Tragbarer elektrochemischer Biosensor für nichtinvasive medizinische Anwendungen – Wearables für die Gesundheit –

Wearable electrochemical bio sensor for non invasive applications – Wearables for health –

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Kurzfassung

In diesem Paper wird die Entwicklung und Herstellung eines Biosensors auf flexiblen PET-Substraten beschrieben und die elektrochemische Bestimmung der Konzentration von Biomolekülen in Flüssigkeiten vorgestellt. Dabei zeigten sich nur kleine Abweichungen zwischen den Werten gemessen mit der traditionellen Silizium-basierten Sensorik und den Sensoren auf biegsamen PET-Substraten, auf welchen die Metallelektroden entweder mittels Nassätzung oder mit funktionellem Siebdruck hergestellt wurden.

Abstract

In this paper the development and production of flexible bio sensors on PET foil is described. Moreover the electrochemical measurement of bio molecules concentration in fluids by these sensors are presented. It is shown that there are only minor deviations between values measured by sensor made by traditional silicon based technology and those produced on flexible PET foils where the metal electrodes have been manufactured either by wet etching or by functional screen printing.

1 Introduction

Continuous monitoring of vital signs will become more important as the number of older patients increases. In light of this increase, the demand for devices that support and observe patients continues to grow. Therefore, it is important not only to treat people suffering from these diseases, but also to monitor changes in the health and well-being of healthy, older patients. This is especially critical in ambient assisted living and in rehabilitation. Examples include checking glucose levels for diabetes management, observing lactate levels for endurance training, analyzing pathogens for diseases, and therapeutic monitoring during patient treatment. Nonetheless, laboratory testing for determining the level of biomolecules in the body is often cost intensive. These costs can be reduced through the use of mobile electrochemical biosensors; however, most of these sensors require in vitro samples, which make continuous monitoring difficult. Therefore, there is an interest in developing non-invasive, wearable electrochemical biosensors that continuously measure biomolecules in sweat, tears, saliva, and interstitial fluid [1].

2 Reference sensor elements

Reference measurements were taken by using conventional silicon bio sensors [2] which are shown in Figure 1. These sensors have been fabricated in conventional micromechanics processing steps like homogeneous metal layer deposition (Au) by electroplating, lithography and wet / dry etching.

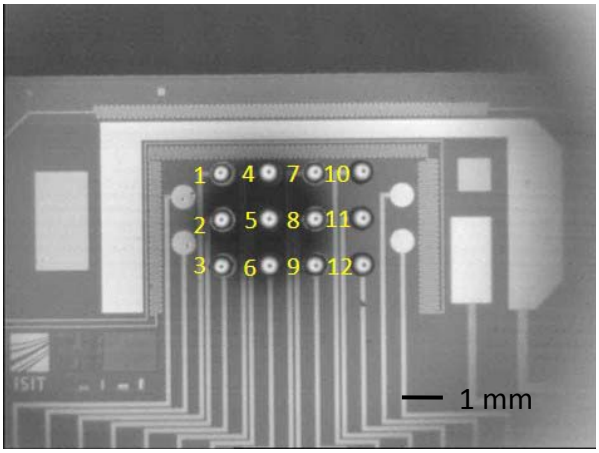

Figure 1 Microscopy of a silicon based bio sensor.

3 Flexible Sensor fabrication

Three different flexible sensors were produced and tested: Wet etched sensors from gold foils (Figure 2a), screen printed sensors using gold and silver/silver chloride inks (Figure 2b), and screen printed sensors using those metal inks along with a dielectric ink to passivate electrode tracks.

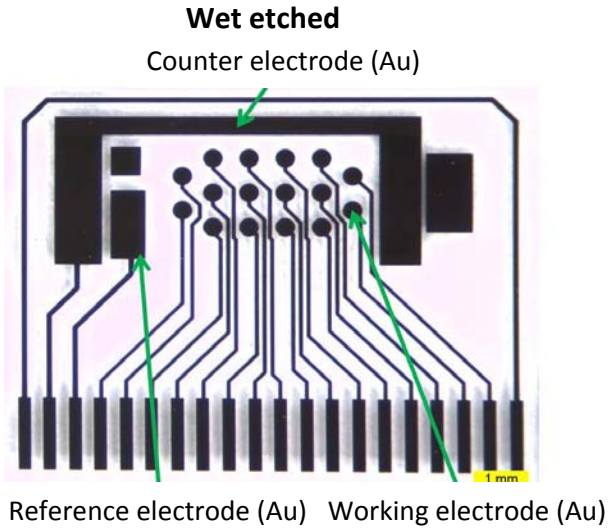

Figure 2a Microscopy of wet etched sensors.

