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Design of a CMOS-Based Multichannel Integrated Biosensor Chip for Bioelectronic Interface with Neurons

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Abstract — **In this paper we present the design and prototyping of a 24-channel mixed signal full-customized CMOS integrated biosensor chip for *in vitro* extracellular recording of neural signals. Design and implementation of hierarchical modules including microelectrode electrophysiological sensors, analog signal buffers, high gain amplifier and control/interface units are presented in detail. The prototype chip was fabricated by MOSIS with AMI C5 0.5 µm, double poly, triple metal layer CMOS technology. The electroless gold plating process is used to replace the aluminum material obtained from the standard CMOS process with biocompatible metal gold in the planner microelectrode array sensors to prevent cell poisoning and undesirable electrochemical corrosion. The biosensor chip provides a satisfactory signal-to-noise ratio for neural signals with amplitudes and frequencies within the range of 600µV – 2mV and 100 Hz to 10KHz, respectively.**

I. Introduction

THE planar microelectrode array (pMEA) is an important tool for non-invasive recording in the fields of neuroscience and biosensing. It can be used for extra-cellular measurement of the induced voltage on an electrode underneath a cell upon the occurrence of an action potential. With the principle of capacitive coupling, the sensed electrode signal amplitudes typically range between 100 µV and 1mV, depending on the cell type. With increasing cell-electrode distance or upon less direct cell-electrode contact, signal amplitudes may become arbitrarily small. Thus, neural signal conditioning and processing microelectronics units are necessary to integrate with the pMEA sensor for achievement of best measurement performance in noise and power dissipation. The processing circuitry, which can access the addressed electrode sensing-site, buffers and amplifies the neural signals and performs analog-digital conversion for digital processing or RF transmission of the neural signals, is a common technique to precondition and postprocess the neural signal sensed by pMEA [1, 2]. Introducing fully customized ASIC into the microelectrode array substrate provides an efficient technique for on-chip preliminary neural signal conditioning and processing, which establishes the possibility of creating the biosensor system on chip (SoC) with a large number of sensing-sites for simultaneous measurement without introducing significant noise from the signal conditioning and processing circuitry [3]. Integration and packaging of the microelectrode array with analog and digital signal processing and control circuitry into a lightweight, low power dissipation and low noise ASIC is highly desirable for neurophysiological applications [4].

In this research work, we have developed a fully customized biosensor chip for sensing the propagation of action potentials. With the paralleled multiple sub-circuits, this prototype multi-site planar microelectrode array biosensor integrates multiple sensing sites, analog neural signal buffers and high gain amplifiers on the same substrate. The electroless gold plating post-CMOS processing and packaging techniques applied to the standard CMOS biosensor chip improves the biocompatibility and stability in the aqueous cell culture environment. To interface the biosensor chip with the PC system, a Motorola ColdFire MCF5307 microcontroller based electronic system was setup to serve as the interface between the biosensor chip and the computer system, which implements the functions of A/D conversion, biosensor chip control signal generation, digital signal processing and data/command communication between the biosensor chip and the client PC using the Matlab/Simulink platform.

II. Biosensor System Architecture

Fig. 1 depicts the biosensor chip architecture and the functional blocks of the biosensor system setup. The

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integrated sensor array consists of four major blocks: 24 (4 × 6) microelectrode array sensor pixels, 24 parallel analog signal processing channels repeated with each electrode sensor contact, 24-to-1 analog multiplexer and digital control/interface circuits. Spaced at uniform distance of 150μm (center-to-center), the 4 by 6 microelectrode array sensor pixels with the dimension of 60 μm × 60 μm are implemented by planar metal in this design, which sense the changes of internal cell action potentials using capacitive coupling. Connected to each of the microelectrode array sensors, the addressable analog signal processing channels buffer and amplify the neural signals taken directly from each sensor contact. Each analog channel consists of a two-stage preamplifier with a midband gain of 20dB via resistive feedback, a shared gain stage operational transconductance amplifier (OTA) with capacitive feedback configuration and the control circuitry. This design provides high input impedance in the first stage to prevent the undesired electrical affect on the microelectrode contacts. After being buffered, the 24 signals are time multiplexed by a 24-to-1 analog multiplexer to reduce the number of output leads. The analog multiplexer is controlled by 5-bit digital sequence, which periodically selects one of the 24 channels causing the signal from its sensor pixel to be placed on an output wire. The output is serial in nature, with the signal from only one microelectrode sensor contact appearing on the output wire at a time. An additional OTA based high gain output amplifier interfaces the output of the preamplifier buffer to an external pad of the biosensor chip. With the capacitive feedback network, this stage applies substantial gain (40-70dB) to the buffered neural signal before driving it out onto the output lead of the biosensor chip.

