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Fully parallel 512-ch dual-mode electrophysiology and neurochemical amplifiers

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***Abstract*—The electrical potential recordings using a large microelectrode array from neuronal cultures has been widely used to monitor neural spike activities and cellular activities. However, this approach does not monitor neurochemical release, and therefore only contains indirect information regarding synaptic neurotransmission. At the synapses, these action potentials instigate the secretion of neurotransmitters. Neurochemical recordings, based on electrochemical methods, enable the direct monitoring of synaptic transmissions with single-vesicle resolution as well as the excellent temporal resolution in the microsecond scale. The neural spike activities and the neurotransmitter secretions are related; however, one cannot be used to predict the other because of the complex vesicle trafficking and exocytosis processes. Here, we present a dual-mode amplifier array which integrates 256-ch transconductance amplifiers and 256-ch transimpedance amplifiers. The dual-mode amplifier array enables the simultaneous recordings of electrophysiology and neurochemical activities. Capturing both neurochemical and neural spike (action potential and local field potential) activities would provide comprehensive spatiotemporal images of the brain activities.**

***Keywords*—Amperometry, dual-mode amplifier, electrophysiology, fast-scan cyclic voltammetry, microelectrode array, neural interface, neurochemical recordings**

I. Introduction

The electrical recordings using a MEA from neuronal cultures have been widely used to monitor neural spike activities and cellular activities. However, this approach contains indirect information regarding neurochemical activities which is a crucial process in neurotransmission. Neurochemical transmissions are mediated by rapid and nanoscopic events in which membrane-bound neurotransmitters are released in quantal events. Each vesicle secretion merely takes microseconds to milliseconds. The neural spike activities and the neurotransmitter secretions are related; however, one cannot be used to predict the other because of the complex vesicle trafficking and exocytosis processes. Capturing both neurochemical and neural spike (action potential and local field potential) activities would provide a comprehensive image of the brain activities.

Several high-density MEAs have been proposed to perform electrophysiology with enhanced spatiotemporal resolution [1]–[5]. The developments were focused on electrical potential measurements. Action potential recordings are voltage measurements, recorded using a transconductance amplifier (TCA) as opposed to electrical current measurements using a transimpedance amplifier (TIA) for neurochemical measurements. High-density MEA sensors designed for action potential measurements are incapable of measuring the neurotransmitter release. A few recently-reported high-density MEAs integrated a small array of TIAs; however, they lacked in either noise level or active electrode count to be applicable for high-density neurochemical recordings. A multifunctional CMOS chip with an array of 59,760 on-chip electrodes [6], can provide a high channel count of up to 2048 electrodes for simultaneous voltage recordings. However, the multifunctional CMOS chip featured only 28 TIAs for neurotransmitter detection using cyclic voltammetry with the 100s of pA_{RMS} noise level. This noise level surpasses the typical amplitude of neurotransmitter release by a factor of 10 or more and cannot resolve neurochemical release events.

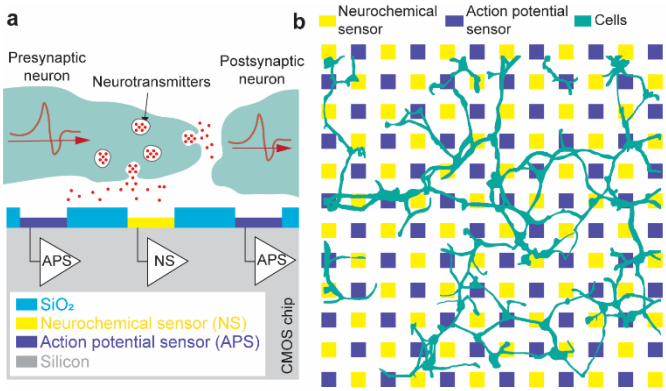

Fig. 1. High-density dual-mode neurochemical-electrophysiology microelectrode array system. (a) Using the dual-mode sensor, both action potential and neurochemical activities are simultaneously monitored using the integrated sensor. (b) The novel neurochemical-electrophysiology sensor can be used to investigate synaptic function from a large neural network.

