

Optimization Techniques for Miniaturized Integrated Electrochemical Sensors

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Abstract: Electrochemical sensors are integral components of various integrated sensing applications. In this work, we provide details of optimizing electrochemical sensors for CMOS compatible integrated designs at sub-mm size scales. The focus is on optimization of electrode materials and geometry. We provide design details for both working electrode and reference electrode materials for hydrogen peroxide sensing applications which form the basis for many metabolic sensors. We also present results on geometrical variations in designing such sensors and demonstrate that such considerations are very relevant for optimizing the overall sensor performance. We also present results for such optimized sensors on actual CMOS platforms. The methods presented in this work can be adopted for countless applications of electrochemical sensing platforms. *Copyright © 2015 IFSA Publishing, S. L.*

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1. Introduction

Implantable electrochemical sensors have been attracting considerable interest owing to their integration with electronic circuitry required for truly wireless implants [1]. These sensors can provide selective and sensitive results in complex environments; in vivo environment being a very relevant example. For example, glucose sensors utilizing electrochemical techniques have been shown to work for long term implanted applications with potential for successful human applications [2]. However, these sensors have typically been part of large (cm scale) systems. It has been shown that miniaturizing the overall size of the implantable system can be very beneficial for minimizing the foreign body response to such implants [3]. The small size is advantageous in reducing the bio-

fouling problems associated with such implants since it leads to minimal disturbance in the body leading to minimal inflammation [4]. Hence, such miniaturized systems can provide accurate and long-term measurements of analyte in complex environments e.g. body fluids [5].

As the sensors are made smaller and fully integrated; it becomes more and more challenging to achieve high sensitivity, stability, and longevity. However, these are the important requirements for real-world applications. Hence, this work is focused on optimizing the electrochemical sensors for small scale (near and sub mm) applications. The techniques presented here can be used for many other applications involving electrochemical cell designs.

The signal processing circuitry for wireless sensors is mostly based upon Complementary Metal Oxide Field Effect Transistor (CMOS) technologies.

In most cases, sensors are designed on separate dies and are then integrated with signal processing circuitry using bonding/assembly techniques to realize fully functional devices [6-7]. This leads to difficulty in miniaturization, increase in cost, and decrease in overall system performance and reliability [8]. CMOS technology itself provides excellent control and processing functions with extremely small footprint and power requirements [9]. Hence, a completely integrated electrochemical sensor as part of the CMOS platform itself can provide extreme miniaturization and cost reduction. Hence, the miniaturized sensors in this work are designed to be completely integrated with the CMOS platform designed for wireless sensing.

The top metal materials available in the CMOS process (e.g. Al, AlCu) are not suitable for electrochemical sensing for longevity and sensitivity for relevant analyte [10]. Hence, material optimization techniques have to be employed to create sensors with long term performance. Moreover, no rigorous design approach is available to design these sensors optimally at small size scales intended in this work. Typically, an empirical approach is used with some simple sensor geometries to provide large enough signal [10]. This approach can be suitable for some applications but is inefficient for optimization requirements of implantable miniaturized sensors.

In the next sections, we present a methodological approach towards optimizing the design of a fully integrated electrochemical sensor on CMOS compatible substrates. We will start with the design criteria, and then provide methods of material optimization, fabrication and design optimization. Finally, we present results to demonstrate the effectiveness of our technique.

2. Design Criteria

The underlying design criteria for our sensor are sensitivity and longevity for metabolic sensing applications. Glucose sensing for diabetic patients is an important relevant example. The design constraints include sensor size, biocompatibility and non-toxicity of materials, and operation time. In our typical application, the sensor area is restricted to a 500 μm by 500 μm square on a CMOS chip, due to other system level constraints. The sensor can be fabricated on the top metal layer having the circuit underneath. This allows for direct integration of the sensor with the CMOS circuitry without the need of any complex bonding mechanisms. This improves sensor reliability, minimizes system size and allows for microfabrication of the devices in a batch process.

The electrochemical sensor consists of three electrodes forming a complete electrical circuit through an external readout mechanism (e.g. a current meter) [11]. The electrodes are Working Electrode (WE), Reference Electrode (RE) and

Counter or Auxiliary Electrode (CE). For some designs, the CE and RE can be combined to result in a two electrode system. In this work, we focus our attention on three electrode designs because of the availability of a separate RE which can provide near-nernstian stability, thus minimizing sensor response variations. This also allows to decouple the design of RE and CE which allows for more degrees of optimization [11]. An integrated 3-electrode based electrochemical sensor is depicted in Fig. 1.

