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Nanostructured electrodes for biocompatible CMOS integrated circuits

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ABSTRACT

This paper reports on the adaptation of standard complementary metal oxide semiconductor (CMOS) integrated circuit (IC) technology for biocompatibility, enabling a low-cost solution for drug discovery pharmacology, neural interface systems, cell-based biosensors and electrophysiology. The basis for the process is the anodisation of IC aluminium electrodes to form nanoporous alumina. The porous alumina was electrochemically thinned to reduce the alumina electrode impedance. For applications where a porous electrode surface is either preferred or acceptable, we demonstrated that porosity can be manipulated at room temperature by modifying the anodising electrolyte to include up to 40% polyethylene glycol and reducing the phosphoric acid concentration from 4% (w/v) to 1%. For applications requiring a planar microelectrode surface, a noble metal was electrodeposited into the pores of the alumina film. Limited success was achieved with a pH 7 platinum and pH 5 gold cyanide bath but good results were demonstrated with a pH 0.5 gold chloride bath which produced planar biocompatible electrodes. A further reduction in impedance was produced by deposition of platinum-black, which may be a necessary additional step for demanding applications such as neuronal recording. During this work a capability for real-time electrochemical impedance spectroscopy (EIS) was developed to study anodisation, barrier oxide thinning, oxide breakdown and electrodeposition processes. To study the pore morphology, focused ion beam (FIB) was employed to produce cross-sectional cuts of the IC features which were inspected by SEM with an 'In-lens' detector.

The anodisation process and the optional electrodeposition steps require only simple bench equipment operated at room temperature and is therefore a viable route for manufacturing low-cost biocompatible electrodes from standard CMOS ICs.

1. Introduction

The concept of using standard complementary metal oxide semiconductor (CMOS) integrated circuit (IC) technology for biological sensors is appealing due its ubiquity and low cost. Potential markets for such sensors include drug discovery pharmacology, neural interface systems, cell-based biosensors and electrophysiology research tools [1]. Unfortunately biological environments are often damaging to IC components—the semiconductor industry spent decades developing passivation and packaging technologies to keep electronic components separate from hostile external environments. In principle, electrodes can be formed by opening the IC passivation to form windows onto the aluminium conductors below, this being standard practice where bondpads are formed to allow off-chip connection via bondwires. However, a pivotal issue has been the difficulty in exposing the standard aluminium metal to biological media. Our previous work has confirmed that aluminium electrodes corrode in cell culture media [2]. For research purposes additional microfabrication can be undertaken in a cleanroom environment to deposit biocompatible platinum electrodes on top of the passivation but this may make products prohibitively expensive if scaled to high volume sensor production. In ref. [2] we demonstrated the feasibility of low-cost post-processing that can convert the electrochemically active aluminium to biocompatible nanoporous alumina by anodisation. It was demonstrated that the electrical potential and currents required for this process were compatible with CMOS technologies. We proposed that several potential electrode designs were feasible: the porous alumina could be used directly as the electrode or the pores could be filled with a noble metal to form an electrochemically stable and biocompatible planar surface. This paper shows how the electrical characteristics of a porous alumina electrode can be optimised by thinning the alumina barrier oxide that underlies the porous layer. We study

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the anodisation of the CMOS aluminium alloy and show how this is different from anodisation of pure aluminium substrates.

As presented in ref. [3], it may be desirable to modify the surface porosity for cell-based porous alumina electrodes to improve adhesion. For this previous work, a phosphoric acid anodising electrolyte was selected to enable flexible one-step anodisation at voltages between 20 V and 120 V resulting in inter-pore distances up to ~300 nm. This was achieved at room temperature, without burning and avoiding high current densities that are incompatible with the CMOS implementation. Electropolishing [4] and two-step anodisation processes [5] are not practical with the CMOS metallisation due to the layer's limited thickness of ~1 μm. The phosphoric acid electrolyte had been demonstrated to be biocompatible, enabling good cell vitality and cell-substrate adhesion. The work had therefore established that the surface chemistry resulting from the anodisation in phosphoric acid was suited to this application: surfaces produced using other anodisation electrolytes such as oxalic and sulphuric acids remain less well characterised with respect to cell culture. Lower porosities can also be achieved by using oxalic or sulphuric electrolytes, but anodising at voltages up to 120 V requires the temperature to be lower than room temperature to avoid burning and high current density [6]. This would require cooling apparatus that does not fit well with our objective of developing a low-cost manufacturing process. We have therefore extended the work of Chen et al. [7] on pore size manipulation using polyethylene glycol (PEG) by changing their 15 °C experiment condition to 21 °C. This same technique also enables lower anodising voltages to be used (i.e. voltages that are more readily implemented in CMOS) for a given porosity. Additionally, we present a novel method of measuring the electrode impedance in real time during anodisation and electrodeposition.