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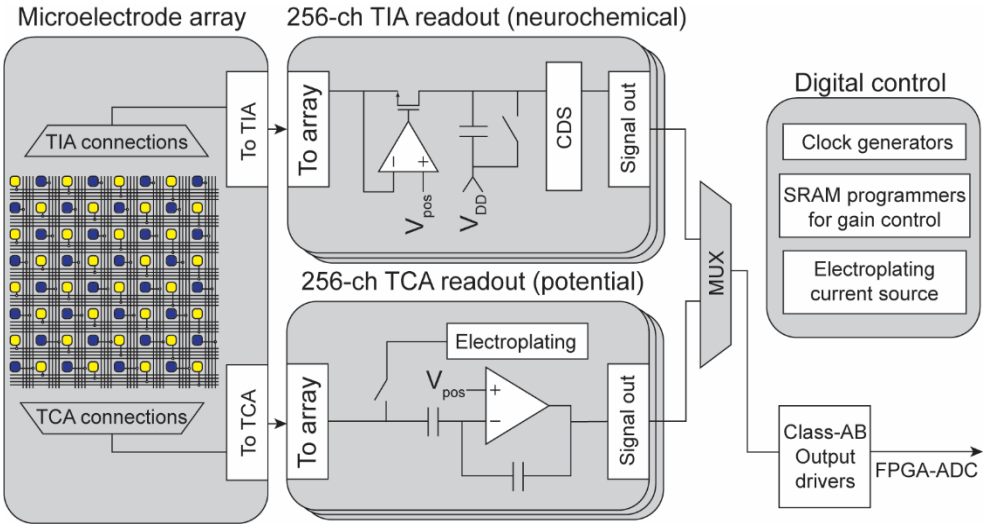

Fig. 2. Design of dual-mode neurochemical-electrophysiology amplifiers using 0.35 µm technologies. The neurochemical-electrophysiology MEA includes a 512 microelectrode array, 256-ch TIA array, 256-ch TCA array, multiplexers, digital controllers, and output drivers.

Here, we present a dual-mode amplifier array which integrated 256-ch TCA and 256-ch TIA. The dual-mode amplifier array can be used to simultaneously monitor neurotransmitter release and action potential propagation from neural networks and enable the dynamic investigation of neural activities, synaptic functions, and potential temporal deterioration caused by neurodegenerative disorders (Fig. 1). The presented work builds on the recent development of a high-density neurochemical sensor that is capable of directly measuring neurotransmitter release at single-vesicle resolution [7]–[9]. The TIA design can operate both amperometry and fast-scan cyclic voltammetry (FSCV), which are two common neurochemical recording methods.

II. Dual-mode amplifier array design

A. System design

A single silicon chip integrates a 512 on-chip microelectrode array that are connected to the on-chip amplifiers (Fig. 2). Half of the on-chip electrodes (256) connects to 256 TIAs for neurochemical recordings and the other half connects to 256 TCAs for potential measurements. Each TCA includes electroplating circuitry to allow electrodeposition of platinum black directly on each electrode. The outputs from TIA and TCA arrays are multiplexed and connected to class-AB output drivers. The multiplexed signals, from the output drivers, are then sampled using an external data acquisition system (FPGA-ADC). The chip also integrates peripheral circuits including clock generators, SRAM programmers, and global electroplating circuitry.

B. CMOS fabrication

The dual-mode amplifier array is fabricated using a standard 0.35-µm process (Fig 3). The size of the entire amplifier array and the microelectrode array is 2.45 mm × 3.57 mm (Fig. 3a). The microelectrode array is at the center of the chip and the amplifier arrays are split into each side of the electrode array. The microelectrode array is in a checkerboard pattern where each electrode is spaced to 16 µm in both vertical and horizontal directions.

III. Scalable amplifier designs

Scalable amplifier designs are critical in creating a high-density amplifier array. In both TIA and TCA designs, the small dimension of the design is prioritized while retaining the noise and gain performance.

