An Electrochemical Dopamine Sensor with CMOS Detection Circuit

Feng-Lin Zhan[2] , Li-Min Kuo[2],Shi-Wei Wang[2],
and Michael S.-C. Lu[1,2]
[1]Department of Electrical Engineering and
[2]Institute of Electronics Engineering
National Tsing Hua University,
Hsinchu 300, Taiwan, R.O.C.
Email-Address: sclu@ee.nthu.edu.tw

Wen-Ying Chang[3], Chih-Heng Lin[3],
and Yuh-Shyong Yang[3]
[3]Department of Biological Science and Technology
National Chiao Tung University,
Hsinchu 300, Taiwan, R.O.C.

***Abstract*- This paper presents the use of interdigitated microelectrodes as the platform for electrochemical sensing of the neurotransmitter dopamine. Gold electrodes with gaps ranging between 3 μm to 7 μm are fabricated by the lift-off technique. The reduction and oxidation potentials for dopamine are determined by voltammetry using the fabricated microelectrodes. A CMOS sensing circuit is used to amplify the electrochemical current produced by the working electrodes. Experimental result shows that for a dopamine concentration of 10 μM, the measured current value is 11 pA.**

I. INTRODUCTION

Parkinson's disease is a degenerative disease of the nervous system associated with trembling of the arms and legs, stiffness and rigidity of the muscles and slowness of movement. Until now, in humans, a deficiency of the neurotransmitter dopamine in the basal ganglia of the brain has been known well to play a critical role in Parkinson's disease [1]. Dopamine acts like a brain chemical to transmit messages to parts of the brain for coordination of body movements. The main pathological symptom in Parkinson's disease is the preferential loss of dopamine neurons in substantia nigra par compacta [2].

With the advances in microfabrication, microelectrodes have become a popular platform for use in electrochemical detection. Immunoassays based on redox reactions have great potential to be incorporated in lab-on-chip systems. The integration of signal-conditioning circuits for system miniaturization could be the next step for self diagnosis at home. Recently a 16×8 CMOS sensor array chip for electrochemical detection of DNA sequences has been developed [3]. Microelectrodes with a narrow linewidth, especially in the micrometer range, provide the capability for more sensitive detection than their macro-counterparts, as the chemical products produced at one side of the electrodes may be readily collected at the other side of adjacent electrodes and regenerated to the original states. Thus the anodic and cathodic currents increase due to the phenomenon of fast redox recycling. Microelectrodes of 30-μm think were reported by Honda et al. [4] for electrochemical detection of alpha-fetoprotein (AFP) at 6 ng/mL. Paeschke et al. [5] reported microelectrodes with a sub-μm gap, which is in the same order as the diffusion layer thickness, to improve the collection efficiency. Since dopamine oxidation can form polymeric quinones, the use carbonaceous material has been suggested to enhance the electrodes for improving the detection limit [6].

The dopamine sensor presented in this work combines the techniques from microfabrication, electrochemical sensing, and integrated circuit design. By amplifying and integrating the produced current over a capacitor, the sensing circuit shows a measured current value of about 11 pA at a dopamine concentration of 10 μM. The results indicate promising potential for use in future clinical applications.

II. SENSOR FABRICATION

For fabrication of the interdigitated microelectrodes, a 0.5-μm low-stress silicon dioxide was first deposited on a p-type silicon substrate by low-pressure chemical vapor deposition. The fabrication involves lithography, evaporation, and the lift-off steps as shown in Fig. 1, Micrograph of the fabricated electrodes (50-nm Au + 5-nm Cr) is shown in Fig. 2. The metal pads were encapsulated by epoxy after wirebonding for measurements performed in liquid environment.

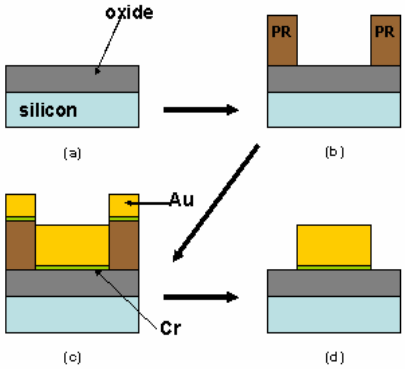


Figure 1. Schematic of the fabrication process.