2. Experimental methods

The overall process investigated was to convert aluminium electrodes which corrode in cell culture media to bio-inert porous alumina by anodisation, then reduce the impedance by thinning the alumina barrier oxide. For some applications such as neuronal recording, a low impedance electrode is required to minimise Johnson noise. Therefore, to further reduce impedance or to provide a planar electrode surface, filling the pores with a noble metal was studied. To reduce cost and avoid difficulties with analysis of microelectrodes (typically 700 μm^2), preliminary experiments were performed on coated glass coverslips with metal layers that matched the metallisation of CMOS ICs. Later experiments were performed using CMOS ICs with an array of 48 planar microelectrodes.

2.1. Coverslip fabrication

The relevant CMOS metal layers were reproduced on 22 mm × 32 mm glass substrates, coated (Teer Coatings, UK) to represent the same CMOS metallisation as the ICs (austriamicrosystems AG, 0.8 μm process). This comprised ~40 nm of titanium followed by ~960 nm of aluminium alloy (Al–1.0 wt%Si–0.5 wt%Cu). The glass coverslip substrate performed a similar role to the interlayer dielectric (i.e. the insulator that separates metal tracks) of the ICs. For the evaluation of the influence of Si and Cu alloying elements on the vertical orientation of the nanopores, coverslips to be used as controls were similarly coated but with pure aluminium (99.9 wt%) instead of the alloy.

2.2. IC fabrication

Multiple electrode array (MEA) ICs were fabricated by austriamicrosystems AG, Germany, supplied in 48-lead ceramic dual-in-line packages (DIP) with removable die-cavity lids. These evaluation ICs were passive devices with no transistors: an array of 48 electrode pads, each 30 μm diameter and pitched 190 μm apart, was connected directly to the pins of the ceramic package (Fig. 1). Glass chambers were bonded to the top of the ceramic package and the bondwires isolated from the medium in the chamber by encapsulation using Silastic® 9161 (Dow Corning, UK) elastomer.

2.3. Anodisation

Unless otherwise stated, anodisation was performed at 30 V or 60 V using a 0.4 M (4%, w/v) phosphoric acid electrolyte at 21 °C. Anodisation at 60 V in 0.3 M oxalic acid electrolyte at 15 °C was used in the evaluation of pore structure (anodisation times are discussed in Section 2.6). Anodisation was performed by holding the coverslip in a miniature crocodile clip and submerging approximately 2 cm^2 of its length into the electrolyte. Porosity manipulation experiments were performed using coverslips in 0.05–0.4 M (0.5–4%) phosphoric electrolyte with 375 mM–2.0 M (15–80%, w/v) of PEG-400 (Sigma–Aldrich, UK) at 21 °C. Porosity was measured via image analysis using the open-source ImageJ software [8]. Platinum counter electrodes were used for all experiments: a 4 cm^2 mesh electrode for coverslips or 1 cm^2 plate electrode for ICs.

2.4. Stand-alone impedance spectroscopy

Measurements were taken at open circuit potential (OCP) and room temperature between 0.01 Hz and 10^4 Hz which has been shown to be sufficient to characterise porous alumina [9,10]. The electrochemical impedance spectroscopy (EIS) was performed

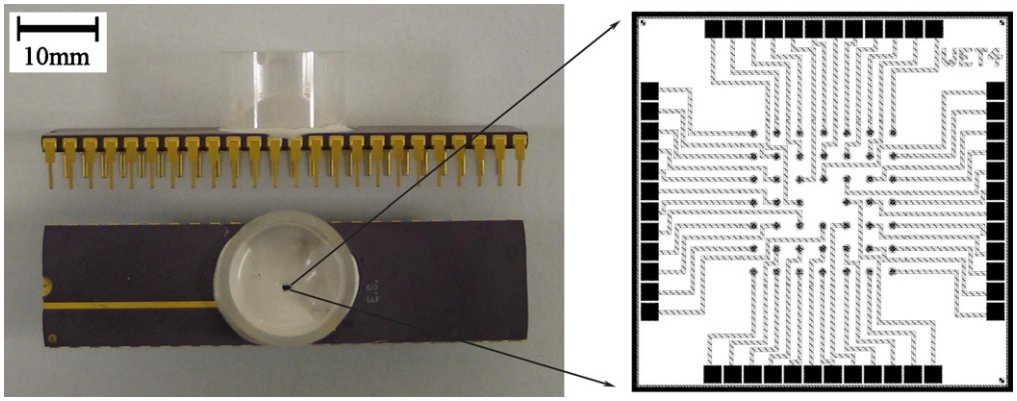

Fig. 1. An assembled CMOS device and schematic of the electrode array. Each of the 48 electrodes is connected directly to a pin of the ceramic package. The square IC has 3.2 mm sides.