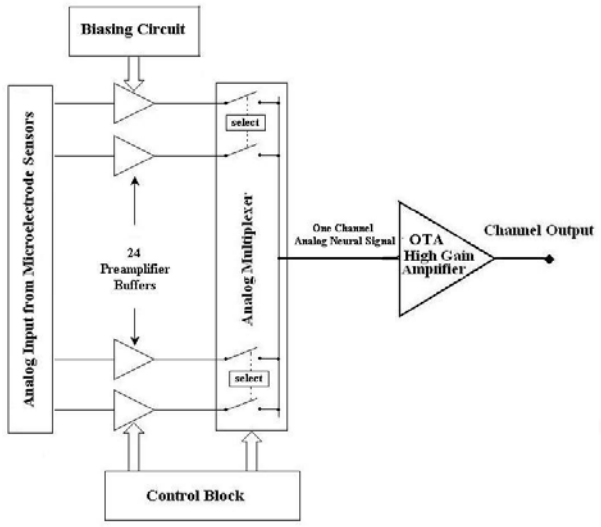

Fig. 1. Architecture of the biosensor chip.

III. Biosensor Building Blocks Design

A. Planar Metal Sensor Pixels

The layout of the planar metal sensor pixels are implemented with three layers of metals: metal 1, metal 2 and metal 3 with the top glass open, which is similar to the pad of the IC chip. This will leave the metal open to the external world and not covered by the glass after the IC fabrication. We shrink down the size of the individual planar metal sensor pixel compared with the pad of the IC chip to make the sensor pixels fit into the 1.5×1.5 mm^2 die size.

B. Preamplifier Buffers

The preamplifier buffers are mainly responsible for the circuit noise performance. Since the microelectrode sensors sense the action potential through capacitive coupling with the cell membrane, the parasitic capacitance presented to the sensors is important. Furthermore, the signals to be detected are typically of order 100 μV – 1mV peak to peak [5]. Therefore, on-chip buffering to produce high drive capability and low output impedance is very critical for the next stage neural signal amplification. The preamplifier buffers can also minimize the possible cross talk of neural signals and charge injection associated with MOS transistor switching. Charge injection could significantly disturb adjacent neural signals sensed by the microelectrode array sensors as charge is injected back into the neuron under test. Since multiplexing is used on-chip, the preamplifier buffers must be able to drive the subsequent amplifier at high-speed.

The preamplifier buffer is implemented with a two-stage amplifier configured with the closed-loop gain of 20dB via resistive feedback. The schematic diagram of the preamplifier buffer with the biasing circuitry is shown in Fig. 2. The two-stage amplifiers are extensively used in the various analog and mixed-signal circuits designs due to its simple structure and robustness [6].

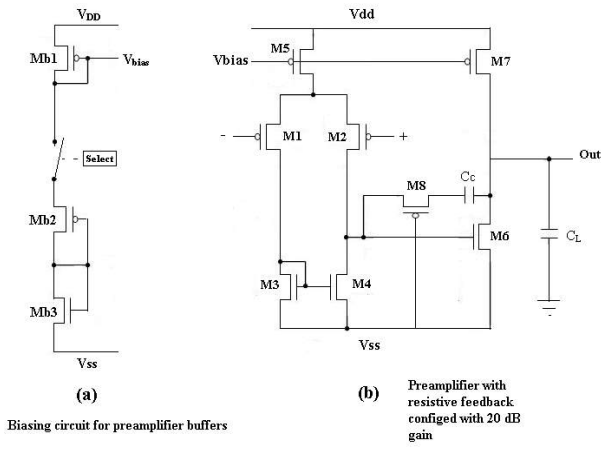

Fig. 2. Schematics of the preamplifiers.

