Applying Time-Sharing Technique in a Multimodal Compact Low-Power CMOS Neurochip for Simultaneous Neurochemical and Action Potential Recording

Mohammad Poustinchi, R Greg Stacey and Sam Musallam

***Abstract*— Brain is an electrochemical system and recent studies suggest simultaneous measurement of interrelated brain's electrical and neurochemical activity may lead to better understanding of brain function in addition to developing optimal neural prosthetics. By exploiting opamp Time-sharing technique to minimized power dissipation and silicon area, we have fabricated a power efficient implantable CMOS microsystem for simultaneous measurement of Action Potential (AP) and neurotransmitter concentration. Both AP-recording and neurotransmitter sensing subsystems share a single 653 nW amplifier which senses picoscale to microscale current that corresponds to micromolar neurotransmitter concentration and microscale AP voltage. This microsystem is fabricated in CMOS 0.18 µm technology and tested using recorded signals from dorsal premotor cortex (PMd) area of a macaque monkey in our lab.**

I. Introduction

Simultaneous fast measurements of APs and neurotransmitters could also prove invaluable for basic neuroscience. Many questions regarding the interplay of APs and neurotransmitters remain, such as how the temporal dynamics of neurotransmitters regulate their function [1], and the role of evoked versus spontaneous neurotransmitter release [2]. The relationship between APs and neurotransmitters, which regulate how efficiently APs are transmitted between neurons, is a fundamental component of how the brain processes information, and chronic simultaneous measurements of both could have many applications. Thus a neural interface should not only detect the action potentials but also measure the neurochemical concentrations in synaptic areas, as shown in Fig. 1.

Many neurological diseases such as epilepsy and Parkinson's are associated with signature increases or decreases in neurotransmitter levels [3,4,5]. By monitoring these levels, a brain machine interface could react to pathological brain states or relay the information for treatment of the disease. Indeed, the relative concentration of neurotransmitter GABA has been shown to be a viable signal for the detection of seizure onset [6]. In addition to detection, the dynamics of neurotransmitter levels could also provide invaluable information for understanding the disorders.

Even in the absence of pathological brain states, real time monitoring of neurotransmitters provides brain machine interfaces with complementary information to electrophysiology. Changes in neurotransmitter concentration reflect release and uptake of the molecule by synapses, and modulate the probability that an action potential will be generated. Synaptic activity that does not lead to an action potential, and therefore would not be picked up by conventional extracellular electrodes, could still be detected by brain machine interfaces sensitive to neurotransmitter levels. These signals could potentially be used to aid in the control of neural prosthetic, and represent information not contained in the timing of action potentials.

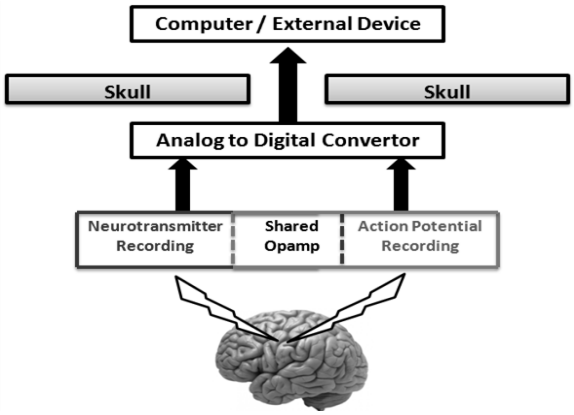

Fig 1. System level block diagram of an Action Potential and Neurotransmitter recording interface

Fig. 2. Electrochemical Dual Dual mode, shared opamp Circuits fabricated in CMOS 0.18 um

