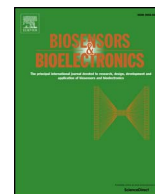




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## Multi-parametric rigid and flexible, low-cost, disposable sensing platforms for biomedical applications

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### ABSTRACT

The measurement of  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{H}^+$  is essential in medicine and plays an important role in the assessment of tissue ischemia. Microfabrication, inkjet- and screen-printing can be used for solid contact ion selective electrodes (ISE) realization; these, however, can be non-standardized, costly and time consuming processes. We present the realization of ISEs on post-processed electrodes fabricated via standardized printed circuit board (PCB) manufacturing techniques. *In vitro* results are presented from two rigid platforms (32 ISEs) for liquid sample dip-stick measurements and two flexible platforms (6 and 32 ISEs) for post-surgical intestinal tissue monitoring, each with a common reference electrode (RE). These are combined with optimized tetrapolar bioimpedance sensors for tissue ischemia detection. Both electroless and hard gold PCB finishes are examined. Apart from the electroless rigid platform, the rest demonstrated comparable and superior performance, with the pH sensors demonstrating the greatest deviation; the flexible hard gold platform achieved a sensitivity 4.6 mV/pH and 49.2 mV/pH greater than the electroless flexible and rigid platforms, respectively. The best overall performance was achieved with the hard gold flexible platform with sensitivities as large as 73.4 mV/pH, 56.3 mV/log [ $\text{Na}^+$ ], and 57.4 mV/log [ $\text{K}^+$ ] vs. custom REs on the same substrate. Simultaneous measurement of target analytes is demonstrated with test solutions and saliva samples. The results demonstrate superior performance to other PCB-based pH sensors and  $\text{Na}^+$  and  $\text{K}^+$  PCB-based sensors with comparable performance to potentiometric sensors fabricated with other techniques, paving the way towards mass-produced, low-cost, disposable, multi-parametric chemical sensing diagnostic platforms.

### 1. Introduction

The measurement of various ionic species is essential in biomedical applications where, for example, sensor-enabled surgical drains, catheters and implants with high accuracy, minimal drift, low cost and disposability are needed. Electrolyte homeostasis is vital for human health, as many metabolic processes and organ functions depend on it. Consequently, its disturbance can be detrimental and it is associated with increased morbidity, mortality and prolonged overall hospital stay. Tissue ischemia (i.e. insufficient tissue oxygenation) disturbs homeostasis and leads to changes in tissue pH, while the intracellular and extracellular concentrations of  $\text{K}^+$  and  $\text{Na}^+$  also change due to failure of the cell membrane pumps (Chung et al., 2014; Cosofret et al., 1995; Mir et al., 2014; Tahirbegi et al., 2013, 2014). Monitoring these ions can thus provide valuable insights into the state of tissues. In surgical intestinal anastomosis, one of the most challenging complications is anastomotic leakage (AL) (Millan et al., 2006; Nerstrom et al., 2016). Tissue oxygenation is essential for the healing of an anastomosis and thus plays a

dominant role in AL. Currently, ALs are diagnosed at a mean time of 12 days post-operatively (Chadi et al., 2016). Within 24 h post-operation, intramucosal pH of less than 7.28 has been reported in patients who went on to develop AL (Hirst et al., 2014; Millan et al., 2006).

Microfabrication techniques are used to pattern metal electrodes and deposit selective membranes onto rigid, flexible and stretchable substrates (Chung et al., 2014). However, these approaches can be costly since often these are not standardized processes readily available for mass production. Alternative techniques include screen-printing (Fay et al., 2011) and inkjet-printing (Komuro et al., 2013; Sjoberg et al., 2016). The latter is a maskless fabrication method with reduced ink waste. It is, however, mainly limited to research laboratories. The optimization of the printing parameters is a laborious process and, being a direct-write technique, it is not suitable for high-throughput batch-fabrication.