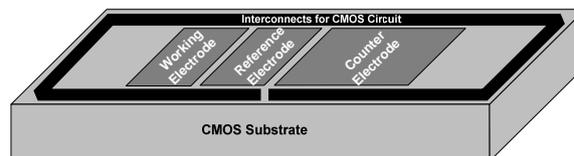


Fig. 1. CMOS Integrated Electrochemical Sensor.

For proper electrochemical operation, each of the sensor electrodes has to be designed for its particular role in the sensor application. For example, the sensing mechanism takes place on the WE. Hence, it needs to be properly designed and functionalized for sensing the analyte of interest. The CE is designed to complete the electrical circuit by allowing some electrochemical reaction which is equal but opposite to the reaction at the WE. The RE should be able to provide a near-nernstian behavior, hence always resulting in same reference potential in the same solution [11].

Optimization of sensor depends on material and geometry optimization. In terms of electrode materials, the WE should be extremely conductive and electroactive, even in thin films. The CE material should allow a wide set of reactions to balance the WE reaction current. The RE material should be inert and stable for long time [11]. In terms of geometry, the CE should be much larger than the WE to allow the WE reaction current to control the current in the readout circuit [11]. To minimize voltage drop through the solution, the RE should also be as close to the WE as possible [11]. RE should also be designed to have minimal effect on diffusion of species to the WE and CE.

All of the above mentioned considerations have to be considered in designing integrated electrochemical sensors. In the next sections, we will describe the optimization procedure for both the material and the geometry of the sensors.

3. Material Optimization

Selection of the electrode material is very important for the sensor design. The electrode materials are required to be very conductive and chemically stable for small-scale operation at extended life-time. At the same time, these materials should be electroactive and biocompatible. Noble

metals such as Pt, Au, Ir and their alloys have many favorable properties in this regard [12].

Both Au and Pt have been used for metabolic sensing applications [13]. For our applications, a test was conducted to verify the suitability of both metals for our applications. Hydrogen peroxide sensing forms the basis of many metabolic sensing applications involving oxidoreductase enzymes [14]. Hence, we used thin film (100 nm) planar electrodes, both of Pt and Au, for hydrogen peroxide sensing using Cyclic Voltammetry (CV) from 0 to 1 V vs. Ag/AgCl RE at scan rate of 0.01 V/seconds in high peroxide concentration (50 mM). It was found that thin film Pt (as well as bulk Pt electrode) can retain a stable interface for much longer time than Au (contrary to bulk Au electrode) during a continuous CV experiment in hydrogen peroxide solutions. High peroxide concentration (50 mM) was used for accelerated testing and to emulate possibly large peroxide builds up during sensor off time in real applications. The tests were repeated for multiple samples after different thin film fabrication methods (sputtering, ebeam) were used to fabricate the test samples. The results were similar for all cases.

The films after CV are shown in Fig. 2. The interface where the electrodes were immersed in the peroxide solution is clearly evident for Au electrode due to corrosion. However, for Pt, the material stays intact and the sensor response over time doesn't show any significant variations. This indicates that Pt thin films can endure this process much better than Au. For bulk electrodes, both Pt and Au showed sustainable performance. We believe that this is due to the formation of a surface layer of Au based materials (e.g. in oxidized states) which are porous and hence are not effective in stopping the process in thin films. This means that over long time and with peroxide accumulation, thin layers of Au can dissolve, hence reducing sensor lifetime and repeatability.