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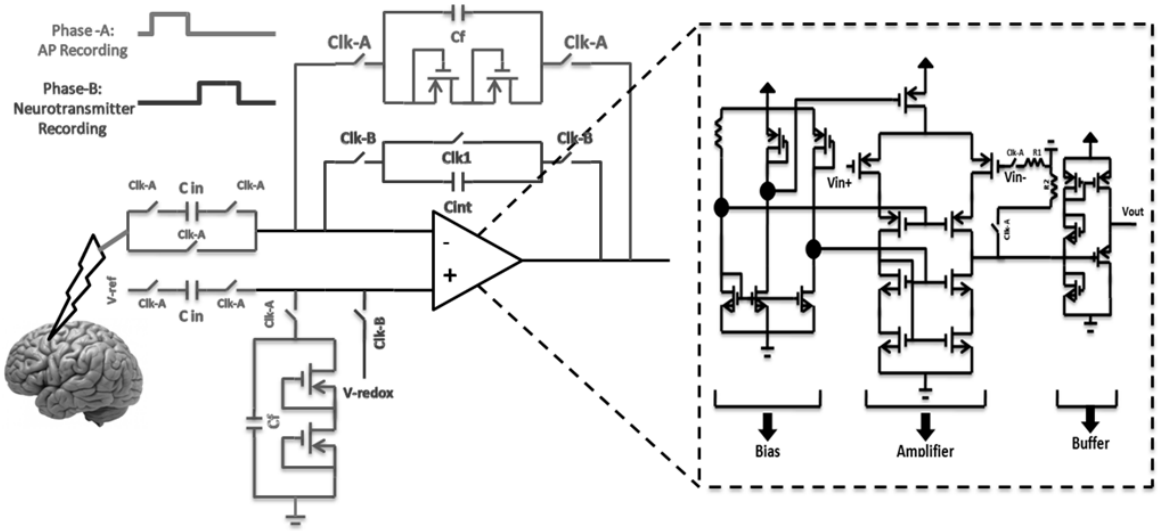

Fig. 3. Dual mode, shared opamp electrochemical neural interface.

We developed a low power implantable microsystem which measures AP and neurotransmitter simultaneously. Both action potential recording and neurotransmitter measuring subsystem share a single low power opamp which has 63.57 dB DC Gain and 4.6 KHz bandwidth while consuming 653 nano watts. This technique is called "opamp time sharing" or "shared opamp" which reduces the power consumption significantly. Since one of our ultimate goals is to apply this neural interface in an implantable neural prosthetic; microsystems's power efficiency is crucial. The system should operate on minimum power to avoid over heating the brain tissue. In addition frequent battery replacement and surgical procedures to replace the implants are unnecessary.

This dual recording interface, Fig. 2., is fabricated in CMOS 0.18 µm technology and tested using recorded signals from parietal reach region (PRR) and dorsal premotor cortex (PMd) of an awake, male macaque monkey in physiology division of our lab.

II. Electrochemical Recording Circuit Design

The electrochemical neural interface consists of two parts, an action potential recording and neurochemical measuring subsystems as shown in Fig. 3. By applying time-sharing technique, both subsystems are connected to a single opamp by CMOS switches. This leads to significant power dissipation and area reduction which is invaluable for implantable neural prosthetics. We employ a two phase none over lapping clock with variable frequency; in phase A the neural interface operates as an action potential recoding interface that detect brain's micorscale electrical activities and in phase B it operates as a low power potentiostat that measures pico to microscale current which corresponds to neurotransmitter concentration.

The shared element is a single stage, telescopic operational amplifier fabricated in CMOS 0.18 um technology as shown in Fig. 3. The main reason of selecting this topology is its low power dissipation in addition to its high gain and input referred noise. In addition since there is no capacitor, amplifier occupies a very small area. The main drawback of telescopic amplifier is its limited swing; but based on AP and Current range, the achieved swing is adequate. We have an on chip biasing circuitry which adds to system accuracy and mobility. The neural amplifier is design to operate in weak and moderate inversion region to minimize power dissipation. It has 63.57 dB DC Gain and 4.6 KHz bandwidth while consuming 653 nano watts, as shown in Fig. 3. Furthermore; the amplified signal is buffered in order to drive the ADC. A source follower voltage buffer is used to prepare the amplified signal for further processing. The amplifier speciation is selected based on the nature of the measuring signals which will be discussed in more detail. More over its power dissipation is one of the lowest reported to date, as shown in Table I.

TABLE I
Low Power Amplifier Specifications and Comparison.