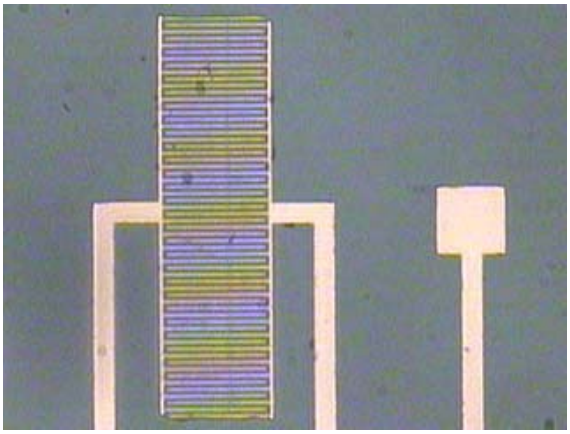


Figure 2. Micrograph of fabricated microelectrodes.

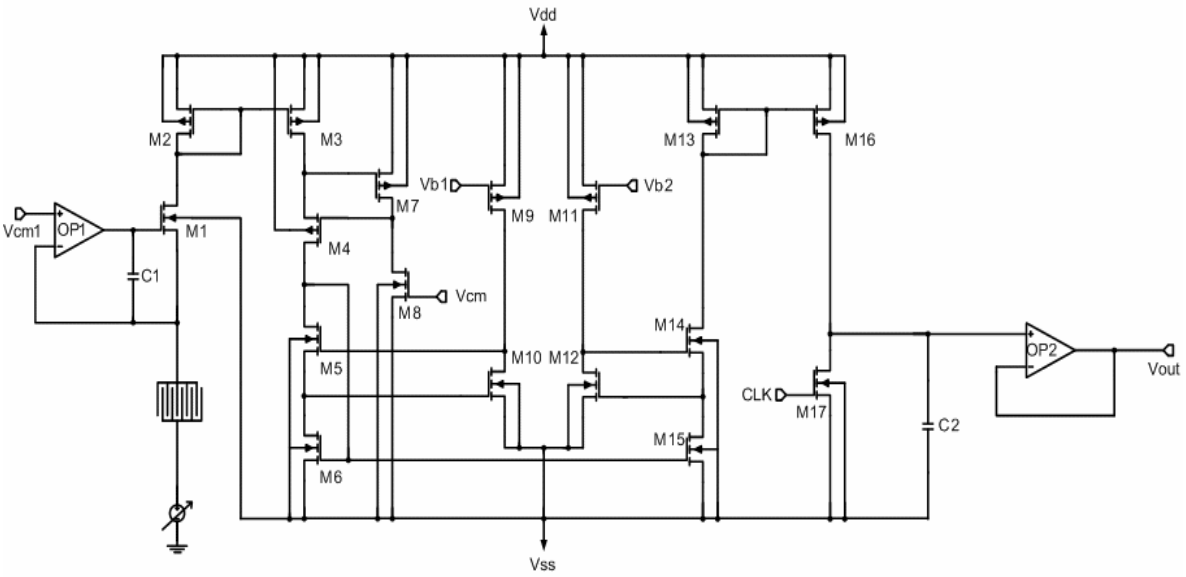


Figure 3. Schematic of the current-sensing circuit.