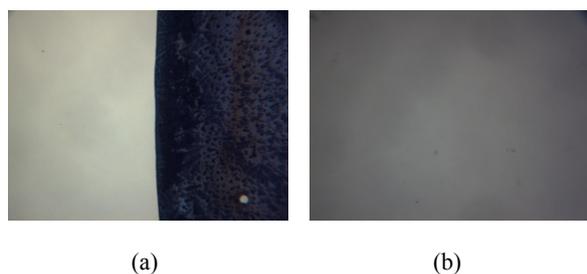
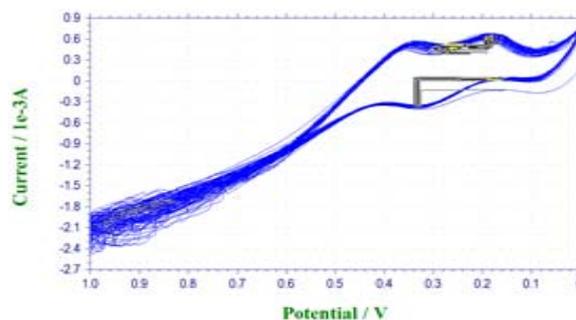
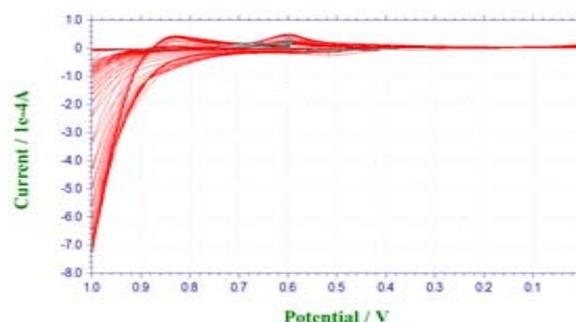


Fig. 2. Effect of Peroxide testing on WE materials (a) Au, (b) Pt.

The CV obtained during the electrode testing (Fig. 3) show a similar response where Au thin film (in contrast to Au thick film) electrodes 'corrode' in the solution (response dies down with time) while the Pt electrodes (both thick and thin film) don't corrode an appreciable amount (response doesn't die down).



(a) Thin Film Pt Electrode



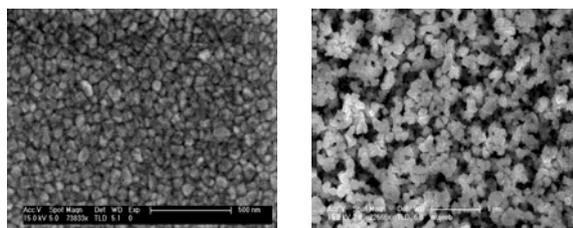
(b) Thin Film Au Electrode

Fig. 3. Voltamograms for Hydrogen Peroxide testing of electrode materials (a) Pt (b) Au.

In blood or other complex fluids, both Au and Pt can be poisoned by chloride ions and many other species (e.g. amino acids) due to surface adsorption. However, nanopatterned Pt has shown to have high stability against these blood agents [15]. Nonetheless, since these sensors are not used in direct contact with blood, but in interstitial fluid, this is a less critical problem [16]. For applications in blood, sensor electrodes will have to be coated with special materials for filtering (e.g. Nafion) [17].

Reference electrodes also play a critical role during electrochemical sensor operation. There are many different reference electrode materials which can provide stable voltage readings in solution to form stable and repeatable potential differences between electrodes for proper sensor operation [18]. For solid-state integrated operation, the Ag/AgCl electrode is a suitable option, especially since the Chloride ion concentration in body stays relatively consistent [18]. We fabricated such electrodes by depositing a thin film of Ag on the RE and using low-power chlorine plasma to convert the top layer in AgCl. SEM imaging of these layers confirmed the formation of crystalline structure which is a good indicator for AgCl formation. The resulting layers are shown in Fig. 4.

Although, the Ag/AgCl electrode can provide very stable performance, its formation needs extra fabrication steps and introduces a different material in the fabrication process. Also, formation of AgCl is a special process due to the surface conditioning requirements of the Ag electrodes.



(a) Ag (b) AgCl

Fig. 4. SEM of Sensor Electrodes.

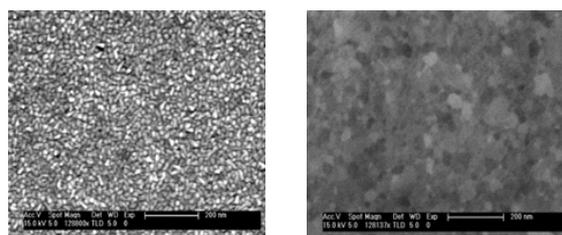
As Pt is already used for the other sensor electrodes, use of Pt based reference electrode can make the fabrication process much simpler and reliable. For the small scale sensors with reasonably small currents; Pt electrodes can act as quasi-reference electrodes. For amperometric measurements, such small variations of reference electrode are not a significant problem. Hence, bare noble metal (e.g. Pt) electrode can itself be used as a RE for some applications [18].