Specifications	This Work	[7]	[8]
Fabrication Year	2013	2013	2013
Technology (µ m)	0.18	0.18	0.18
DC Gain (dB)	63.57	48.36	55.9
3dB Bandwidth (KHz)	4.6	3.7	1 to 10
Phase Margin (deg)	84.45	59	63
Supply Voltage (V)	1	0.9	1
Output Swing (V)	-0.3,+0.3	-0.2,0.2	-0.3, 0.3
Power (µ W)	**0.653**	**3.7**	**13**

A. Action Potential Recording Sub-System

Recording of neural activity has been done using bench-top biomedical instrumentation equipment. These equipments are stationary, bulky and limited to few recording channels. Since 1971 (Wise at Stanford) there have been remarkable efforts to miniaturize the recording systems using JFET and CMOS technology [9]. By increasing the number of recording channels, amplifier's low power dissipation is more essential than ever since each channel requires an amplifier. Several promising low power designs have been reported [9,10]. To design an optimum low power neural amplifier, it is important to understand the nature of action potential first. The AP's magnitude ranges between -300 to 400 uW and its bandwidth is between 0.1 to 3.5 KHz [11]. In phase A, Our neural interface operates as action potential recording system with one of the lowest

power dissipation reported to date, Table I. To validate the subsystem performance, we have used action potentials which were recorded in physiology division of our lab.

In order to eliminate the DC artifact the microsystem should act as a band pass filter. The mid-band gain of the filter is decided by the capacitors ratio C_{in}/C_f , the bandwidth is $g_m/2\pi C_{load} \times C_{in}/C_f$. The lower cut off frequency is given by $1/2\pi R_{feedback} C_f$. To achieve sub hertz lower cut off frequency the feedback resistive element should be in giga ohms order. A linear resistance with such value consumes a lot of silicon area. Therefore, the resistor element is implemented as a diode connected MOS transistor in sub-threshold region.

We applied chronic multi-electrode arrays in an awake, behaving male macaque monkey. Figure Fig. 4, shows 50 waveforms from one neuron in dorsal premotor cortex (PMd) area. These waveforms were recorded approximately six months after array implantation. The initial signal magnitude was between -99.4 to 39.78 uV and amplified to -0.15 to 0.06 V as shown in Fig. 4.

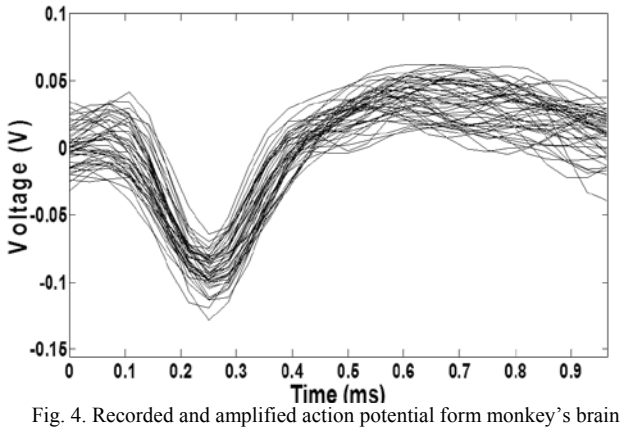

Fig. 4. Recorded and amplified action potential form monkey's brain PMd

B. Neurotransmitter Recording Sub-System

In Phase B, the neural interface operates as a current conveyor potentiostat that detects picoscale to microsclae current which corresponds to micromolar neurotransmitter concentration. Previous studies suggest that electrochemical sensors are suitable for neurochemical sensing [12, 13]. Every neurochemical is related to a certain voltage [14]. To measure neurotransmitter concentration, this voltage is applied between the working and reference electrode. The potential difference produces a reduction-oxidation (red-ox) current which is proportional to the neurotransmitter concentration [15]. Our goal is to implement a device that possesses high sensitivity, high chemical selectivity, and fast temporal resolution. Thus we are applying Fast-scan cyclic voltammetry technique which possesses good chemical selectivity while maintaining subsecond temporal resolution [16].

$V_{red\text{-}ox}$ is applied across R_{Sensor} (Electrode) as shown in Fig. 3. $I_{red\text{-}ox}$ which is proportional to neurochemical concentration, accumulates charge on C_{INT} over the integration period $T_{INT.}$ Output voltage is calculated by Equation (1). Fig. 5 shows the measured red-ox current in response to addition of 20 uM Dopamine (neurotransmitter).

$$V_{out} = \frac{1}{C_{INT} \times R_{Sensor}} \int_0^{T_{INT}} V_{red-ox}\, dt \qquad (1)$$