The realization of electrodes fabricated using standard, widely available commercial printed circuit board (PCB) technologies presents a simple, low-cost solution for the production of different sensors,

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where the potential for large-volume production allows economies of scale to significantly reduce the cost. In (Bozkurt and Lal, 2011) an implantable flexible PCB microelectrode array was presented for extracellular stimulation in invertebrates. The Cu structures were Au-plated either chemically (electroless or immersion plating) or electrochemically (electroplating). The latter resulted in greater surface roughness (hence a larger electroactive surface) and complete electrode Au-coating, as opposed to the former, where electrode side walls were left uncoated. To address this, the top passivation opening was made smaller than the electrode, such that the electrode sidewalls are not exposed. In (Kassanos et al., 2015), a flexible PCB-based tetrapolar bio-impedance sensor was presented with optimized geometry and electric field properties for monitoring the mucosa of the intestinal tract during induced ischemia in a porcine model.

The use of PCB electrodes for the realization of potentiometric sensors was examined in the work of (Moschou et al., 2015; Prodromakis et al., 2011; Trantidou et al., 2013). In (Prodromakis et al., 2011) Au-plated Cu electrodes (500  $\mu\text{m}$  in diameter) on rigid PCB substrates were coated by sputtering 150 nm  $\text{TiO}_2$ . This led to a sensitivity to  $\text{H}^+$  of  $\sim -22$  mV/pH. The same PCB electrode structure was used in (Trantidou et al., 2013) where a Parylene C film deposited on the PCB was selectively plasma-treated, leading to a sensitivity of  $-16.3$  mV/pH and drift rates of 2.5–20 mV/h. In (Moschou et al., 2015) rigid-PCB-based Ag/AgCl reference electrodes (RE) based on vias with diameters of 300  $\mu\text{m}$  to 1 mm were presented. These achieved a drift less than 1 mV/20 days at pH 7. Together with a PCB-based pH sensor utilizing a 200 nm thick indium tin oxide (ITO) layer, a sensitivity of  $-45.8$  mV/pH was demonstrated.

In this paper, the realization of ISEs on post-processed electrodes fabricated using standardized PCB manufacturing is presented. Results are presented from two rigid 34-electrode arrays intended as dip stick measurement platforms for liquid sample analysis (e.g. urine, blood, saliva), each using different Au-plating. The work was then extended to two flexible PCBs. One is intended to be wrapped as a ring to be placed within the intestinal lumen to monitor tissue ischemia following surgical anastomosis. The second platform is a miniaturized patch for the same application. To the author's knowledge, this is the first example of such multi-parametric sensing systems with rigid or flexible PCB technologies. This paper presents a number of novelties: (i) demonstration of  $\text{K}^+$  and  $\text{Na}^+$  PCB-based potentiometric sensors, (ii) PCB-based pH sensors with improved performance, (iii) examination of both electroless and electrochemical PCB Au-plating on sensing performance, (iv) incorporation of custom REs on the same substrate with the ISEs forming multi-electrode multi-parametric potentiometric sensing arrays, (v) use of commercially fabricated flexible PCBs and (vi) incorporation on the substrate of an optimized tetrapolar bioimpedance tissue ischemia sensor (Kassanos et al., 2015), allowing multi-modal sensing.

## 2. Materials and methods

### 2.1. Design and fabrication of PCBs

All electrode arrays were designed using Altium Designer version 15.1.16 (Altium, Ltd.). Commercial PCB manufacturers (Eurocircuits, Mechelen, Belgium and P.W. Circuits, Leicester, UK) were used for the fabrication of the electrode platforms of Fig. 1. Rigid FR-4 (flame retardant), flexible polyimide (PI) substrates, liquid photoimageable solder masks (LPSM), PI coverlays, electroless nickel immersion gold (ENIG) and hard gold finishes were used for the various designs, as summarized in Table 1. A discussion on materials used in PCB manufacturing can be found in the Supplementary information (SI, Section S1, Table S1, S2).

