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A Configurable IC for Wireless Real-Time *In Vivo* Monitoring of Chemical and Electrical Neural Activity

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***Abstract*— A 16-channel chip for wireless *in vivo* recording of chemical and electrical neural activity is described. The 7.83-mm^2 IC is fabricated using a 0.5-µm CMOS process and incorporates a 71-µW, 3rd-order, configurable, ΔΣ modulator per channel, achieving an input-referred noise of 4.69 µV$_{rms}$ in 4-kHz BW and 94.1 pA$_{rms}$ in 5-kHz BW for electrical and fast-scan voltammetric chemical neurosensing, respectively. Brain extracellular levels of dopamine elicited by electrical stimulation of the medial forebrain bundle have been recorded wirelessly on multiple channels using 300-V/s fast-scan cyclic voltammetry in the anesthetized rat.**

I. Introduction

Rapid long-distance communication in the nervous system primarily occurs via electrical impulses (action potentials) conducted along the neuronal axon to the synapse. In the extracellular cleft of this junction between two neurons, however, communication is mediated through the release and uptake of biochemical molecules (neurotransmitters) [1]. Understanding brain function on a fundamental level, therefore, requires measurements of both electrical and chemical activity to provide a more holistic image of neural signal pathways.

Many researchers have previously developed integrated circuits for recording neuroelectrical activity. A review of research into this area can be found in [2], [3]. Amperometric detection (the simplest form of electrochemical sensing) has also been widely used as a rapid monitoring technique that directly converts the extracellular concentration variations of electroactive neurotransmitters into electrical currents to be measured by sensor interface circuitry.

Single- and multi-channel interface circuits for amperometry have been previously reported in [4]-[7]. However, it is often postulated that amperometry might not be well suited for a complex biological matrix *in vivo* due to limited chemical specificity.

Fast-scan cyclic voltammetry (FSCV) is another electrochemical detection technique that not only provides measurements on the same time scale (~100 ms) as that of neurotransmission, thus making real-time monitoring of brain chemical dynamics possible, but also offers superior chemical selectivity, because a chemical signature (cyclic voltammogram) is recorded to identify the detected species. Hence, FSCV is recognized as the best choice for monitoring endogenous neurotransmitters in ambulatory animals [8].

This paper reports on the design, implementation, performance characterization, and biological testing of a versatile wireless recording chip that features multichannel monitoring of neurochemical activity, using FSCV as well as amperometry, and neuroelectrical activity (e.g., extracellular neural action potentials or local field potentials, LFPs).

II. System Architecture

Fig. 1 shows the architecture of the proposed wireless recording chip. Each channel incorporates a continuous-time 3rd-order ΔΣ modulator (ΔΣM) that can be individually configured either as a low-input-impedance current-driven front-end for neurochemical monitoring or a high-input-impedance voltage-driven front-end for neuroelectrical recording. A monolithic data fusion core (DFC) with sixteen 8-bit configuration registers selects a single channel, all 16 channels, or any combination among 2, 4 or 8 channels for monitoring, and constructs the resulting serial output bit-stream for wireless transmission using a back-end frequency-shift-keyed (FSK) transmitter at 433 MHz after encoding.

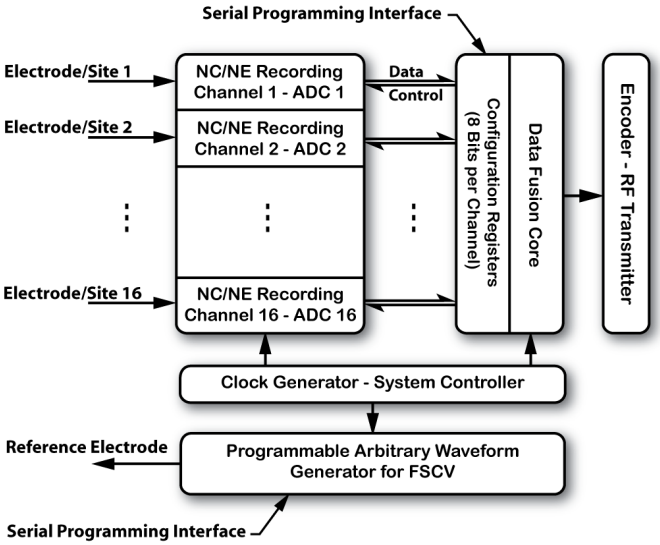

Fig. 1. Architecture of the microsystem for wireless neurochemical (NC) and neuroelectrical (NE) monitoring.