C. Addressing Unit

The bio-sensor chip has a 5-bit address decoder to address the 24 analog signal channels in the sensor array, which implements the function of a 24-to-1 analog multiplexer. When a channel is addressed, its associated preamplifier buffer bias current is turned on activating the preamplifier. Also, when addressed, the output of the corresponding unity gain buffer is connected to the input of the high gain amplifier. The on-chip 24-to-1 analog multiplexer serves as site-selection circuits, which can be used to select site of the 4 by 6 contact arrays. Driving the 5-bit address decoder's input A0-A4 with an on-chip five-bit binary counter will enable the spatial sequencing of the sensing contacts. When the 5-bit binary counter begins with the all-low state, i.e., 00000, the first channel is addressed, and the sensed neural signal is placed on the output wire. As the counter sequences through the consecutive binary numbers from 00000 to 10111 (no state defined for binary number from 11000 to 11111), the adjacent contact will be addressed in sequence and the corresponding neural signal will be placed on the output wire. The multiplexing rate for the readout system is governed by the clock rate of the binary counter, which may vary for different application purposes. The clock of the 5-bit binary counter is generated by the on-chip ring oscillator.

D. Gain-stage Amplifier

The gain-stage amplifier will apply substantial gain to the buffered signal to bring it from the level of hundreds of micro-volts to a couple of volts. High gain, low noise, low power consumption and small area on chip are the primary concerns in designing the pre-amplifier buffer and gain-stage amplifier. When designing the gain-stage amplifier in this project, we considered the operational transconductance amplifier (OTA) with capacitive feedback configuration shown in Fig. 3. The ratio of the feedback capacitors C_1/C_2 determines the closed-loop gain of the OTA amplifier. The cascode topology is chosen at the output stage to boost the open loop gain of the OTA with the trade-off with the output swing. Since both of the two input nodes of the OTA amplifier are floating, the DC biasing path is necessary for both of the input nodes of the OTA amplifier without introducing the clock-controlled switched capacitor circuitry. The diode connected pMOS transistors are considered as large resistors for the DC biasing purpose as illustrated in Fig. 3(a). After the gain-stage amplification, the external off-chip electronics can do some further processing on the amplified signals, such as A/D conversion and data transferring to computer system via different communication methods (RS-232, USB).

IV. Biosensor Fabrication And Package

The prototyped biosensor chip was fabricated by MOSIS using AMI C5 0.5μm, double poly, triple metal layer CMOS technology. The electroless gold plating process as the post-CMOS processing and packaging techniques were applied to the biosensor chip to promote the biocompatibility and stability in the aqueous cell culture environment. Fig. 4 illustrates microphotograph of the biosensor chip and its functional blocks including the sensing area of the fabricated 4 by 6 microelectrode array sensors, reference electrodes and analog signal processing channels with built-in logic control/interface units.

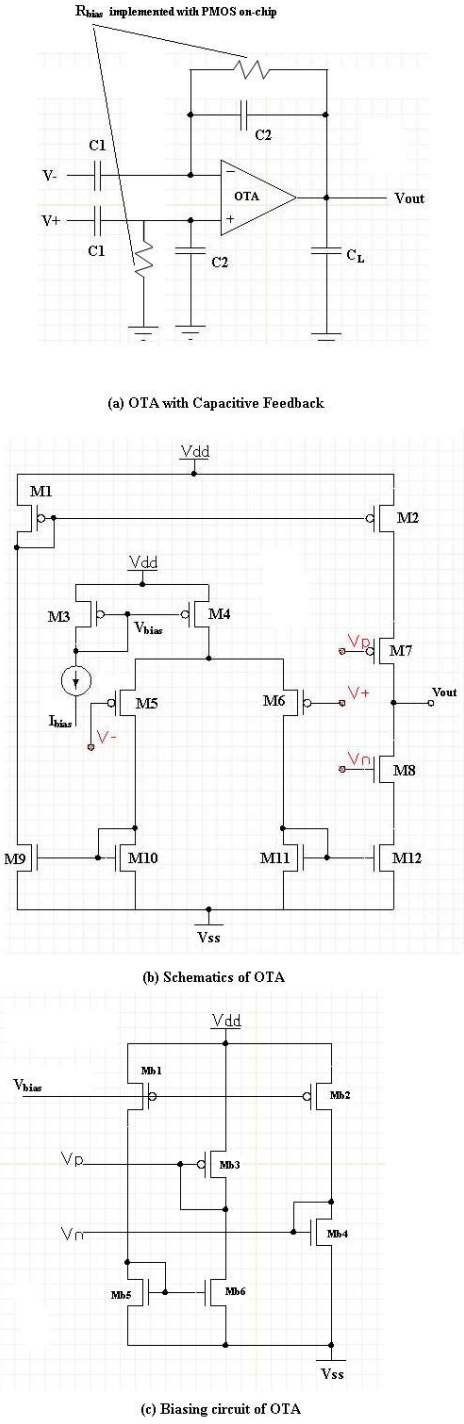

Fig. 3. Schematics of the OTA based high-gain amplifier.

