A Capacitively-Coupled CMOS-MEA with 4225 Recording Sites and 1024 Stimulation Sites

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Abstract
A CMOS-based MEA with 4225 recording sites and 1024 stimulation sites is used to achieve high spatiotemporal resolution in in-vitro neural tissue interfacing experiments. Active area is 1 mm × 1 mm or 2 mm × 2 mm, respectively. A thin high-k dielectric serves as sensor interface between solid-state chip and biology.

1. Introduction
During the last decade, CMOS-based MEAs [1-6] have attracted huge attention, since they promise increased spatiotemporal resolution in extracellular interfacing with neural tissue and cultivated neural networks compared to their classical passive counterparts.

Different approaches have been published concerning the interfacing technique as such, namely to use noble metal electrodes [2-4, 6] or purely capacitive recording / stimulation sites utilizing a high-k dielectric covering the respective interfacing electrodes [1, 5]. Moreover, also different readout techniques are in use, focusing on entire area imaging [1, 2, 5] or high spatial selectability concerning the positions in space to be monitored [3, 6].

In this paper, we present a CMOS chip using a purely capacitive recording/stimulation approach aiming for full chip or selected (entire) area neural tissue activity imaging.

2. Methods and System Setup
A schematic cross section of the extended CMOS process used, a photo of the chip surface, and an assembled chip are shown in Fig. 1.

We use a 6 metal standard 1.8 V 180 nm CMOS process with 3.3 V devices for analog and I/O purposes. A thin TiN electrode covered by a 30 nm Ti-Zr high-k oxide [7] is then fabricated on top of the CMOS wafer. The recording electrodes are connected to the gates of related sensor transistors.

The layout of the various metal layers used for the electrical interconnects on the chip is configured such that these layers also provide an efficient light shield for the active CMOS devices in the silicon substrate, allowing operation of the chips under illumination or in combination with light-based stimulation of the biological content.

The chips provide 4225 recording sites and 1024 stimulation sites, recording site diameter is approximately 8 μm, recording site pitch is 16 μm (design A) or 32 μm (design B). The stimulation sites have a far larger area and are arranged in between the recording sites as shown in the chip surface photo in Fig. 1b).

The chips are assembled on a 5.5 cm x 5.5 cm carrier PCB (Fig. 1c)) which also provides the electrical contacts to the reader unit (Fig. 2). That unit consists of further gain stages, A/D converts the signals, and further processes the sampled signals. The output is connected to a standard PC workstation equipped with custom data-management software.
3. Design Issues

In Figs. 4 and 5 the concepts of stimulation and recording circuitry are depicted. Each stimulation site can be connected to three different stimulation signals (whereas in practice frequently one of the related signal lines is held at GND potential), that can be defined by software and are generated by the chip operating unit, or left floating. For that purpose a 2048 bit signal (2 bit for each stimulation site, cf. Fig. 4) is serially transmitted to the chip and stored in a related shift register which meanders through the entire array. For each stimulation site a simple decoder circuit controls switches operated as 1-to-4 multiplexer. In the transistor level realization, the decoding functionality is directly realized by the transmission gate arrangement used as switches. The stimulation circuitry can handle signals with 3.3 V peak-to-peak amplitude.

The basic recording technique is schematically sketched in Fig. 5. The recording electrodes are directly capacitively coupled to one recording transistor per site and sense the local variation of the electric potential in the electrolyte near the electrode. The induced voltage variation on the gate of sensor transistors causes a variation in their drain-to-source current similar as in [1, 5].

Every 200 ns a column of 65 transistors, which share a common source connected to the column line, is activated by lowering the column voltage by the column select circuit. Every transistor of the array has its drain terminal connected to a corresponding row line, so that the 65 drain currents of the active column are fed out separately to the off-chip acquisition unit. Transistors of non-active columns do not conduct any current so that they do not contribute to the current of the row lines. The acquisition unit converts the current signals into voltage signals, removes transistor operating-point related offsets, digitizes and eventually transmits the data to the PC.

The gates of the recording transistors are biased (not shown in the figure for simplicity) with the biasing branch being in a high-ohmic state during regular recording operation. For this reason a second device operated as switch is implemented within each sensing site. After having assigned a voltage to all gates of the recording devices by closing these switches, they are opened and the recording gate nodes become sensitive to potential changes in the electrolyte. The opened switches formally modify the transfer function of the recording sites into a high-pass filter function. However, the time constant is far below the minimum frequency of all signals of interest.
The maximum acquisition full frame rate of 77 kHz allows consideration of frequency components above 30 kHz. Of course, the operating frequency can also be scaled down resulting in a reduced noise floor. Imaging of only a portion of the entire array allows for further SNR improvement.

Last but not least it should be mentioned that the system also provides the possibility to calibrate each one of the 4225 sensor sites.

4. Measured Results

Fig. 6 shows exemplary measurements of spontaneous activity of a guinea pig retina measured by a chip with and without digital post processing (low-pass filtering): a signal-to-noise ratio of approximately 10 V/V is obtained.

Further exemplary results from guinea pig retina are shown in Fig. 7. There, a chip with 16 µm recording site pitch and 32 µm stimulation site pitch is used. The position of the recording sites depicted in rectangles in the different plots is counted from the left side and from the top of the array. Extracellular voltage traces are plotted for nine neighbouring recording sites. After an electrical stimulus, which is also captured by the sensors and is responsible for the first negative peak visible in every trace, a passive tissue response is recorded on all electrodes. For stimulation three columns of stimulation sites are used at the right border of the chip. Stimulus induced neural activity is detected by the subset of four electrodes underneath a retinal neuron (top-right plots). A blanking circuit, typical solution for commercial available MEAs based on metal electrodes [8], is not needed.

Further details with emphasis on biological aspects are provided elsewhere [9].

5. Summary

In conclusion, a CMOS-based MEA with 4225 capacitively coupled recording sites and 1024 capacitively coupled stimulation sites has been demonstrated. Measurements with biological contents reveal proper functionality.

References


Figure 7: Neural activity measured from a guinea pig retina at nine adjacent positions. Chip with 16 µm recording site pitch and 32 µm stimulation site pitch. The position of the recording sites depicted in rectangles in the different plots is counted from the left side and from the top. The activity is triggered by electrical stimulation using 3 columns of stimulation sites at the right border of the chip. A sawtooth pulse with 1 V amplitude, 500 ms rising edge, and 100 µs falling edge is used. Stimulus induced neural activity is visible in the top-right pixels.

Acknowledgement
Support and funding of this project by the German Ministry of Education and Research and Projektträger Jülich is gratefully acknowledged, reference 0315636A.