A Wireless Optoelectronic Neuroscience Platform for Chronic Fluorescence Sensing in Freely Behaving Rodents

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***Abstract*—We present a new head mountable wireless fiber biophotometry microsystem conceived to detect fluorescent signal fluctuations correlated with neuronal activity. The proposed system incorporates all aspects of a conventional tethered fiber-based biophotometry system encompassed into a wireless microsystem. The interface includes an LED as excitation light source, a custom designed CMOS biosensor, a multimode fiber, a microcontroller (MCU), and a wireless data transceiver enclosed within a 3D-printed, small and light weight, plastic housing. Precisely, the system incorporates a new optoelectronic biosensor merging two individual building blocks, namely a low-noise sensing front-end and a 2^{nd} order continuous-time $\Sigma\Delta$ modulator (CTSDM), into a single module for enabling high-sensitivity and high energy-efficiency photo-sensing. The proposed CMOS biosensor is implemented in a 0.18-μm CMOS technology, consuming 41 μW from a 1.8-V supply voltage, while achieving a peak dynamic range of 86 dB over a 50-Hz input bandwidth at a 20-kS/s sampling rate. This new interface opens new avenues for conducting *in-vivo* experiments with live animals.**

***Index Terms*— Optoelectronic biosensor, Fluorescence, Fiber photometry, Wireless, $\Sigma\Delta$ modulator, Neuroscience, Freely moving.**

I. Introduction

Wireless optoelectronic neural interfaces are transforming the way neuroscientists are investigating the relationship between brain function and behavior in live animals models. Genetically encoded calcium indicators such as GCaMP6 and RCaMP are widely utilized in calcium fluorescence sensing and brain imaging [1]–[3]. The voltage-gated calcium channels and the calcium indicator kinetics range from 30 to 50 ms [4]. A miniaturized head-mountable fluorescence interface based on a CMOS image sensor was developed to measure neural activity from single cells to large population of cells [5]. However, neural activity can only be collected at the surface of the brain with this approach. In contrast, fiber photometry can measure fluorescence light from deep brain structures using an implanted optical fiber [6]. A conventional fiber photometry setup typically consists of a high-performance microscopy system including different modules such as lasers, dichroic filters, photoreceivers, fiberoptic cannulas, fiber photometry consoles, etc., and using long tethered fibers to deliver light inside the brain and to retrieve fluorescence signals [7]. A bench-top lock-in amplifier, coupled to a femtowatt silicon photoreceiver and mounted on a microscope, is typically used to retrieve the fluorescence signal from the illuminated tissue. Such experimental setup is reliable and precise, but impractical for conducting long-term photometry experiments with live laboratory animals, due to the fiber/cable tethering and risk of breakage or injury.

This work presents a new custom integrated high-precision CMOS biophotometry sensor used as the main building block of a head mountable fiber photometry device including a wireless transceiver and a diffuse excitation light source for chronic utilization with live laboratory mice. The high-precision CMOS biophotometry sensor uses a new charge accumulation sensing front-end merged with a 2^{nd} order continuous-time $\Sigma\Delta$ modulator to collect the fluorescence light emitted from the tissue under low illumination. The proposed wireless head mountable fiber photometry system is light weight and addresses the shortcomings of bench top fiber photometry systems while providing excellent precision. The paper is organized as follows. An overview of the presented wireless biophotometry system is provided in Section II. The design of the CMOS biosensor circuits is covered in Section III. The implemented wireless fiber photometry prototype is described in Section IV. The measured performance of the fabricated chip, and the results obtained with the whole fiber photometry system are presented in Section V. Conclusions are drawn in Section VI.

II. Proposed System Architecture

A. System Overview

The block diagram of the proposed head-mountable wireless fiber photometry system is shown in Fig.1. The system consists of a new custom integrated CMOS fluorescence biosensor, a wireless data transceiver unit (nRF24L01P, Nordic Semiconductor), a power management unit (PMU), a diffused light excitation source (a blue LED, LUXEON Rebel), a 3D-printed housing, passive optical signal conditioning components, and a single multimode optical fiber ($400\mu m$ fiber, ThorLabs). The device is designed to be small and lightweight enough to fit on the head of a laboratory mouse. The LED is coupled with an implanted multimode