Since Pt interface potential is sensitive to pH and peroxide interference, it can't provide an extremely stable reference potential required for some applications. However, it has been shown that some noble metals covered with their oxide also act as pseudo-reference electrodes (e.g. Pd/PdOx, Ir/IrOx) [18]. Hence, coating Pt with a suitable insulating layer can perform as a stable RE. For example, a somewhat inert layer of surface oxide can be used to make a Pt/PtOx RE. Such Pt based reference electrodes can also be used in harsh environments for longer durations compared to Ag/AgCl based electrodes. Since Pt is a noble and very inert material, it is not easy to oxidize it even with strong oxidizers such as hydrogen peroxide. In this work, Pt oxidation was attempted using strong oxygen plasma as well as using strong acidic oxidizing agents (like sulfuric acid) at elevated electrochemical potentials. Oxygen Plasma exposure in Reactive Ion Etching systems showed some oxidizing effects on the Pt surface and the electron diffraction studies showed some Oxygen as part of the film. The films were heated for long time to release any oxygen physically adsorbed on the surface prior to such testing. However, it is difficult to confirm the chemical nature of such thin films reliably. Nonetheless, the resulting RE resulted in higher electrochemical stability suggesting that the film had become a better reference electrode material than bare Pt. SEM's of the films are shown in the Fig. 5.

4. Geometrical Optimization

To fulfill the sensor design constraints, some of geometrical optimization procedure is required. For large scale (macro) devices, this is not very significant, although still relevant, since adequate performance can be achieved using many different types of geometries.

However for small scale devices it is very important to study all the factors that can affect sensor performance. In this work, the designs were mainly based upon rectangular elements as the CMOS process layouts only allow rectangular designs. There are different possible designs that can fit within the allowed sensor region (a 500 um by 500 um rectangle). A combination of Finite Element Modeling (using COMSOL) and experimental verification was used to converge to the best possible sensor design. Some chosen designs (named by alphabets) are shown in Fig. 6. Here, the WE and CE material is Pt and the RE material is Ag (before Chlorination).



(a) Pt (b) PtOx

Fig. 5. SEM of Pt based RE materials.

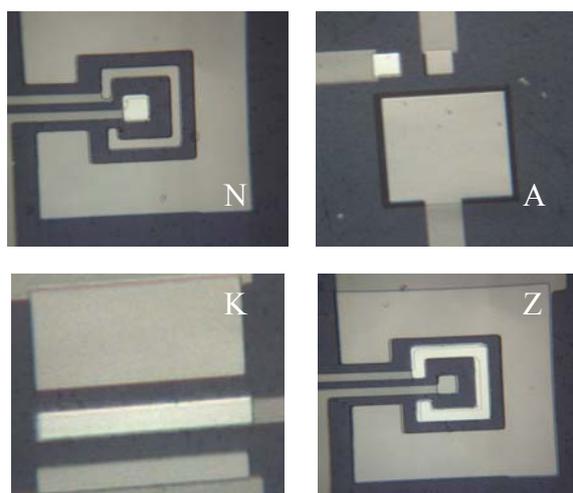


Fig. 6. Integrated Sensor Geometries.

The designs were tested experimentally to compare their performance to choose the best design. Deductions can be made from the best design to formulate the criterion for the optimized geometry as a starting point for other applications.

5. Fabrication

Sensors were fabricated on different CMOS compatible substrates (insulated Si, glass, CMOS dies). Sensors on insulated Si were used for prototyping to be able to optimize the designs

without the need of multiple CMOS runs. For CMOS, the top metal pad openings were used to define the electrode shapes for sensor design. Photolithography was used for defining electrode patterns on the different substrates. This was followed by evaporation of 10/100 nm of Ti/Pt layer and solvent liftoff. Another lithography step was used to define the RE, followed by evaporation of 200 nm of Ag followed by solvent liftoff. A low-power (10 mW) Chlorine Plasma in a Unaxis RIE system was used to form a thin layer of AgCl on top of the Ag film. A typical resulting sensor is shown in Fig. 7. In this case, the WE and CE are covered by Pt and the RE is covered by Ag/AgCl.