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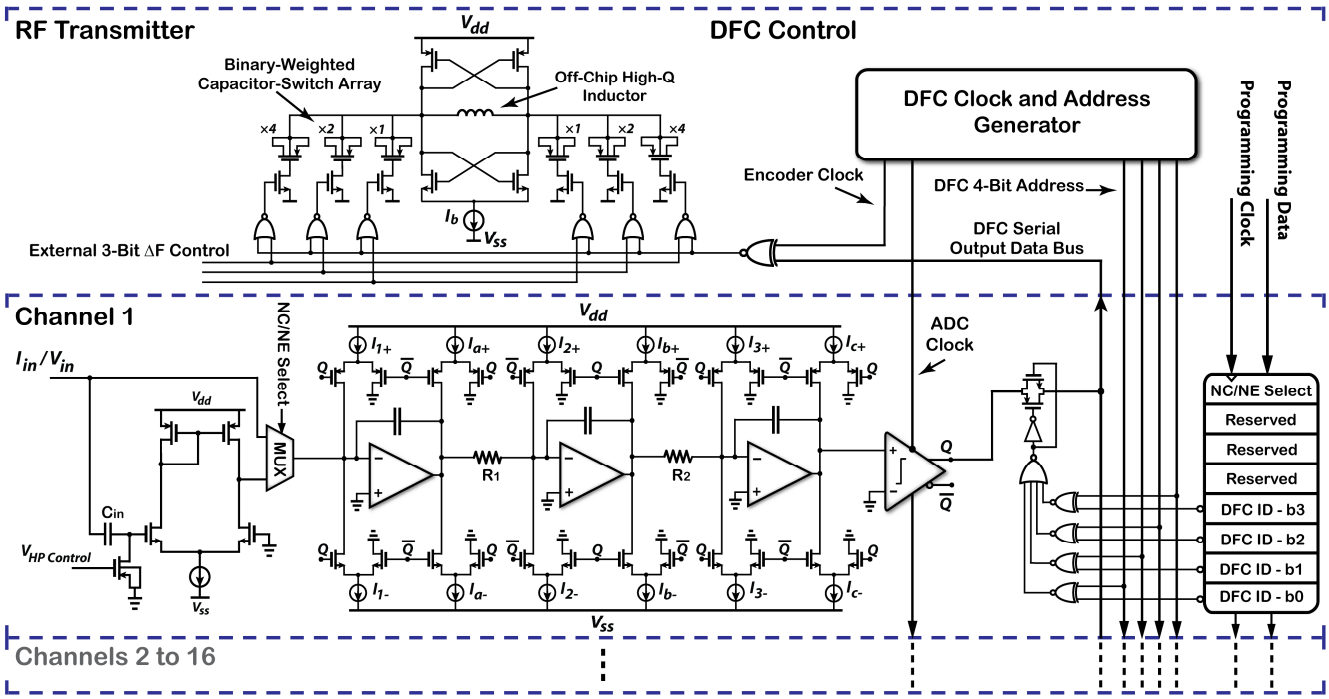

Fig. 2. Transistor-level circuit schematic of one recording channel in the wireless system.

The chip also incorporates a programmable arbitrary waveform generator to produce the triangle FSCV voltage waveform applied to the reference electrode, while the working electrodes are kept at virtual ground by the chip in a two-electrode setup for neurochemical sensing. One channel continuously records the FSCV waveform for monitoring, calibration, and channel identification at the external receiver. The decimation filter is implemented in software on the receiver side to offer the flexibility for dynamic trade-off between data conversion speed and required resolution.

III. Integrated Circuit Architecture

Fig. 2 depicts the circuit schematic of one wireless recording channel. The core sensing module is a continuous-time 3rd-order ΔΣM with a single-bit quantizer that occupies 850 × 180 μm^2 in silicon area and dissipates 27.1 μA from a 2.5-V supply when clocked at 640 kHz. It is designed to be stable in the targeted input range of ±750 nA suitable for FSCV-based neurochemistry at a recording microelectrode [8], and reliably converts a wide range of currents directly into digital data with no need for current amplification that can be inherently noisy, nonlinear and thus unsuitable for very-low-current sensing applications.

While I_1, I_2 and I_3 (1.2 μA, 0.8 μA and 1.2 μA, respectively) are the main feedback current source pairs for addition/subtraction in the ΔΣM, additional sets of current source pairs ($I_{a\text{-}c}$ equal to $I_{1\text{-}3}$, respectively) are also used to relax the bandwidth and slew rate requirements of the integrating amplifiers, allowing a current draw of only 4.4 μA per amplifier.