III. SENSING CIRCUIT DESIGN

For detection of the electrochemical current in the range between pA to μA as produced by the dopamine redox reaction, a CMOS circuit, as shown schematically in Fig. 3, has been designed and fabricated by using the TSMC 0.35-μm 2P4M CMOS process. The circuit contains three cascaded current mirrors in shunt to provide a current gain of about 50. The output impedance in the current mirror is finite, and as a result, the output current would be sensitive to the fluctuations of the drain-source voltage across M3 due to channel-length modulation although a long-channel device is used [7]. To obtain a stable drain-source voltage across M3, a current conveyor (M4, M7) is utilized to enhance the output impedance [8]. Similarly, M12 and M14 enhance the output impedance of M15. Transistor M9 is used to bias the feedback circuit. Under low current sensing situation, M5 would be operated in the triode region. The transistor M6 always operates in the saturation region. A double-poly capacitor of 100 fF is used to integrate the amplified current to a voltage value, which is subsequently output after a buffer circuit. An external clock signal resets the output and controls the integration time.

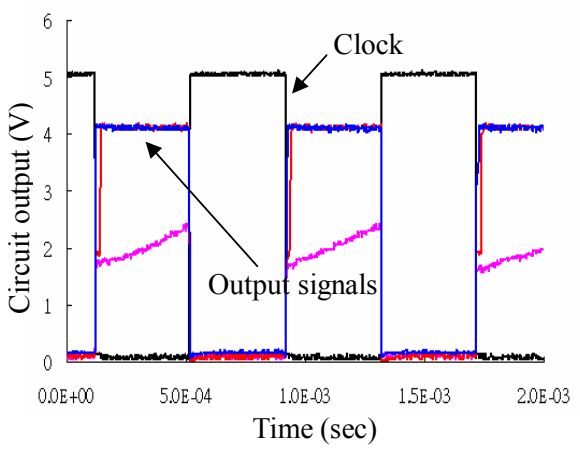
IV. EXPERIMENT

The circuit characterization in Fig. 4 shows the output voltage waveforms corresponding to input current values from 80 pA to 1 μA as provided by a sourcemeter (Keithley). The voltages rise to about 4.1 V as predicted by simulations.

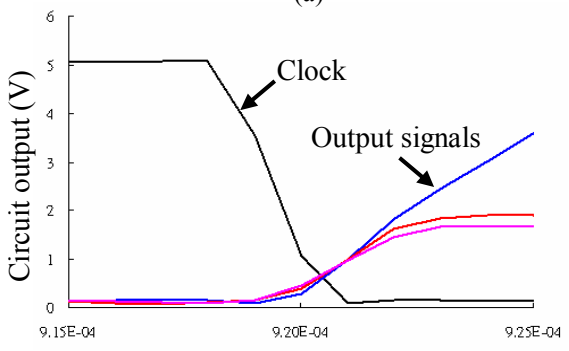
Next cyclic voltammetry using the fabricated microelectrodes was performed to identify the respective oxidation and reduction potentials. Molecules adjacent to the electrode will be oxidized or reduced in the cyclic voltammetry. Electroactive functional groups presented on the electrode surface can also be oxidized or reduced, producing additional background current. The presence of an electroactive species, such as dopamine, may produce only a small increase in the background current. Since the microelectrodes have a stable background value over several seconds, it can be subtracted to reveal the real changes in current.

The cyclic voltammetry of dopamine at different concentrations (0.02 mM to 20 mM) was performed using the fabricated microelectrodes (150 μm in length, 7 μm for gap and 140 pairs) and measured by an electrochemical workstation (Model 701B, CH Instruments, Austin, TX). A series of well-defined peaks were obtained with a good reversibility. Fig. 5(a)

shows a pair of reductive and oxidative peaks where the curves have the maximum absolute values of current. The scan rate on electrode was 0.1 V/s with the potential ramping from -0.2V to 0.8V. After subtraction of the background current due to the phosphate buffer solution, the peak current during reduction is plotted with respect to concentration in Fig. 5(b), which shows a minimum measured current of 10 nA at 20 µM. For comparison, the voltammetry experiment was also performed using a commercial electrode setup consisting of a gold working electrode, a platinum auxiliary electrode, and an Ag/AgCl reference electrode. The curves depicted in Fig. 5(c) correspond to concentrations from 0.2 mM to 2 mM. The redox peaks occur at similar potentials as in Fig. 5(a).



