vivo testing of sensors in pigs is part of the future work.

In conclusion, this paper presents a unique sensor design and an innovative user experience for real-time, continuous in-vivo glucose monitoring. The proposed system represents a leap forward from the state-of-the-art solutions in the diabetes management space (e.g,. continuous glucose monitors). Additionally, it was shown that the proposed design can be readily translated into a platform for sensing different species in-vivo such as lactate, O_2, etc. through chemistry modification, as well as into a multi-analyte sensing platform.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bios.2018.09.077.

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