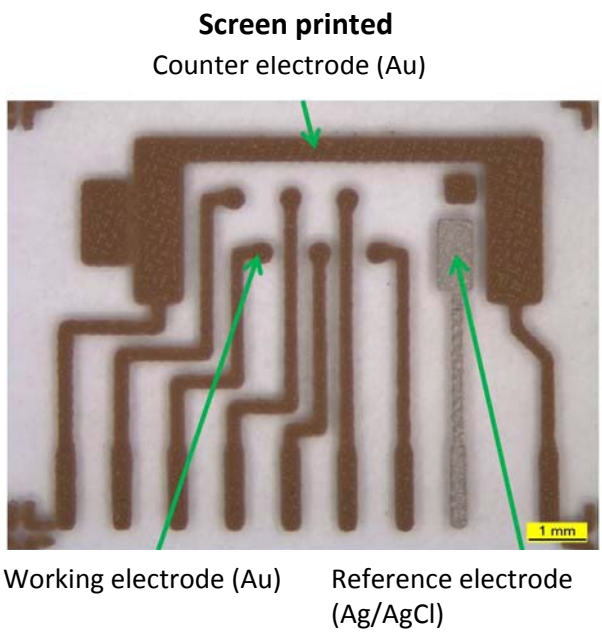

Figure 3b Microscopy of screen printed (no dielectric) sensors.

In an additional version of the screen printed sensors, shown in figure 2c, some carbon working electrodes were added. These sensors will be used for the combination of the immunosensor and an enzyme sensor principle in the future. Up to this point there have been no measurements done with these sensors.

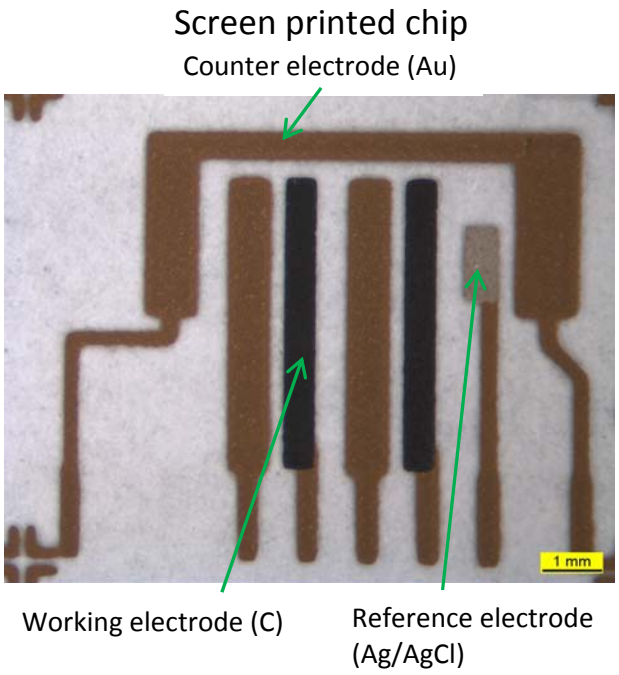

Figure 4c Microscopy of screen printed sensors with carbon, gold and silver-/silver chloride electrodes.

One of the best ways to integrate a biosensor in a wearable device such as a smart armband or bandage is to print biosensing materials on a flexible substrate like PET, in order to allow for the sensor to conform to the body. As shown in Figure 2a,b, wet etching and screen printing materials on PET is used to evaluate the feasibility of integrating multiple sensor electrodes on a flexible substrate. These materials were then tested for functionality in an immunoassay. A comparison of results from these immunoassays can be seen in Figure 3a/b, where the silicon chip serves as a reference for assay function.