### 2.2. Electrode post-processing and functionalization

All experiments are performed using an Ivium potentiostat/galvanostat (Ivium Technologies, Netherlands). Cyclic voltammetry,

including electrochemical electrode cleaning (using a solution of 50 mM  $\text{H}_2\text{SO}_4$  and a sweep potential between  $-0.4$  and  $0.6$  V at 100 mV/s) and electropolymerisation, were performed in three-electrode mode using a commercial Ag/AgCl BASI RE and a Pt counter electrode in a  $\text{N}_2$  purged solution. Double-distilled (DI) water was used for the preparation of all solutions. Further details on electrode post-processing and functionalization can be found in the SI (Section S2).

Microscope images were obtained with a Keyence VHX-2000 microscope. Atomic force microscopy (AFM) images were obtained with an Asylum Research (Ca, USA) MFP-3D Classic AFM instrument. Images of  $10 \mu\text{m} \times 10 \mu\text{m}$  electrode areas were acquired using the tapping mode and PPP-NCHR probes. The obtained AFM images were analysed using the WSxM1 software (Horcas et al., 2007).

## 3. Results

### 3.1. Rigid and flexible electrode platform designs

The four platforms developed are summarized in Table 1. The electrodes of Fig. 1(a), (b) and (c) were of 1 mm diameter, however, the exposed area of the electrode was defined by a 500  $\mu\text{m}$  diameter solder mask opening similar to (Bozkurt and Lal, 2011), to avoid the exposure of partially plated Cu or Ni from the edges and sidewalls of the electrodes. Platforms 1 and 2 were laid out to form a  $\sim 10$  cm long dip stick and are simply the rigid equivalents of Platform 3 (Fig. 1(c)). The minimum track width and distance between tracks was 150  $\mu\text{m}$ , and  $45^\circ$  angles were used in the interconnects (Fig. 1(a)(i), (b)(i) and (c)(i)).

Platform 3 is intended to be wrapped in a ring to be placed within the intestinal tract lumen in the vicinity of an anastomosis in order to monitor tissue ischemia as an early marker for anastomotic leakage (Hirst et al., 2014; Kassanos et al., 2015), as illustrated in Fig. S1(a), (b). This was designed such that it fits a large array of electrodes within a 2.5 cm diameter suitable to fit within the small intestine and to allow mapping of the target analytes along the anastomosis. The electronics based on a 32:1 multiplexer (Analog Devices ADG732) also constrained the electrode number. The additional 2 electrodes are used as a common reference electrode and as a biasing electrode for differential measurements (similar to (Hammond et al., 2004)).

Platform 4 is a small flexible patch (Fig. 1(d)) for small tissue area assessment, with 100  $\mu\text{m}$  minimum track width and distance between tracks. As evident from the CAD (computer aided design) layout of Fig. 1(d)(ii), rounded corners and teardrop connections to the bonding pads located on the bottom side of the board were also used. These allow greater flexibility and durability of the tracks. The electrodes are 400  $\mu\text{m}$  in diameter and the active region of the electrode is defined by a 300  $\mu\text{m}$  opening in the coverlay. There are 6 electrodes for the development two pH,  $\text{Na}^+$  and  $\text{K}^+$  sensors, one extra bias electrode and a large parallelogram electrode (400  $\mu\text{m} \times 1.35$  mm copper structure with a coverlay opening defining the RE area of 300  $\mu\text{m} \times 1.3$  mm) to serve as a common RE. This device is intended as a miniature multi-parametric sensing patch that can be interrogated by a dedicated application specific integrated circuit (ASIC), which is currently being designed, as in Fig. S1(c).

In all platforms, a tetrapolar bio-impedance sensor (Kassanos et al., 2015) optimized for tissue ischemia monitoring in the gastrointestinal tract is also incorporated. In Platform 3 the additional bio-impedance sensor is based on the design of (Ivorra et al., 2003). The combination of ionic measurements with electrical bioimpedance allows their corroboration, as tissue impedance changes are related to ischemia.

In all platforms, more than one electrode is allocated for each analyte. In Platform 3, this allows assessing ionic concentrations over large tissue areas. In all platforms, it also provides averaging and redundancy, i.e. having additional sensors if one fails and a way to minimize false positives/negatives.

It is evident from the images of Fig. 1(a), (b) and (c), that the electrode surface is rough and that there are scratch-marks on the

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