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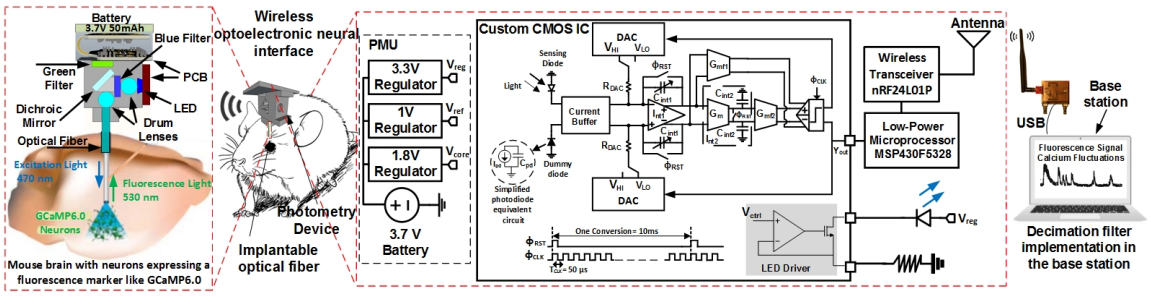

Fig. 1. Block diagram of the proposed optoelectronic neural interface. The system can excite a genetically encoded indicator like GCaMP6 expressed by the neurons of a transgenic mouse, and can record fluorescence signal through a single multimode optical fiber coupled to the proposed custom integrated biosensor. The system transmits the neural data wirelessly to a base station connected to a computer host. The biosensor, the LEDs, the optical fiber, and the different passive optical components are enclosed within a lightweight wireless fiber photometry prototype that can be mounted on the head of a laboratory mouse for chronic utilization.

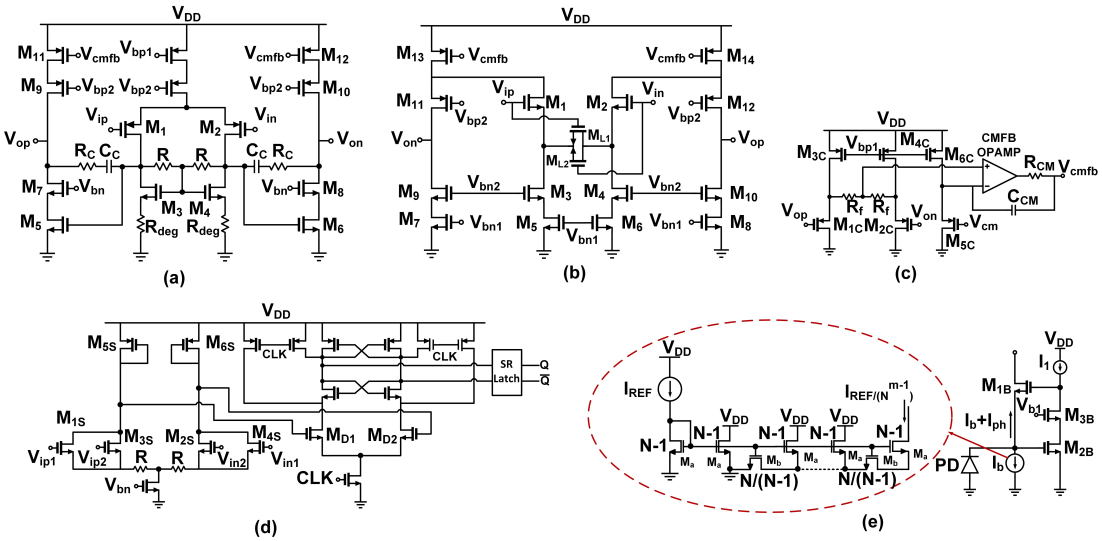

Fig. 2. Circuit schematic of all building blocks used to implement the custom CMOS biosensor depicted in Fig. 1(a) the low-noise two-stage opamp used in the I_{int1}, (b) the linearized folded cascode opamp used in the I_{int2}, (c) the common mode feedback circuit, (d) the feed-forward coefficient summation and quantizer circuit, and (e) the input buffer associated with a current splitter.

optical fiber to illuminate and retrieve the fluorescence signal from deep brain structures. The excitation/emission light is separated by the optical filters (i.e., excitation bandpass filter 470/24 nm, emission bandpass filter 535/50 nm, Chroma Technology), lenses, and a dichroic mirror (495 nm, Chroma Technology). The fluorescence signal is collected by the CMOS custom integrated biosensor, and then transmitted to the base station located a few meters away through a low-power short range 2.4 GHz ISM data link. A LED driver circuit controls the LED light and stabilizes its forward current.