To configure a channel for electrophysiological studies, an ac-coupled open-loop transconductance (G_m) block converts the μV-range neuroelectrical input voltages to currents manageable by the same ΔΣM for further processing. The G_m block occupies a silicon area of 100 × 180 μm^2, draws 3.6 μA, and incorporates a 4-pF on-chip capacitor (C_{in}) and a subthreshold PMOS transistor for dc baseline stabilization with its highpass cutoff frequency controlled by an externally applied control voltage ($V_{HP\text{-}Control}$) [9].

To initialize the chip, an 8-bit register per channel is serially programmed with a 4-bit address and a single mode-select bit to configure the channel for either chemical or electrical neural recording. Three bits are currently unused and reserved for future expansions of chip functionality.

To implement the wireless link, we have developed a cross-coupled oscillator that employs two sets of binary-weighted switched capacitors as the frequency tuning element with an external high-Q inductor, and operates near 433 MHz with a programmable ΔF from 2 to 14 MHz in steps of 2 MHz. The tail current is externally controllable from 100 to 500 μA [10].

The waveform generator consists of a timing controller, a 128 × 8-bit memory, an 8-bit charge-redistribution DAC and an analog output buffer. The buffer draws 22.6 μA and incorporates a class AB output with rail-to-rail I/O capability to generate the FSCV waveform with a programmable sweep rate of 100 to 500 V/s typically used in neurochemistry [8].

The chip was fabricated using the AMI 0.5 μm double-poly triple-metal n-well CMOS process, and measured 2.7 × 2.9 mm^2 including the bonding pads. Fig. 3 shows a microphotograph of the fabricated chip.

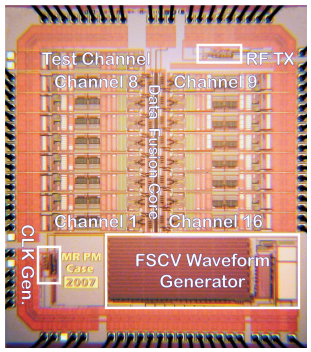

Fig. 3. Microphotograph of the 2.7 × 2.9-mm^2 IC.

IV. Measurement Results

A. Benchtop Characterization

The top plot in Fig. 4 depicts the measured frequency spectrum of the digital data bit-stream at the output of one ΔΣM in neurochemical sensing mode for a 1-kHz, 10-nA$_{pp}$ sinusoidal input current. The resulting current resolution as a function of the decimated sampling frequency (i.e., twice the decimation filter bandwidth) for amperometry (up to 100 Hz) and FSCV at various sweep rates is also shown in the bottom plot. A current resolution of ~10.2 pA was achieved in amperometry by setting the decimation filter bandwidth to 50 Hz in software. Setting the decimation filter bandwidth to 5 kHz instead allowed one to achieve a current resolution of ~94.1 pA in 300-V/s FSCV. The peak-to-peak amplitude of the FSCV waveform was taken to be 1.5 V (-0.4 to 1.1 V) and 100 data points were sampled during each triangle voltage scan duration (10 ms for 300-V/s FSCV) [8]. Table I summarizes the measured chip performance characteristics.

B. Flow Injection Analysis – In Vitro Characterization

For *in vitro* characterization and *in vivo* biological testing, carbon-fiber microelectrodes (CFMs, typically 10 µm × 250 µm) were fabricated as previously described in [11]. The fabricated chip was interfaced with a CFM as the working electrode placed in a flow cell. All measurements were collected in buffer containing 150 mM NaCl and 25 mM HEPES (pH = 7.4). Buffer was pumped at a rate of 2 mL/min. A bolus of dopamine at different concentrations was applied to the flowing stream via a loop injector driven by a pneumatic actuator. A silver/silver chloride wire was used as a standard electrochemical reference electrode.

Fig. 5 depicts a standard calibration curve for dopamine oxidation current versus concentration measured using both wireless (the CMOS chip) and wired (a commercial benchtop potentiostat) systems. Dopamine concentrations of 0.125, 0.25, 0.5 and 1 µM were applied. A linear response was achieved that exhibited a measured sensitivity of ~10.3 nA/µM, in excellent agreement with the wired system.