A. Tiny transimpedance amplifier design

The TIA design is based on a regulated cascode amplifier (Fig. 4a). The oxidation/reduction current passes through M2 transistor and enters the current mirror formed by M3 and M4 transistors. The W/L ratio between M3 and M4 can be programmed to allow dynamic switching of transimpedance gain. The available effective ratios in this chip are 30.8:1, 15.4:1, 7.7:1, and 3.75:1. The reduced current is generated from M4 and is integrated into C_{int}. In order to enable bipolar measurement, M1 transistor generates an offset current level [10]. This offset current can be either added or subtracted to the current incoming

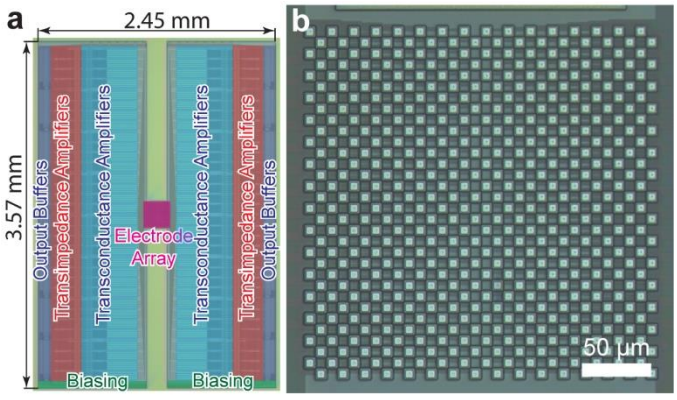

Fig. 3. The dual-mode microelectrode array system in a silicon chip. (a) The total area for the 512-ch dual-mode microelectrode array including the embedded amplifiers is 2.45 mm × 3.57 mm. (b) The microelectrode array is integrated on-chip.

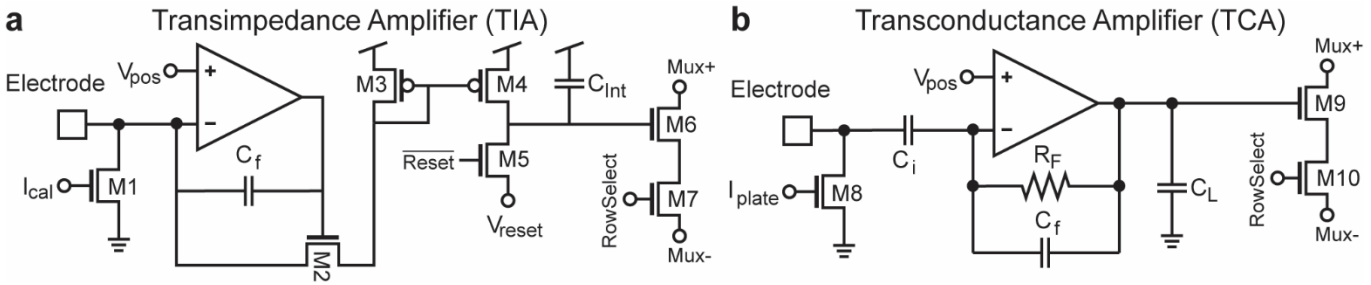

Fig. 4. Highly scalable transimpedance and transconductance amplifier designs. (a) The transimpedance amplifier is an integrating amplifier with a switchable current mirror to adjust the transimpedance gain and dynamic range. This allows for a various mode of neurochemical recordings including amperometry and fast-scan cyclic voltammetry. (b) The transconductance amplifier is for measuring action potentials and local field potentials. Each amplifier integrates electroplating circuitry to enable the electrodeposition of platinum black.

from the electrode, while maintaining the same current direction through M2. The current integrating in C_{int} is periodically read as an output voltage using a multiplexer (M6 and M7). Once the voltage is read out, the reset of M5 clamps the voltage output to a reset level (V_{reset}) to initiate the next cycle of integration. The transimpedance gain of this amplifier is defined by several factors, including the current division set by the current mirror (div), the capacitance of C_{int}, and the integration period (t_{int}).

$$Gain\ (A/V) = \frac{C_{int}}{t_{int} \times div} \quad (1)$$

The current division can be turned off in which case the electrode current is integrated directly into C_{int}. Each transimpedance amplifier occupies 180 µm × 20.5 µm space. To minimize the space per amplifier, the half shared structure is adapted [11]. A total of 256 TIAs occupies 0.945 mm^2 space.