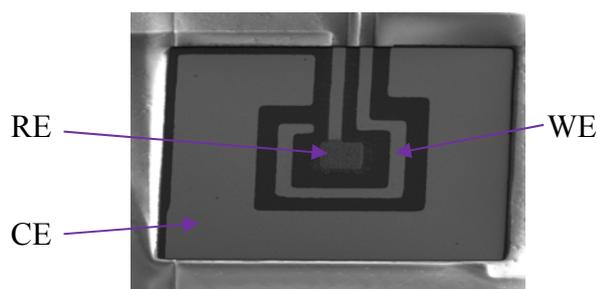


Fig. 7. Integrated Electrochemical Sensor.

6. Cleaning

The sensors were thoroughly rinsed with DI water before testing. Then, the sensors were connected to a CHI 7051D Potentiostat to be cleaned electrochemically before any further functionalization and testing. Cyclic Voltammetry scans were performed between -0.3 V to 1 V vs. Ag/AgCl electrode in dilute sulfuric acid solution (0.01M) until stable results were obtained [19]. This ensured that the exposed surfaces are electrochemically clean and reproducible.

7. Testing and Results

The prototype sensors were connected to a CH Instruments 7051D Potentiostat to make measurements. The sensing part was immersed in a solution inside a test beaker. The solution was spiked with different concentrations of test samples and the electrochemical data was measured (using different techniques including cyclic voltammetry, chronoamperometry, impedance spectroscopy, constant potential electrolysis and impedance-potential curves). For some experiments, this was done on a hot plate to get measurements at body temperature (37°C). Phosphate Buffered Saline (PBS, pH=7.4) solution was used as background solution.

Each sensor design was fabricated with both a Pt RE and Ag/AgCl RE as shown in Fig. 8.

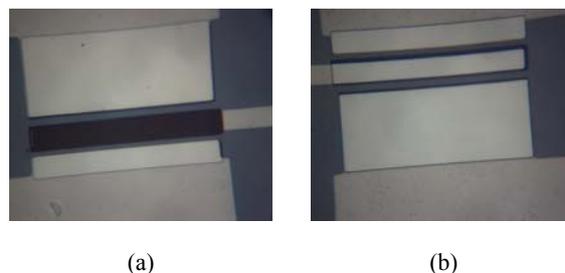


Fig. 8. (a) Design M w/Ag/AgCl RE
(b) Design M w/Pt RE.

The stability of the RE was tested first by measuring its potential relative to a commercial stable RE, which in our case was Ag/AgCl RE from CH instruments. Secondly, Cyclic Voltammetric measurements were performed using sensors utilizing either the Ag/AgCl RE or the Pt RE. Results indicated that Ag/AgCl RE proved more stable than Pt RE especially at higher reference potentials as seen in Fig. 9. This is due to interference from species reacting with Pt at such potentials, most notably hydrogen peroxide. However, it also shows that a Pt RE can still be used for less sensitive applications. Although, bare Ag showed a pretty stable response, peroxide interference had some effect on it. The formation of AgCl layer on top makes it more independent of conditions in test fluid. Also, since the chloride ion concentration in body remains pretty constant, the Ag/AgCl RE can be used without any special concentrated coatings (e.g. saturated KCl). After Chlorination, AgCl became quite stable and peroxide did not have any appreciable effect on it. Bare Pt showed more issues regarding stability and peroxide interference. Oxidation (PtOx) proved to increase stability and decrease peroxide interference effects as expected.

The results from the RE tests are summarized in Table 1. These results indicate that although the Ag/AgCl electrode is quite stable, the 'Pt/PtOx' electrode can be suitable for many applications where small voltage perturbations can be tolerated.

The sensor geometries can be compared based upon their performance for appropriate sensing applications. Hence, the geometries were compared using hydrogen peroxide testing to determine their sensitivity as it is the underlying sensing mechanism for most metabolic sensors employing oxidoreductase enzymes [14]. For a typical peroxide sensor, results of amperometric experiments at 0.6 V cell potential (vs. Ag/AgCl RE) are shown in Fig. 10.

Comparison of different geometries for sensor response was performed using such experiments. Both Ag/AgCl RE and Pt RE based geometries were compared. The comparison of maximum sensor currents at the 0.6 V potential between WE and RE (Ag/AgCl or Pt) using amperometry is shown in Fig. 11.