C. Biological Experiments – In Vivo Characterization

Acute biological tests were performed on urethane-anesthetized, adult, male rats. A twisted bipolar stimulating electrode was implanted in the medial forebrain bundle (MFB) and 3 CFMs in the caudate-putamen, a rich dopamine

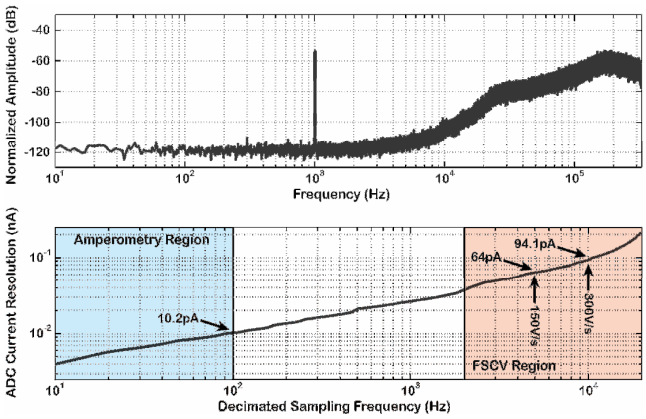

Fig. 4. Measured frequency spectrum of one ΔΣM output for a 1-kHz, 10-nA$_{pp}$ input current (top) and the resulting ADC current resolution measured versus the decimated sampling frequency for amperometry (up to 100 Hz) and FSCV (at various sweep rates) modalities of neurochemical sensing (bottom).

TABLE I
Summary of Measured Chip Performance

FRONT-END: NEUROCHEMICAL SENSING MODALITY			
	150-V/s FSCV	***300-V/s FSCV***	***Amperometry***
Input Range	±750 nA		
Power Dissip.	71 µW (@ 2.5-V supply – 680 kHz sampling freq.)		
Signal BW	dc to 2.5 kHz	dc to 5 kHz	dc to 50 Hz
Input Noise	64 pA$_{rms}$	94.1 pA$_{rms}$	10.2 pA$_{rms}$
FRONT-END: NEUROELECTRICAL SENSING MODALITY			
	Action Potential		***LFP***
Input Range	±35 mV		
Power Dissip.	80 µW (@ 2.5-V supply – 680 kHz sampling freq.)		
Signal BW	1.1 to 5 kHz	0.5 to 7 kHz	1 to 100 Hz
Input Noise	4.69 µV$_{rms}$	7.13 µV$_{rms}$	11.3 µV$_{rms}$
FSCV WAVEFORM GENERATOR			
Sweep Rate	100 to 500 V/s (typically 300 V/s)		Programmable
Scan Freq.	0.5 to 42 Hz (typically 10 Hz)		Programmable
Power Dissip.	99 µW (250 V/s – 10 Hz)		2.5-V Supply
Memory Size	128 × 8 bits		-
DAC	8 bits		-
Load Drive	0 to 100 nF		Capacitive
RF TRANSMITTER			
Communication	FSK @ 433 MHz		-
ΔF	2 to 14 MHz		Programmable
Received Power	-60 dBm (w/ 5-cm monopole TX and 50-cm RX antennae)		@ 0.5 m
Power Dissip.	1 mW		2.5-V Supply
Total Power Consumption in 4-Ch. TX = 2.9 mW @ 5.44 Mb/s (Encoded)			

-innervated forebrain region implicated in the control of movement. Biphasic current pulses (±300 µA, 50 Hz, 4 ms pulse width) were applied for two seconds (a total of 100 pulses) to the dopamine axons traversing the MFB in order to evoke dopamine release throughout the caudate-putamen. Three channels of the chip (Ch. 4-6) were externally interfaced with the 3 CFMs and configured for dopamine monitoring using FSCV at a sweep rate of 300 V/s and a frequency of ~10 Hz. Fig. 6 shows the wirelessly measured background-subtracted cyclic voltammogram of dopamine recorded in the rat brain on channel 6. The peak current at ~650 mV during the forward sweep corresponds to dopamine oxidation to its quinone, whereas the peak current at nearly -270 mV in the reverse sweep corresponds to reduction of the electroformed quinone back to dopamine.

Fig. 7 depicts the temporal profile of simultaneous, multichannel, dopamine release in the rat caudate-putamen, measured wirelessly after electrical stimulation of the MFB applied at t = 10 seconds for two seconds.

Finally, a single channel of the chip was externally interfaced with another CFM acutely implanted in the ventral pallidum of a second anesthetized rat, and spontaneous extracellular neural activity was recorded wirelessly over a transmission distance of ~0.5 m, with the chip configured for neuroelectrical recording. Fig. 8 shows a 2-s and a 40-ms portion of the recorded data after applying offline linear-phase filtering from 0.3 to 3 kHz.