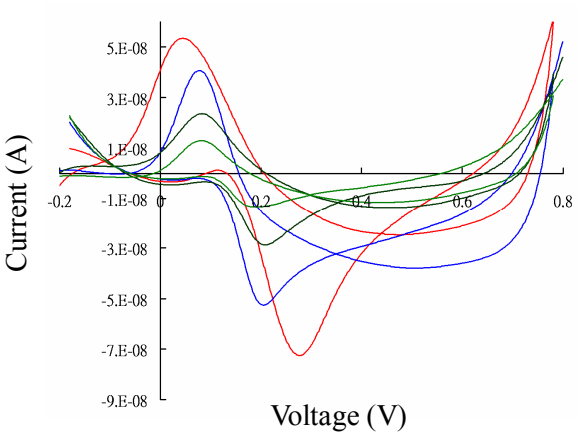
(a)



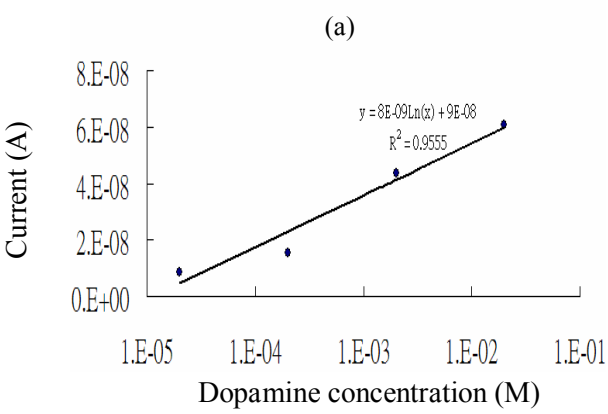
(b)

Figure 4. (a) Sensor output under different current values. (b) The closed-up view.

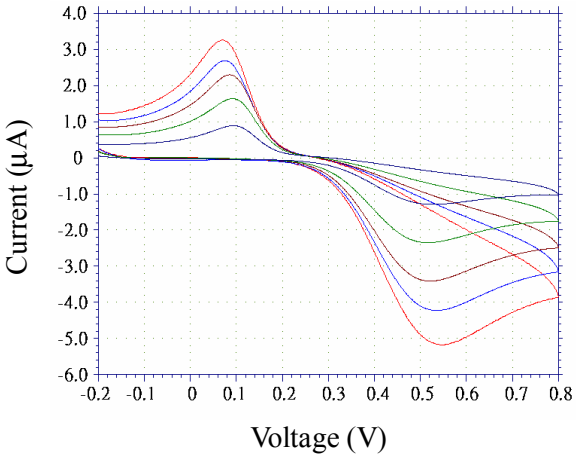
As shown in Fig. 6, the microelectrode chip and the CMOS chip were connected through wirebonding on a PC board. All the pads and the CMOS chip were covered by epoxy. The oxidation potential was 0.45 V by assigning 1.65 V and 1.2 V respectively to the working and auxiliary electrodes.



(a)



(b)



(c)

Figure 5. (a) Measured cyclic voltammograms using fabricated electrodes for dopamine concentrations from 0.02 to 20 mM. (b) Peak current vs. dopamine concentration (voltage = 0.07V). (c) Measured cyclic voltammograms using commercial electrodes for dopamine concentrations from 0.2 to 2 mM.

We successively added in phosphate buffer solution (27 µL, pH = 7), and dopamine portions of increasing concentration of 3 µL (100 µM), 18 µL (200 µM), 12 µL (2 mM), and 10 µL (20 mM). Fig. 7 shows the measured output waveforms with respect to different concentrations. At 10 µM the measured electrochemical current value is 11 pA.

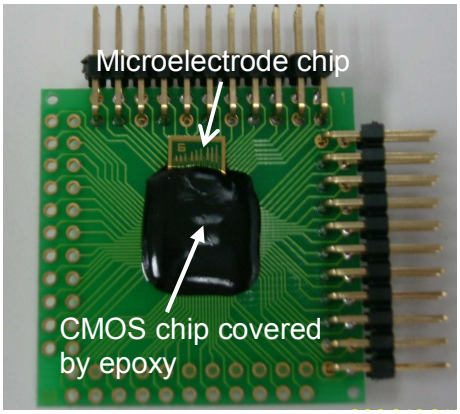


Figure 6. Packaged microelectrode and CMOS chips on a PC board.

