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Miniaturized CMOS-based multi-sensor platform for analytics and diagnostics

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Introduction

Today, bacteria, viruses and specific tumor types are detected with very precise, very large, complex and expensive measurement systems that can only be operated by trained specialists [1]. Other applications, such as biosynthesis in bioreactors or organ-on-chips to reduce animal testing in drug development, use a variety of localized sensors with low spatial resolution for continuous measurement of different parameters [2]. In addition, each individual sensor requires specific external measurement peripherals for data processing. The integration of multiple sensor modalities and measurement principles in a miniaturized sensor array chip will help to process more and more parameters and larger amounts of data in an intelligent, resource-saving and cost-optimized manner.

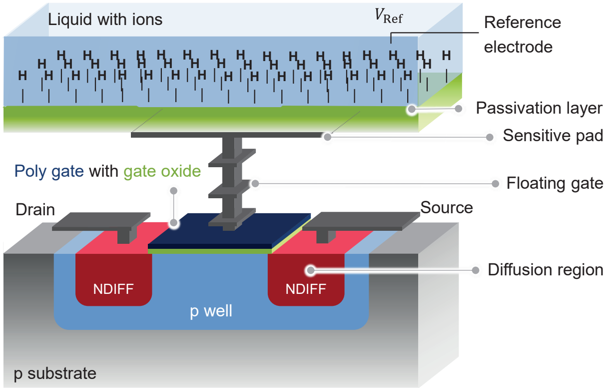

Fig. 1: CMOS ISFET with standard passivation as ion-sensitive layer, extended gate electrode for signal conversion and the MOSFET underneath

Materials and Methods

For this purpose, an integrated multi-sensor platform in CMOS technology was developed, which makes it possible to measure pH value, light and temperature on a microelectronic sensor chip. The core element of sensor design is the CMOS ISFET shown in Fig. 1. The ISFET in CMOS technology differs from the ISFET in a customized process in the design of the gate terminal. It is equivalent to an extended gate electrode (floating gate) in the stack structure of the CMOS process and is connected to the passivation layer, which is sensitive to hydrogen ions (H^+). The adsorption or release of H^+ changes the gate potential, which changes the current flow between source and drain. Accordingly, an electrical signal change proportional to the H^+ ions bound to the surface can be measured. ISFETs in a standard CMOS process can be developed and manufactured more cost-effectively than in a customizable special process. However, this also has several challenges: Firstly, the standard passivation as an ion-sensitive layer evokes a reduced sensitivity regarding the maximum slope according to Nernst of 59 mV/pH at 25°C and an increased signal drift. Furthermore, operating point shifts of the ISFETs and a loss in the conversion of

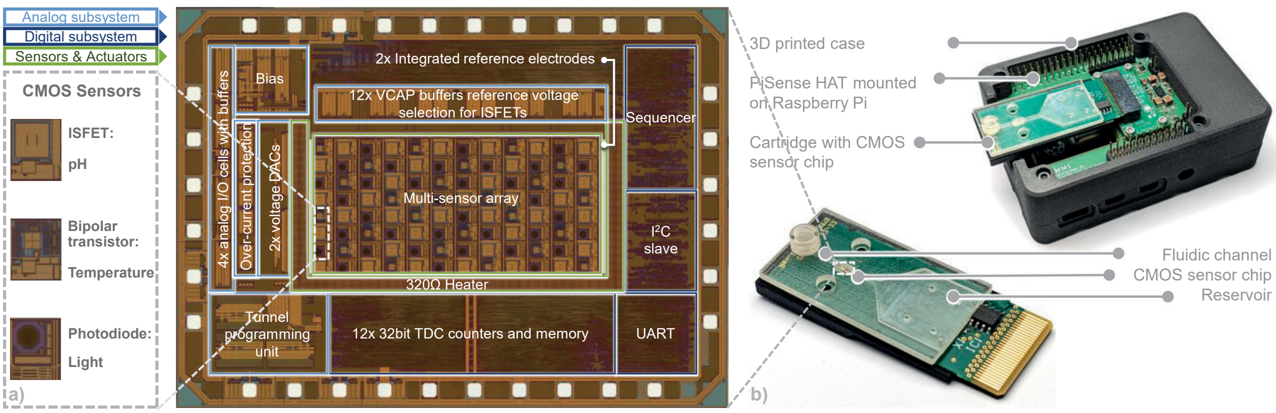

Fig. 2: a) 4.9 mm x 3.5 mm multi-sensor array chip with 36 ISFET pH sensors, 24 temperature sensors and 36 photodiode light sensors; b) mounted and wire-bonded chip with chemically inert encapsulation on a PCB (bottom) and miniaturized Raspberry Pi-based measurement system in a 3D-printed package (top).