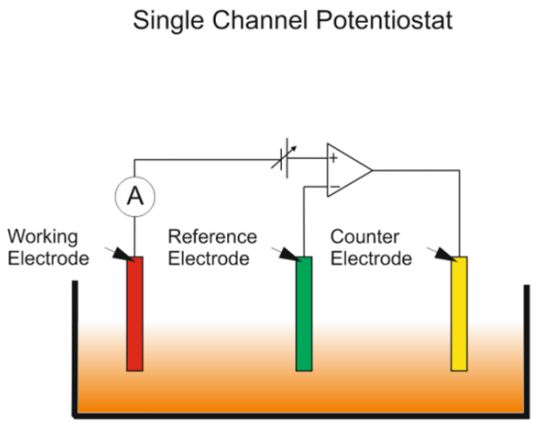

Figure 3a: Schematic of a single channel potentiostat

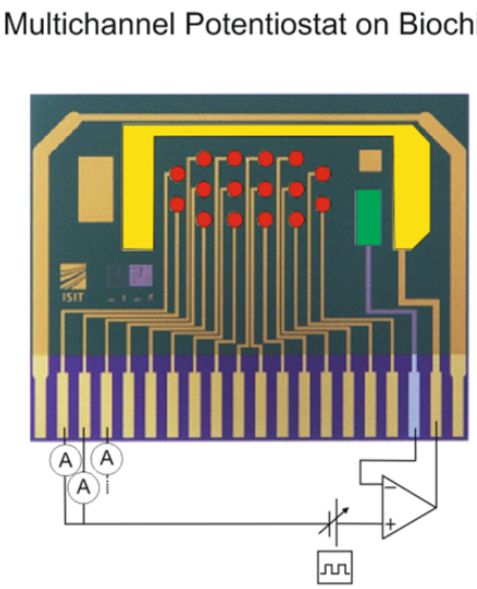

Figure 3b: Schematic of a multichannel potentiostat with corresponding electrode colors overlaid onto the biochip.

Measurements rely on redox cycling for amplification of the signal, in this case using 300 mV for oxidation and -250 mV for reduction, with the MCDDE program (Fraunhofer ISIT) used to control voltage inputs. Anode and cathode switching is done every 480 ms, denoting the cycle time. During a cycle there is a 120 ms sample time for recording, totaling four measurements per cycle.
Origin (OriginLab R) takes the data from MCDDE and records the current readings, with an example current reading shown in Figure 4.

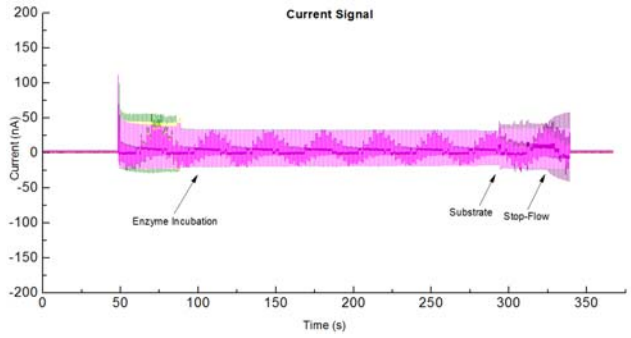

Figure 4: Typical current signal reading of a silicon biochip in an immunoassay, starting with incubation of the enzyme and followed by addition of substrate before stopping the flow for a reading. The different colors represent different working electrodes.

The example shows how current behaves during enzyme incubation, substrate addition, and stop-ow phases. Calculations are done during stop-flow, where no fluids are pumped over the chip.

The absolute value of the anode and cathode readings are then added together to create a graph, with an example shown in Figure 5.

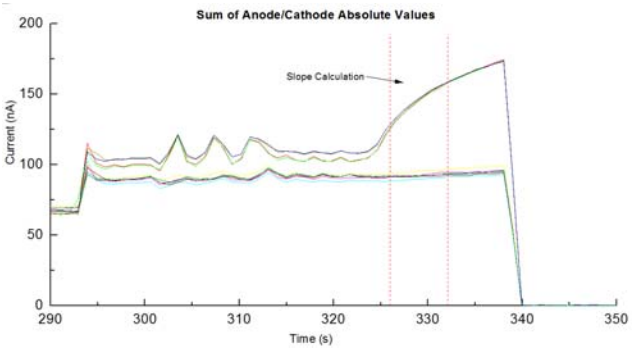

Figure 5: Sum of the absolute values of anode and cathode readings during the substrate and stop-flow phases. Slope values are calculated using linear regression within the dotted lines.

After an offset time of 2 seconds, a 6 second window is used to calculate slope values using linear regression. These slope values are then shown in a bar graph comparing different working electrodes, and thus detection of the analyte; these graphs can be seen as the results in Figures 6a-d.

4 Measurement Results

For the immunoassay tests, the wet etched and screen printed biosensors were spotted with positive control (Anti-Mouse-IgG, 50 µg/ml) and negative control (bovine serum albumin (BSA), 100 µg/ml) solutions of phosphate buffered saline (PBS), pH 7.4, followed by incubation. Amperometry was later conducted on the biosensors connected to a flow cell device, with the spotted silicon chips [2] serving as a comparison to the flexible biosensors. The sensor and device together act as a multichannel potentiostat, which is illustrated in Figure 3a/b. In figures 6a-d measurements of the four different manufactured biosensors are shown.