B. Custom Integrated CMOS Biosensor

Fluorescence biosensors based on charge accumulation typically comprise a sensing module (photodetector), a charge-to-voltage conversion block, a differential capacitive transimpedance amplifier (DCTIA), a low-frequency noise cancellation module, and an analog-to-digital converter (ADC) to collect and convert the detected fluorescence light into output digital codes [2]. In such systems, a large femtowatt photodetector (i.e., a sensing area of 200 μm $\times$ 200 μm) produces a photocharge corresponding to the incident fluorescence light on the detector. The photocurrent is converted into a voltage signal through the front-end charge-to-voltage converter (DCTIA). The output of the DCTIA is followed by a low-frequency noise cancellation block and an ADC to generate a digitized output. The proposed fluorescence biosensor is based on a charge accumulation sensor topology merged with a continuous-time $\Sigma\Delta$ modulator (CTSDM) (shown in Fig. 1). It consists of two photodiodes, a current buffer, a DCTIA, and a 2nd-order CTSDM modulator. In this design, the DCTIA is fused with the first integrator (I_{nt1}) of the CTSDM modulator in order to decrease the amount of hardware and the noise while increasing the power efficiency by minimizing the number of analog building blocks used in the whole biosensor. In fact, the DCTIA simultaneously acts as a pre-amplifier and as a first integrator (I_{nt1}) module in the modulator to improve the energy efficiency and to simplify the whole sensor circuitry. The differential input photodiodes include a sensing and a dummy diode to reduce the dark current effect generated by them [6]. These large photodiodes create a big parasitic

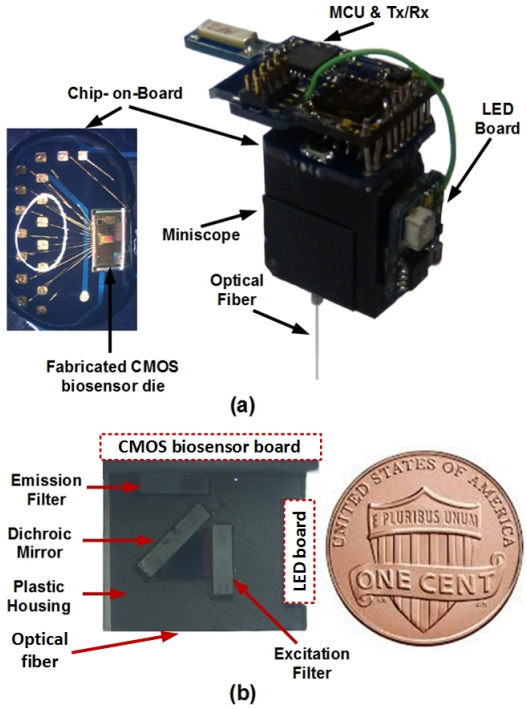

Fig. 3. (a) Miniature fiber biophotometry prototype including the fabricated CMOS sensor, a blue excitation LED mounted on a small board, passive optical components, implantable fiber, plastic housing, etc. (b) side view of the wireless fiber photometry prototype plastic housing including the optical filters (emission and excitation filters) and the dichroic mirror.

capacitance (e.g, 5.7 pF) that can increase the noise and the non-linearity in the DCTIA opamp. Additionally, this large capacitance can reduce the DCTIA feedback factor, and in turns decrease the gain-bandwidth product (GBW), and increase the power consumption. Hence, this design uses a current buffer at the input of the DCTIA to decouple the photodiode parasitic capacitance from the DCTIA and avoid such troublesome effects. The input photogenerated current I_{ph} is integrated on the C_{int1} of the DCTIA. Then, the modulator starts quantizing the input photogenerated current by sending a global reset pulse that resets the voltage nodes and clears the memories in all the analog and digital blocks.