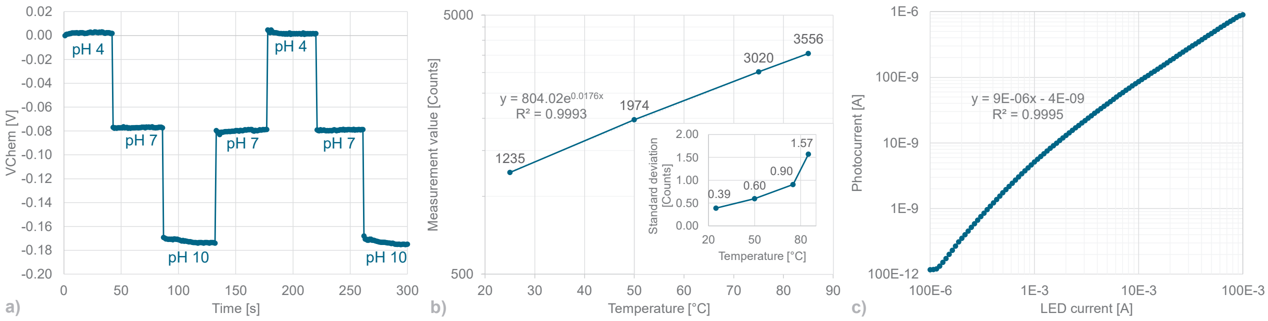

Fig. 3: Signal values averaged over the CMOS multi-sensor array a) of the pH value over time, b) over the temperature with standard deviation and c) of the light sensor photocurrent measurement range over the LED current.

the chemical signal into an electrical signal result from the stack structure and production steps of the CMOS process. To counter this, we implemented sensor and circuit design solutions that use the standard process of CMOS technology. For example, trapped charges at the gate terminal of the transistor can be removed by an integrated tunnel programming circuit. In addition, design aspects and size ratios between the gate electrode and MOSFET determine the strength of the signal attenuation, which has been optimized for maximum possible signal coupling and transmission. Fig. 2 a) shows the developed complex 4.9 mm x 3.5 mm mixed-signal ASIC with a 2.6 mm x 1.2 mm multi-sensor array. It contains 36 ISFET pH sensors, 24 temperature sensors and 36 light sensors (photodiodes). In addition to the goal of developing highly sensitive sensors in a cost-optimized standard CMOS process, circuit solutions have been implemented that enable simplified ISFET operating point programming and automated sensor calibration. The sensor ASIC provides an integrated data digitization with TDCs. The chip can be programmed, and the digitized sensor signals can be read out via a standardized I²C interface. For handling liquid media, a packaging concept was developed in which the chip is bonded to a 54 mm x 22 mm PCB and its electrical contacts are wire-bonded and insulated with a chemically inert potting compound (Fig. 2 b) bottom). The integration of a large number of functions in the sensor ASIC enables the measurement peripherals to be reduced to a minimum, which means that a small, inexpensive Raspberry Pi-based measurement setup (Fig. 2 b) top) with PiSense HAT is sufficient.

Results and Discussion

Fig. 3 a) presents the averaged voltage curve of the 36 ISFETs as a result of the pH change over time with a pH sensitivity of 30 mV/pH, a pH resolution of 0.01 pH (1σ) and a pH drift of 1.8 mV/h. In terms of pH resolution and drift, the ISFETs of the developed CMOS sensor array are up to 10 and 1,400 times better than comparable CMOS ISFET chips in standard CMOS technology according to the state-of-the-art shown in Tab. 1 [3].

Tab. 1: Comparison of the developed ISFET with ISFETs in standard CMOS technology according to the state-of-the-art [3]

Performance	CMOS ISFET [3]	This work
Sensitivity [mV/pH]	20 - 42	30 - 53
Resolution [pH]	0.013 - 0.1	0.002 - 0.01
Drift [mV/h]	90 - 2520	1 - 3

Fig. 3 b) shows the averaged signal values and the standard deviation over the temperature in the range of 25°C - 85°C with a resolution of 0.09°C (1σ) and a very good R^2 of 0.9993. The light sensor has a measuring range of 6 decades (Fig. 3 c) Photocurrent resolution min.: 384 fA (1σ)). It shows high linearity with a very good R^2 of 0.9995. The array structure of the developed CMOS sensor chip enables a spatial resolution for the measurement of substance gradients or for the detection of different analytes. In the future, applications such as point-of-care diagnostics for the detection of pathogens as well as continuous multi-parameter measurement in bioreactors and organ-on-chips should benefit from the multi-sensor platform, e.g. through AI-supported feature extraction.

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