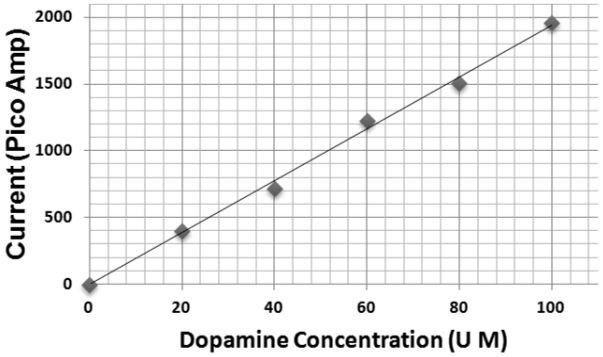

Fig. 5. The red-ox current in response to addition of 20 µM DA

III. CONCLUSION

A power-efficient electrochemical neural interface was presented. Applying time-sharing technique allows both action potential recording interface and neurotransmitter sensing subsystem share a single opamp to decrease power dissipation and silicon area. Simultaneous measurement of brain's electro-chemical activity may aid neuroscientists to achieve a better understanding of brain which lead to improved solutions for nervous system related diseases. In our future work, we apply this interface as a subsystem for an implantable neural prosthetic.

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REFERENCES

[1] Jennings, Katie A. "A Comparison of the subsecond dynamics of neurotransmission of dopamine and serotonin." *ACS chemical neuroscience* 4.5 (2013): 704-714.

[2] Ramirez, Denise MO, and Ege T. Kavalali. "Differential regulation of spontaneous and evoked neurotransmitter release at central synapses." *Current opinion in neurobiology* 21.2 (2011): 275-282.

[3] Obeso, Jose A., et al. "Functional organization of the basal ganglia: therapeutic implications for Parkinson's disease." *Movement Disorders* 23.S3 (2008): S548-S559.

[4] Parrot, Sandrine, et al. "High temporal resolution for in vivo monitoring of neurotransmitters in awake epileptic rats using brain microdialysis and capillary electrophoresis with laser-induced fluorescence detection." *Journal of neuroscience methods* 140.1 (2004): 29-38.

[5] Poustinchi, Mohammad, and Sam Musallam. "Towards an implantale intelligent CMOS neurotrophic factor delivery micro neural prosthetic for Parkinson's disease." In *Neural Engineering (NER), 2013 6th International IEEE/EMBS Conference on*, pp. 863-867. IEEE, 2013.

[6] Treiman, David M. "GABAergic mechanisms in epilepsy." *Epilepsia* 42.s3 (2001): 8-12.

[7] Wilson, William, Tom Chen, and Ryan Selby. "A current-starved inverter-based differential amplifier design for ultra-low power applications." *Circuits and Systems (LASCAS), 2013 IEEE Fourth Latin American Symposium on*. IEEE, 2013.
[8] Wu, C-Y., W-M. Chen, and L-T. Kuo. "A CMOS Power-Efficient Low-Noise Current-Mode Front-End Amplifier for Neural Signal Recording." (2013): 1-1.
[9] Jochum, Thomas, Timothy Denison, and Patrick Wolf. "Integrated circuit amplifiers for multi-electrode intracortical recording." *Journal of neural engineering* 6.1 (2009): 012001.
[10] Seo, Dongjin, et al. "Neural dust: An ultrasonic, low power solution for chronic brain-machine interfaces." *arXiv preprint arXiv:1307.2196* (2013).
[11] Hopfield, J. J. "Pattern recognition computation using action potential timing for stimulus representation." *Nature* 376.6535 (1995): 33-36.
[12] Luo, Tao, et al. "CMOS potentiostat for chemical sensing applications." *Sensors, 2013 IEEE*. IEEE, 2013.
[13] Range, Wide. "Integrated potentiostat for neurotransmitter sensing." *IEEE Engineering in medicine and biology magazine* (2005): 23.
[14] Robinson, Donita L., et al. "Detecting subsecond dopamine release with fast-scan cyclic voltammetry in vivo." *Clinical chemistry* 49.10 (2003): 1763-1773.
[15] Poustinchi, Mohammad, and Sam Musallam. "Low power noise immune circuit for implantable CMOS neurochemical sensor applied in neural prosthetics." In*Neural Engineering (NER), 2011 5th International IEEE/EMBS Conference on*, pp. 695-699. IEEE, 2011.
[16] Poustinchi, Mohammad, and Sam Musallam. "Low power CMOS neurochemical biosensor application in an implantable intelligent neurotrophic factor delivery hybrid microsystem for Parkinson's." In *Biomedical Engineering (MECBME), 2014 Middle East Conference on*, pp. 131-134. IEEE, 2014.