III. Circuit Design and Implementation

In this design, a cascade-of-integrators in feed-forward (CIFF) configuration is adopted to relax the swing requirements in the integrators paths and to reduce adverse impact of the coefficient variations on the modulator performance. The DCTIA is the most critical analog building block of the whole biosensor. It has two functions operating: 1) converting the input charge to a voltage, and 2) realizing the integrator I_{int1} for the modulator. An active RC-integrator is adopted for the first I_{int1} to provide high linearity compared to G_mC counterparts. Fig. 2 (a) shows the two-stage low-noise fully differential amplifier topology with Miller capacitors frequency compensation and with nulling resistors that is selected for the I_{int1}. The output common mode voltage of the I_{int1} is sensed and stabilized by the common mode feedback (CMFB) circuit shown in Fig. 2 (c). The requirement on I_{int2} including the output swing, GBW, slew rate, and DC gain are relaxed with respect to the first stage due to the noise-shaping characteristics of the loop filter. A fully differential classic folded cascode amplifier with Linearization is implemented by M_{L1} and M_{L2}, as shown in Fig. 2 (b). The summation block, which implements the weighted addition of the feedforward path coefficients of the $\Sigma\Delta$ modulator, and a dynamic latched comparator, which only consumes dynamic power and avoid static current consumption, are depicted in Fig. 2 (d). The input current buffer isolates the photodiode parasitic capacitance from the DCTIA illustrated in Fig. 2 (e). It includes a regulated cascode nMOS transistor M_{1B} that is gain-boosted by M_{2B}, M_{3B}, and the current source I_1. A 500-pA DC current I_b is injected into the source of M_{1B} (Fig.2 (e)) to improve the linearity performance at low I_{ph}. The simulation reveals that the total harmonic distortion (THD) of the current buffer output I_{ph} is as high as 110 dB.

IV. Wireless Fiber Photometry Prototype

One important task consists of coupling the excitation light into a single optical fiber and retrieving the fluorescence signal through this same fiber, while rejecting the exciting light to avoid saturating the photodetector. A solution to this problem consists of using different optical filters, including an excitation and an emission filter, to separate the excitation signal from the fluorescence signal. Additionally, a dichroic mirror is used to deflect off the blue light towards the implantable fiber (FT400UMT, ThorLabs) while transferring the fluorescence green light towards the CMOS detector. Two drum lenses are used as well to collimate the excitation light coming from the diffuse LED illumination source and the deflected fluorescence light coming out of the dichroic mirror, the proposed wireless fiber photometry system shown in Fig. 3. It included 3 small electronic boards holding the custom CMOS chip and other off-the-shelf electronic components. The CMOS biosensor chip is wire bonded directly on a small PCB which is glued on top of the plastic housing. The off-the-shelf components, including board comprises the wireless transceiver unit, the power management unit, and the MCU are mounted on a second board located on top of the biosensor board (Fig. 3). The blue excitation LED and its driver circuit are mounted on a 3rd board, which is mounted on the side of the plastic housing. All PCBs are connected together through small rigid wires which are soldered on the edge of the boards and are designed to fit on top and on the side of the plastic housing. The miniaturized device results in a lightweight (3.6 g w/o battery) and compact size of ($22 \times 8 \times 17\ mm^3$) head mountable system.

V. Implementation and Measurement Results

The proposed optoelectronic fluorescence biosensor is implemented in a 0.18-μm CMOS process (shown in Fig. 4). The total static power consumption of the biosensor is 41 μW. The measured spectrum of the CMOS optoelectronic sensor at a full scale input light power is depicted in Fig. 5. The sampling frequency of the biosesnor is 20 kS/s, and the peak SNDR is 70-dB over a 50 Hz signal bandwidth. The DR of the CMOS biosensor can be extended to 86 dB by digitally calibrating the modulator coefficients. The whole

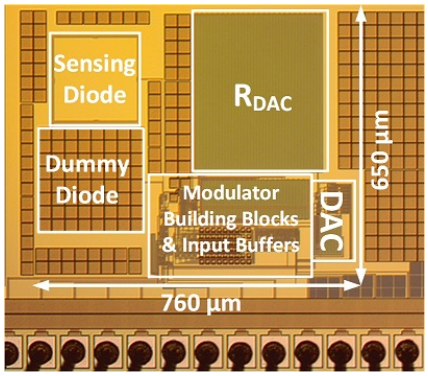

Fig. 4. Fabricated chip microphotograph in a 0.18-μm CMOS process with an area of 0.494 mm^2.