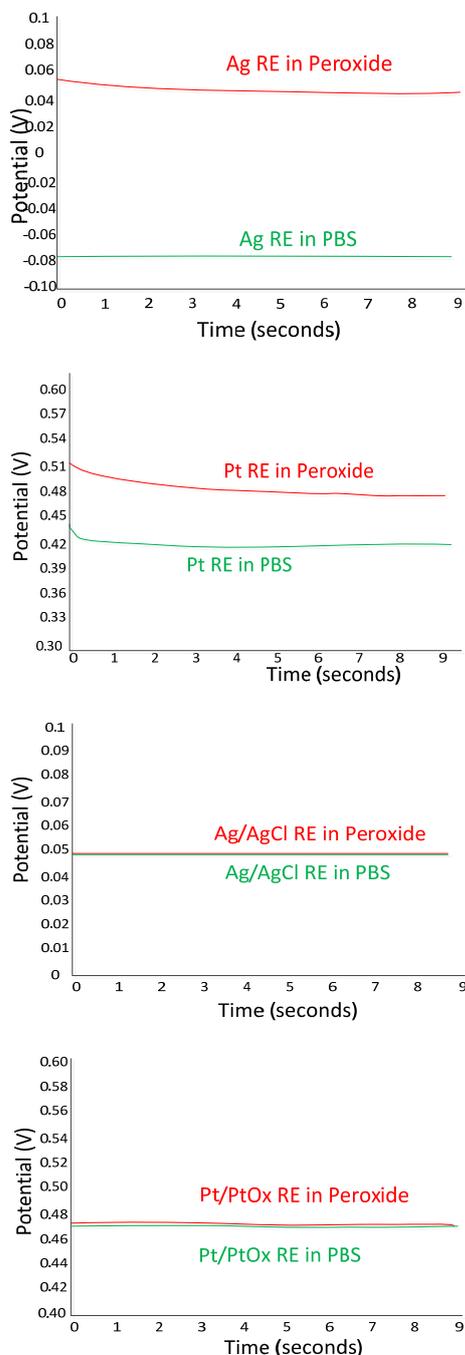


Fig. 9. Comparison between integrated RE Materials.

Table 1. Comparison of RE materials.

Electrode Material	Temporal Stability (voltage change)	Peroxide Interference (voltage change)
Ag	15 mV	120 mV
Pt	30 mV	60 mV
Ag/AgCl	5 mV	3 mV
Pt/PtOx	20 mV	10 mV

The sensors were tested using other methods as well to confirm these findings. Spectroscopic

techniques including Electrochemical Impedance spectroscopy and cell potential spectroscopy are very useful means for such confirmation [20]. These methods were used to confirm the results obtained using amperometric and voltammetric measurements as noted before. For the EIS experiments using the commercial Potentiostat, signal frequency was swept from 100 kHz to 0.1 mHz at a bias of 50 mV.

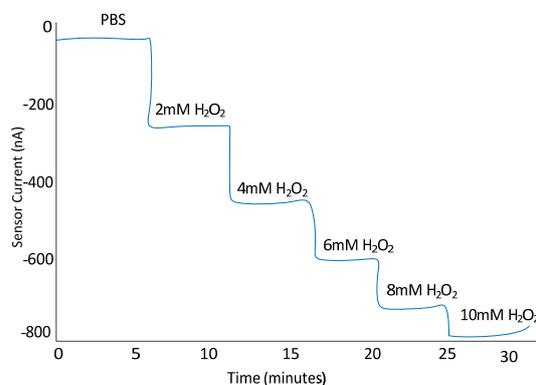


Fig. 10. Hydrogen Peroxide Sensing using integrated Sensors.

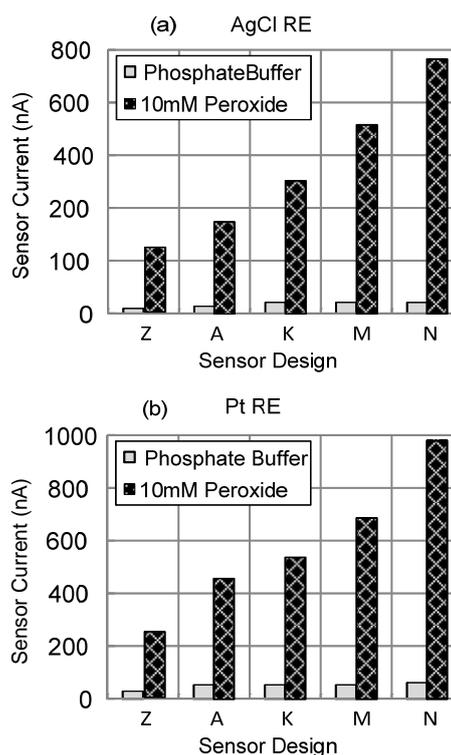


Fig. 11. Comparison of Sensor Geometries for Hydrogen Peroxide Sensing (a) Ag/AgCl RE (b) Pt RE.