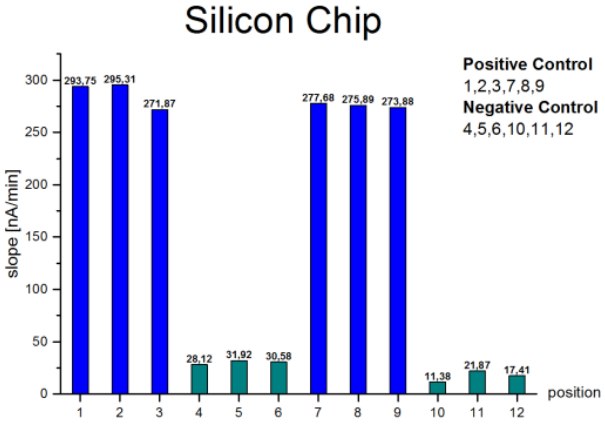

Figure 6a Measurement with Silicon chip.

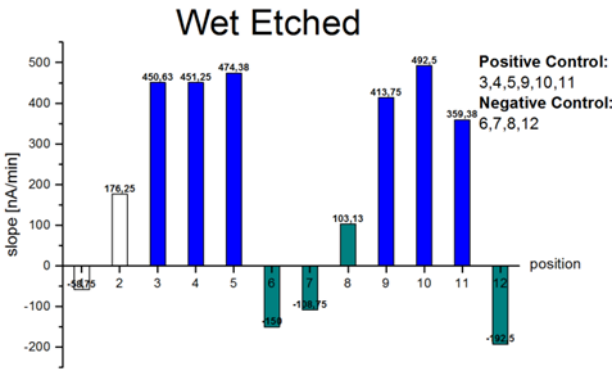

Figure 6b Measurement with PET chip and wet etched structures.

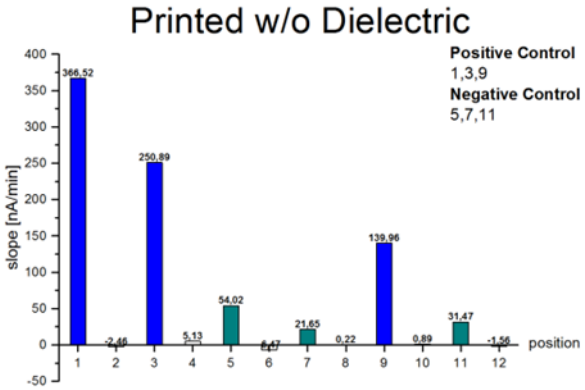

Figure 6c Measurement with PET chip and printed structures without dielectric.

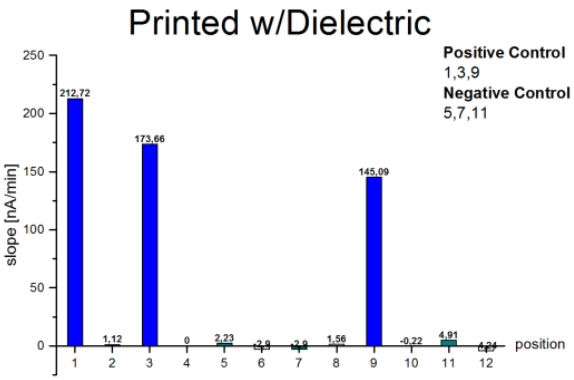

Figure 6d Measurement with PET chip and printed structures with dielectric.

Despite some small differences from the wet etched and screen printed chips, a signal showing the recognition of the positive control, with a weak or no signal from the negative control, demonstrates the proper functioning of the flexible chips.

3 Outlook

Given the results, the next step is to integrate wet etched or screen printed chips into wearables for use in glucose and lactate detection in diabetes monitoring and sports medicine respectively. Continued research in this field worthwhile due to positive market outlook.

4 References

[1] Bandodkar, Amay J., and Joseph Wang. “Non-invasive Wearable Electrochemical Sensors: A Review.” Trends in Biotechnology 32.7 (2014): 363-71. Web.

[2] Barth, Stefan, Lars Blohm, Simone Holz, Gundula Piechotta, Christina Dammers, Michael Kleines, Georg Melmer, Eric Nebling, Christiane Puttman, Joerg Albers, Alexander Kruttgen, and Jorg Nahring. “Rapid Detection of Different Human Anti-HCV Immunoglobulins on Electrical Biochips.” ANTI Antibody Technology Journal (2014): 23. Web.