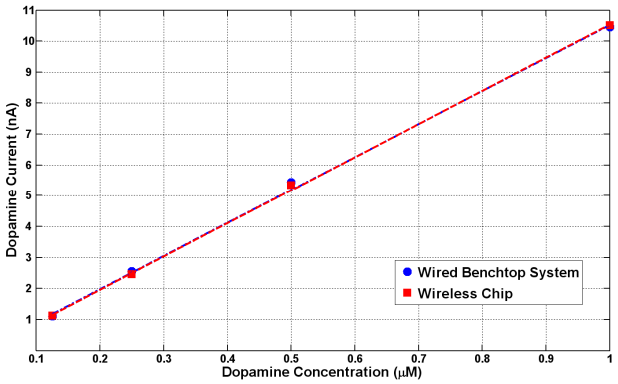

Fig. 5. Standard calibration curve (background-subtracted dopamine current versus concentration) measured in wireless and wired fashions.

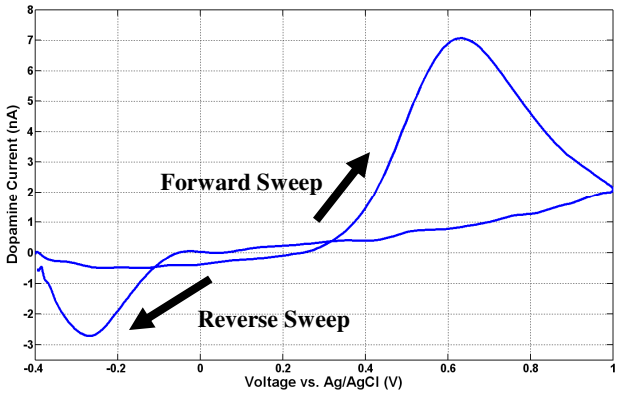

Fig. 6. Background-subtracted cyclic voltammogram of dopamine oxidation and reduction measured wirelessly in the rat caudate-putamen.

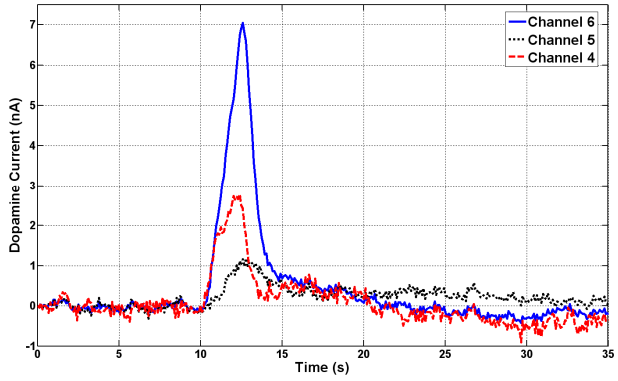

Fig. 7. Simultaneous, multichannel, transient dopamine release measured wirelessly in the rat caudate-putamen after 2 seconds of 50-Hz electrical stimulation applied to the rat MFB at t = 10 seconds.

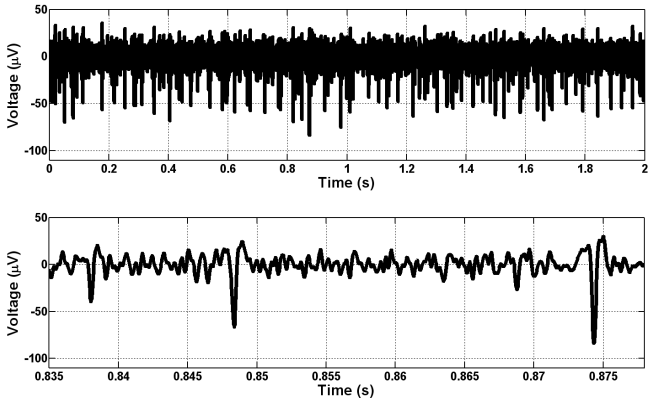

Fig. 8. Wireless *in vivo* recording of spontaneous electrical activity from the ventral pallidum of an anesthetized rat (top) and expanded view of three representative action potentials (bottom). Spike amplitudes are input-referred.

V. Conclusion

We reported on the design, implementation, performance characterization, and *in vivo* testing of a configurable IC for wireless monitoring of chemical and electrical neural activity. The chip has been interfaced with acutely implanted CFMs in anesthetized rats, and successfully demonstrated multichannel recording of electrically evoked dopamine release in the brain using 300-V/s FSCV. The chip also separately recorded spontaneous extracellular neural activity from the rat ventral pallidum.

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