The arrow indicates the direction of increasing frequency on the Nyquist plots. The results confirmed the same trend in electrochemical properties as shown in Fig. 12 (PBS) and Fig. 13 (10 mM Peroxide).

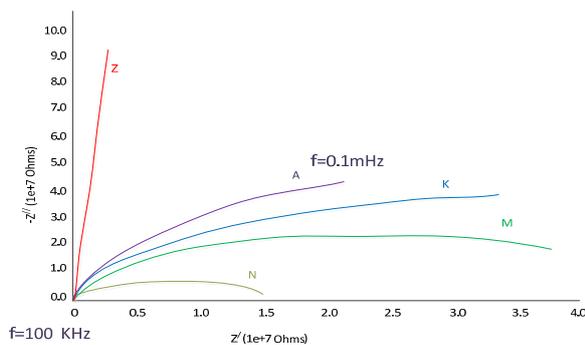


Fig. 12. Electrochemical Impedance of sensor geometries in PBS.

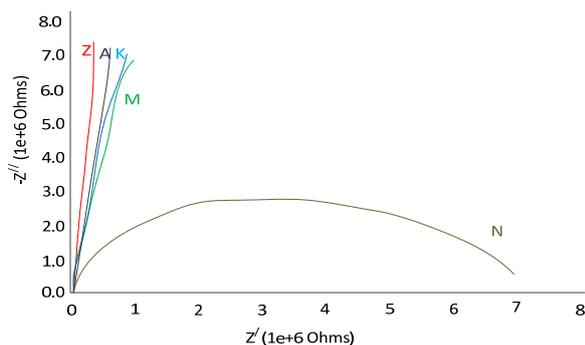


Fig. 13. Electrochemical Impedance of sensor geometries in 10 mM Peroxide.

The geometry with WE closest to both the CE and RE minimizes electrochemical impedance. This can be due to the easier diffusion of species between WE and CE during redox reactions. Also, sensors with Pt based RE provide more current than Ag/AgCl based RE. It is possible due to the thin nature of Pt RE compared to the Ag/AgCl RE as well as by some leakage currents in the Pt RE. This is also possibly due to the higher effective cell potential when Pt RE is used compared to the Ag/AgCl RE. This can be noted by the open circuit potential between the Pt electrode and the Ag/AgCl RE, as depicted earlier in Fig. 9.

Electrochemical Impedance spectroscopy results also demonstrated that the Pt RE based sensors have lower electrochemical impedance compared to the same geometry with Ag/AgCl RE. The same cell potential was used for both Pt and Ag/AgCl electrodes. This is in accordance with earlier results where Pt RE based sensors resulted in more current than Ag/AgCl RE based sensors. This is further illustrated by results shown in Fig. 14.

For the CMOS devices, amperometric tests were performed at 0.6 V vs. Pt RE to test the validity of results obtained using prototype devices. In this case, lower peroxide concentration was used to avoid damage to the underlying Al electrodes. Both Ag/AgCl and Pt were used as reference electrodes. The sensors were wire bonded to a chip carrier which was mounted on a PCB. The PCB was used to connect the sensor to an external Potentiostat (CHI

7051D). Small droplets were used to measure the response of CMOS sensors to PBS and peroxide solutions. The results for Pt RE based sensors are shown in Fig. 15.

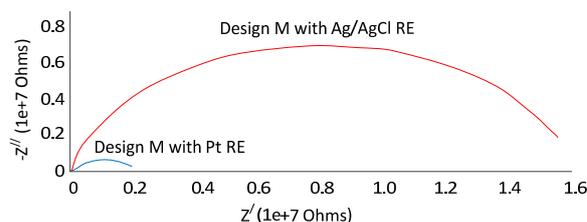


Fig. 14. Electrochemical Impedance of sensor with Ag/AgCl RE versus Pt RE.