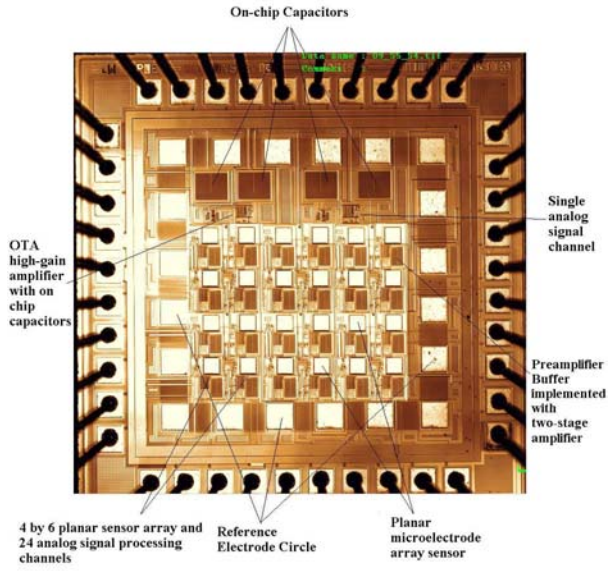

Fig. 4. Microphotograph of the fabricated biosensor chip.

V. Testing System Electronic Setup

To interface the biosensor chip with the computer system, a microcontroller based electronic testing system is necessary to realize four major functions: biosensor chip control signal/sequence generation; A/D conversion of neural signals; digital signal processing and data/command communication between biosensor chip and GUI software running on the computer system. In this research work, a Motorola ColdFire MCF5307 microcontroller based electronic system was setup to serve as the interface between the biosensor chip and the computer system, which realized the full functions listed above. The firmware running on MCF5307 microcontroller was implemented with ColdFire assembly language where on the computer system Matlab platform was chosen to simply the software design work.

The operation of the biosensor chip was demonstrated by the electrical testing experiment. The neural signal was emulated using the D/A function of PCI-DAS1002 data acquisition card in the platform of Matlab Simulink Real Time Workshop. Hodgkin-Huxley neuron model was used as the mathematical model of biological neurons to generate the numerical data of the biopotential signal. The electrical testing results of the emulated neural signal, shown in Fig. 5, demonstrate the proper working of the biosensor chip.

VI. Conclusion

In this paper we demonstrate a successful implementation of an integrated biosensor chip with AMI C5 0.5 μm CMOS technology. This biosensor chip is structured in a hierarchy design and it allows the measurement of propagation of action potentials of neurons. We have proved the full functionality of the biosensor chip with a microcontroller based electronic testing workbench. More detail reports will be published in forthcoming papers with the more biosensor testing related focus.

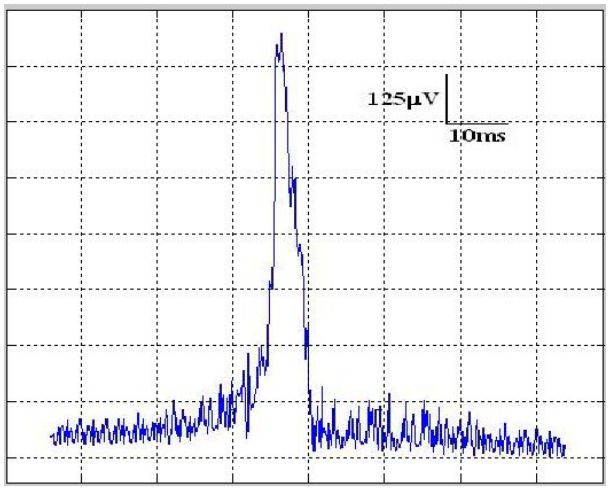

Fig. 5. Electrical testing results of the biosensor chip when emulated neural signal applied.

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