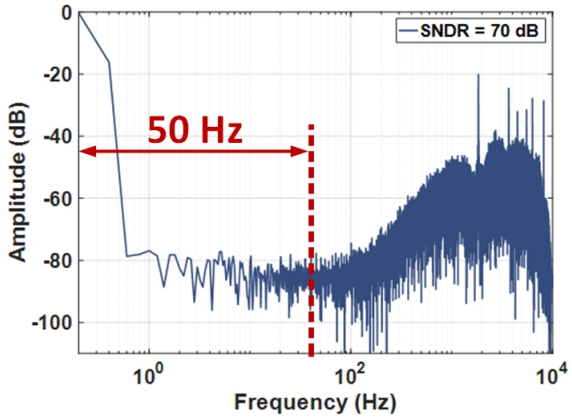

Fig. 5. Measurement results for the SNDR. A 100,000-points FFT is performed on the sensor output at a full scale input DC input light power.

fiber photometry system characteristic are summarized in Table. I. The whole system is evaluated with different fluorescence bead (FluoSpheres) concentrations which are diluted with 0.5 % agarose gel. FluoSpheres concentrations starting from 0.001 % to 0.125 % are loaded in eppendorfs and then the tip of the fiber placed immediately above the agarose-containing FluoSphere, the excitation light source was adjusted such that the light power at the fiber tip to become 50 μW, as shown in the inset of Fig. 6. The whole system is supplied by a 3.7-V, 100-mAh, 2.1-g Lithium-ion battery (Model051417, MYD Technology). The fluorescence signals measured with the system are transmitted to a base station located 2 meters away. The measured fluorescence beads concentrations are shown in Fig. 6.

VI. Conclusion

A wireless optoelectronic neuroscience platform for chronic fluorescence sensing in freely behaving animals has been presented. It achieved high precision as well as high resource and power efficiency by merging the analog front-end with a 2^{nd} order $\Sigma\Delta$ modulator. A DCTIA structure allows canceling the differential dark current from an on-chip dummy and a sensing photodiode both having sensing area of 200 $\times$ 200 μm^2. The proposed biosensor achieves a DR of 86 dB at a sampling rate of 20 kS/s and consuming 41 μW. A miniaturized head mountable system using the

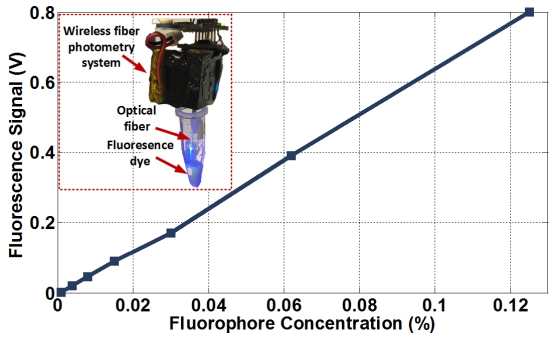

Fig. 6. Fluorescence dye measurement experimental setup including the wireless fiber photometry system and different concentrations of fluorescence beads (FluoSpheres) in 0.5 % AGAR to verify the performance of the proposed fiber photometry system. The output of the biosensor is shown versus different fluorescence bead concentrations.

TABLE I. Characteristics of the fiber photometry system

Parameters	Values
Brain interface	Single optical fiber
Dynamic range	86 dB
SNDR	70 dB
Sensitivity	24 mV/nW
Sampling rate	20 kSamples/s
Bandwidth	50 Hz
Minimum photodetection current	2.46 pA_{rms}
Transceiver center frequency	2.4 GHz
Optical fiber's diameter	400 μm
Dimensions (H $\times$ W $\times$L, the optoelectronic interface w/o battery)	$22 \times 8 \times 17$ mm^3
Weight (the optoelectronic interface w/o battery)	3.6 g
Average LED power (1 LED, 580 mW @ 10%)	58 mW

proposed CMOS biosensor is presented to conduct wireless brain biophotometry experiments with live laboratory mice. The device suppresses the excitation light leakage to the CMOS detector using a set of optical filters and a mirror, thus improving the system SNR compared to conventional approaches based on film filters [8].

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