B. *Tiny transconductance amplifier design*

The TCA design is designed based on a low-power low-noise neural amplifier design [12], with a input capacitor (C_i) and a feedback capacitor (C_f) (Fig. 4b). A feedback pseudo-resistor (R_f) forms a weak leakage path for current to stabilize the negative input of the operational amplifier, which otherwise is floating. The pseudo-resistor is made using diode-connected transistors. The voltage gain of this amplifier is defined by the ratio of two capacitors.

$$Gain\ (V/V) = \frac{C_i}{C_f} \quad (2)$$

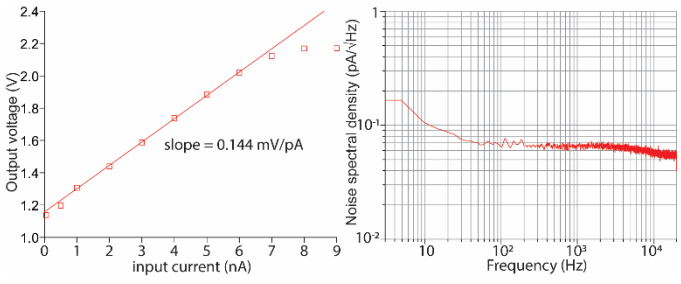

Fig. 5. The transimpedance gain and noise characteristics. (a) The average transimpedance gain across the entire array for the highest gain setting is 0.144 mV/pA. (b) The noise spectral density shows ~7 × 10^{-2} pA/√Hz noise floor.

The output of the voltage amplifieir is then multitplexed using M9 and M10 transistors. For electroplating the electrode, a current source (M8) is connected directly to the electrode node. Each TCA occupies 541 µm × 20.5 µm space. A total of 256 TCAs occupies 2.84 mm^2 space.

IV. Amplifier Characteristics

A. *Transimpedance amplifier gain and noise*

The TIA is tested by injecting known currents into the electrode using M1 (Fig. 4a). In this case, the gain is set to the highest setting which is the equivalent of using 1:1 ratio for the current mirror (M3 and M4). By monitoring the output voltage while sweeping the input current, we can measure the average transconductance gain of 0.144 mV/pA across all 256 TIAs (Fig. 5). As the input current reaches near the limit of the dynamic range, the output voltage starts to taper off above 7 nA. The dynamic range of integrating TIAs is a function of transimpedance gain and integrating period. By using lower transimpedance gain and fast sampling rate, the dynamic range can be increased up to ~4 µA, which is sufficient to operate FSCV.

In this gain setting, the noise spectral density is acquired (sampled at 40 kSamples/s). The noise level is about 4.8 pA$_{RMS}$ with ~20 kHz bandwidth, superior to most CMOS TIA designs [6], [13].

B. *Transconductance amplifier gain and noise*

To determine the gain-bandwidth of each TCA, a small sine wave of varying frequencies is injected into the electrode node directly through a switch (integrated in the chip for testing purposes). The output response is measured while the frequency of the input sine wave is swept between 0.1 Hz to 10 kHz (Fig. 5). Based on the measurued gain-bandwith response, the low frequency cut-off is determined to be ~0.2 Hz and the high frequency cut-off is ~10 kHz.

Noise spectral density is also acquire across the array. The measured average noise level is 29.9 µV across all TCAs.

V. Conclusion and Discussion

A fully parallel 512-ch dual-mode amplifier array is developed by integrating 256-ch neurochemical amplifiers and 256-ch electrophysiology amplifiers. The chip also integrates

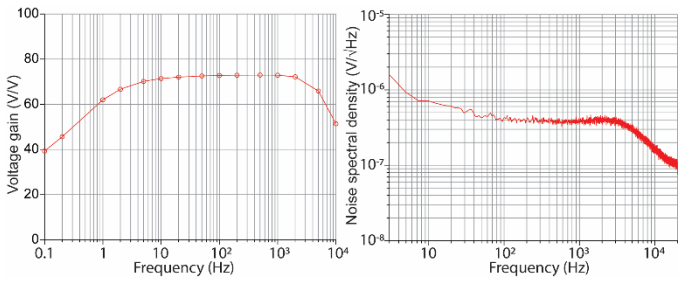

Fig. 6. The transconductance gain/bandwidth and noise spectral density.

512 on-chip microelectrodes for both modalities. The main benefit of the TIA and TCA designs in this work is the scalability. The small dimensions (TIA: 180 µm × 20.5 µm, TCA: 541 µm × 20.5 µm) provides a unique opportunity to integrate a large array in a small silicon chip. We expect that 1000s of TIA and TCA can be integrated in a commonly used silicon reticle size. The dual-mode amplifier array can be used to simultaneously monitor neurotransmitter release and action potential propagation from neural networks and enable the dynamic investigation of neural activities, synaptic functions, and potential temporal deterioration caused by neurodegenerative disorders.

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