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The development of scalable sensor arrays using standard CMOS technology

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Abstract

This paper describes an approach to developing MOSFET-based scalable sensor arrays in an unmodified standard CMOS process. The multiplexed design can be used as either a single-ended or differential circuit to make potentiometric measurements in each cell of the array. The FET-based sensors employ a floating gate electrode structure and use the nitride passivation layer as a pH-sensitive membrane. An implementation of a single-chip 2×2 array fabricated in an unmodified commercial 0.35 μm CMOS process is presented. All signal acquisition is performed in-situ and all readout circuitry is located on-chip. On return from the foundry, the devices are exposed to ultraviolet light to eliminate any difference in threshold voltage. The circuit provides a sufficient linear range that allows the FET devices to operate as pH sensors in the array. A double layer of SU-8 photoresist is used to provide both a biocompatible and waterproof package for the chip. The biocompatibility of the chip surface is investigated using a well-established cell line.

Keywords: Sensor; Array; CMOS; ISFET; Cell culture; In-vitro

1. Introduction

There is considerable interest in developing solid-state-based sensors for integration with medical diagnostic and analytical devices [1]. In the past few years, there has been a tremendous amount of effort to develop non-invasive tools for in-vitro monitoring of cell physiology [2,3]. By using in-vitro, cell cultures can be screened for functional activity to provide statistically significant data relating to the biochemical and biophysical reactions of therapeutic drugs and substances. This screening-based methodology has the potential to benefit a large area of biomedical and biotechnological applications, ranging from basic research to various fields of pharmacological analysis.

In this paper, we present an approach for fabricating MOSFET-based scalable sensor arrays in an unmodified standard CMOS process. The arrays can perform both temporal and high-resolution spatial measurements on an analyte. The basis of the design is a multiplexing circuit that allows each cell in the array to make a potentiometric measurement, either with a conventional silver/silver chloride (Ag/AgCl) reference electrode or by using a differential technique. The complete circuit is implemented on a single-chip using standard library components. The post-processing used to encapsulate the unpackaged chips is also described. Furthermore, an investigation of the biocompatibility of the chip surface is conducted using a Baby Hamster Kidney 21 Clone 13 (BHK21 C13) cell culture.

2. Sensor arrays

2.1. MOSFET-based sensors

In a CMOS process, a polysilicon gate electrode is used to define the self-aligned source and drain regions of a MOSFET. A standard ion selective FET (ISFET) only has an insulator in its gate region, which is in direct contact with the analyte. Therefore, it is necessary to change the design structure of the conventional ISFET so that it can be fabricated in an unmodified CMOS process. Bausells et al. [4] have demonstrated the principle by presenting a pH-sensitive ISFET. The polysilicon gate is connected to the metal layers in the process to form a floating electrode (Fig. 1). The CMOS passivation layer is used as the insulator in contact with the analyte. For most processes, this layer is typically silicon ni-

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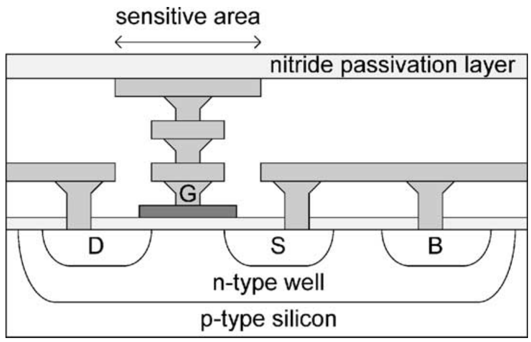

Fig. 1. Cross-section through a MOSFET-based sensor.

tride and/or silicon oxynitride, which gives a sub-Nernstian, but linear ψ_o/pH response. This fabrication principle can be used to develop a scalable sensor array with an unmodified CMOS process.