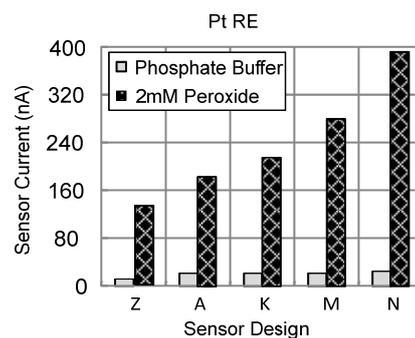


Fig. 15. Electrochemical response of CMOS sensors.

These results followed the same trend in sensor response as the prototype sensors. Again, Sensor N with concentric rectangles demonstrated highest sensitivity. The sensor electrodes didn't show any degradation over multiple tests done over few days for the peroxide concentrations used in this work. The sensors were tested after few weeks and demonstrated similar response, demonstrating the longevity of the solid state sensor interface.

These results indicate that a sensor design with more peripheral area minimizes the impedance between sensor electrodes and hence results in smaller overall impedance and higher signal. Also, the WE size can be increased at the expense of the RE as it results in better overall response (demonstrated by a comparison between design Z and design N).

To test the sensor performance for metabolic applications, these were functionalized using serum Albumin from Bovine and Glutaraldehyde as crosslinking agents for Glucose oxidase immobilization [21]. Glucose was sensed successfully using these functionalized sensors at 0.6 V vs. Pt RE. The sensors for glucose sensing followed the same trend as for peroxide sensing as the fundamental sensing process for glucose sensing is sensing the peroxide from enzymatic reactions happening on the functionalized electrodes. A typical response is shown in Fig. 16. In this case, the sensor response was tested in the physiological range (2-20 mM) of Glucose in PBS.

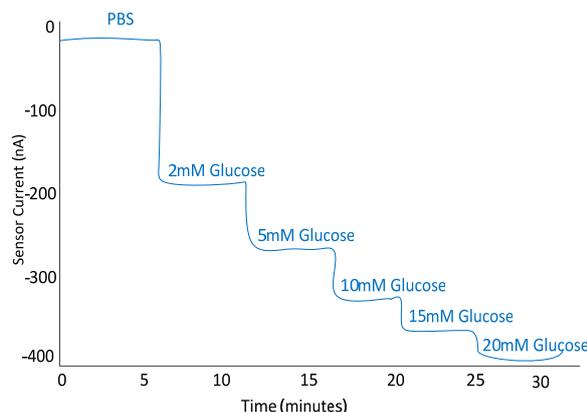


Fig. 16. Glucose sensing using integrated sensors.

This demonstrated that the electrode material and sensor design can be optimized to result in desired response of high output current (100's of nA) with the desired small footprint and in completely integrated form. These design techniques can be used for completely wireless and integrated systems to achieve high performance for real world applications [22].

It is important to emphasize that further enhancements are possible using high surface area electrodes rather than simple planar electrodes. Such electrodes can also be fabricated using CMOS compatible fabrication techniques [23]. This allows for further miniaturization of the sensor which can allow for size reduction in overall system. Alternatively, this can be used for sensing multiple analyte using multiple WE within the same sensor.

8. Conclusions

In this work, we demonstrated that miniaturized (sub-mm) electrochemical sensors can provide adequate performance suitable for integration on CMOS compatible substrates. We showed that design optimization (materials and geometry) can improve the performance of these sensors by manifolds. When operating at small size scale, such enhancements can be crucial as the overall current is quite small otherwise and noise effects can be quite challenging. We also demonstrated that at this small size scale, simple noble metals (e.g. Pt) based electrodes can be used as suitable reference electrode materials. This can eliminate the need of special materials (e.g. Ag) and special processing (e.g. Chlorination), thus simplifying overall fabrication process and reducing cost. Furthermore, we verified the operation of these sensors on actual CMOS substrates, using both hydrogen peroxide and glucose sensing examples. The results indicated that we can indeed get performance enhancement using geometrical optimization techniques described in this work.

Acknowledgments

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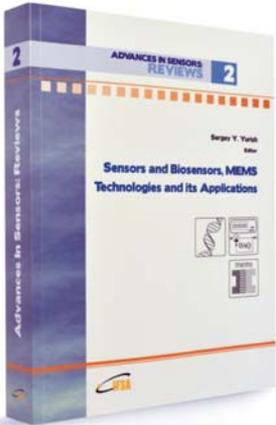
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