2.2. Electrochemical cells

A complete integrated ISFET-based sensor system can be created by using a differential ISFET and ion-insensitive FET pair—biased by a common pseudo reference electrode (PRE) [5]. In principle, the ion-insensitive FET (also called a reference FET or REFET) can be formed by depositing a polymer membrane on the sensitive area of an ISFET to prevent the analyte from reaching the nitride passivation layer [6]. The PRE can be created by evaporating gold on to a standard bond pad. However, there are a number of well-known issues with the performance of ion-insensitive FETs [7]. We are currently investigating the use of different ionophores to form the ion-insensitive FET.

Consequently, the components aforementioned can be integrated into a sensor interface circuit similar to that presented by Palán et al. [8] to form an electrochemical cell. The circuit uses an instrumentation amplifier to make a differential potentiometric measurement between the FET devices, which are electrically identically devices (Fig. 2). Furthermore, this circuit has the option to be used in a single-ended (or non-differential) configuration by making measurements with the ISFET and a conventional reference electrode.

The differential operating principle of the circuit can be demonstrated by considering when $v_G = 0$ V. If the ISFET is operated in the non-saturated region, then v_{S1} can be derived as:

$$v_{S1} = |V_T| + \frac{i_{D1}}{\beta i_{D2} R_{SD}} + \frac{i_{D2} R_{SD}}{2} \quad (1)$$

where β is the transconductance parameter of the ISFET. If the variables (excluding V_T) in (1) are constant, then the drain current i_{D1} and the source-drain voltage $v_{S1,D1}$ are fixed. Therefore, v_{S1} is directly proportional to a change in pH of the analyte, represented by a change in the threshold voltage of the ISFET.

A similar equation can be derived for v_{S2}. Hence, if the ion-insensitive FET is electrically identical to the ISFET but is not sensitive to the analyte, then its threshold voltage will remain the same when there is a change in pH. Thus, v_{S2} will not change and a differential potentiometric measurement between v_{S1} and v_{S2} can be made by the instrumentation amplifier to establish the change in pH of the analyte.

2.3. Single column of cells

An $n \times n$ array is designed by considering a single column of n electrochemical half-cells (Fig. 3). The configuration uses a source-and-drain follower circuit to maintain a constant source-drain voltage v_{SD} for the ISFET in the enabled row. The current source (which provides a constant drain current i_{D1}) and sink are designed as a cascode current mirror circuit to maximise output resistance and thus provide a constant current over a wide range of voltages.

A Kelvin four-terminal multiplexing configuration is used to isolate the measurement of v_S from the current source i_D. Each electrochemical half-cell consists of an ISFET plus two switches S1 and S2. A p-channel transistor is chosen as the ISFET because this has better noise performance at low frequencies than an n-channel transistor [9]. S1 is designed as a transmission gate so that any value of v_S within the

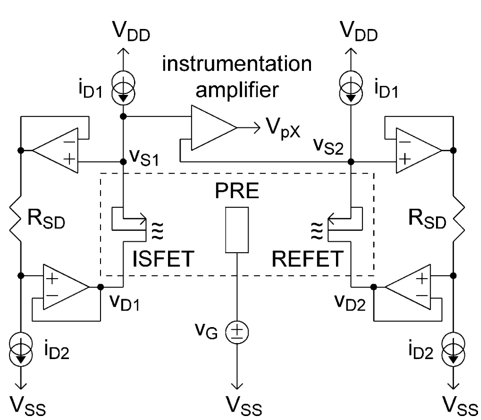

Fig. 2. Schematic of a single electrochemical cell.

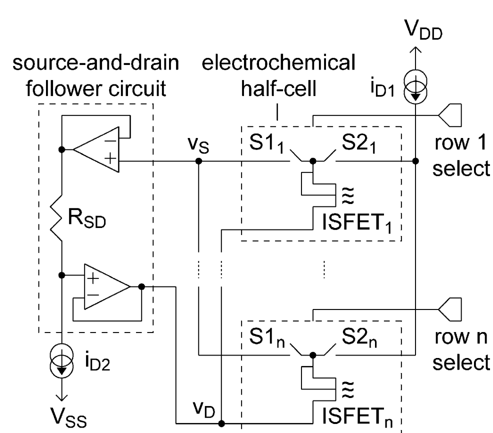

Fig. 3. Schematic of a column of n electrochemical half-cells.