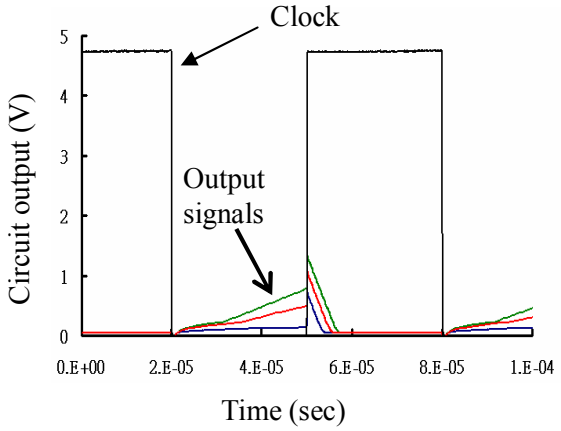


Figure 7. Measured circuit output waveforms for dopamine concentrations from 10 µM to 3.25 mM.

V. DISCUSSION AND CONCLUSION

This work presents the attempt on integrating interdigitated microelectrodes with CMOS circuitry for electrochemical detection. To further enhance the detection linearity, a flow-cell setup with the flow-rate control would be needed to improve the recycling rate of redox reaction. And modification of electrode surface is another way to resolve the detection issue of residues produced by oxidation. A fully integrated CMOS biosensor chip is our goal to accomplish in the future.

ACKNOWLEDGMENT

The authors would like to thank the National Tsing Hua University and the National Science Council, Taiwan R.O.C., for support of this research effort. We are grateful to the National Chip Implementation Center for support of chip fabrication, and the National Center for High-Performance Computing for support of simulation software. Prof. Weileun Fang's generous support of lab equipments is greatly appreciated.

REFERENCES

[1] Y. Agid, F. Javoy-Agid, and M. Rubberg, "Biochemistry of neuro-trasmitters in Marsden CD", Fahn S. eds. Movement disorders 2, neurology London: Butterworths:7, pp.166-230. 1987.

[2] A. M. Owen, J. Doyon, A. Dagher, A. Sadikot, and A. C. Evans, " Abnormal basel ganglia outflow in Parkinson's disease identified with PET implications for higher cortical function," *Brain*, vol. 121, pp.949-965, 1998.

[3] M. Schienle, C. Paulus, A. Frey, F. Hofmann, B. Holzapfl, P. Schindler-Bauer, and R. Thewes, "A fully electronic DNA sensor with 128 positions and in-pixel A/D conversion," *IEEE J. Solid-State Circuit*, vol. 39, no. 12, pp. 2438-2445, 2004.

[4] N. Honda, M. Inaba, T. Katagiri, S. Shoji, H. Sato, T. Homma, T. Osaka, M. Saito, J. Mizuno, and Y. Wada, "Highly effciency electrochemical immuno sensors using 3D comb electrode," *Biosensors and Bioelectronics*, vol. 20, pp..2306-2309, 2005.

[5] M. Paeschke, U. Wollenberger, T. Lisec, U. Schnakenberg, and R. Hintsche, "Highly sensitive electrochemical microsensors using submicrometer electrode arrays," *Sensors and Actuators B*, vol. 26-27, pp.394-397, 1995.

[6] O. Niwa, M. Morita and H. Tabei, "Highly selective electrochamical detection of dopamine using interdigitated array electrodes modified with Nafion/polyester ionomer layered film," *Electroanalysis*, vol. 6, pp. 237-243, 1994.

[7] P. R. Gray, P. J. Hurst, S. H. Lewis, and R. G. Meyer, *Analysis and Design of Analog Integrated Circuits*, *4th Ed*., 2001.

[8] A. G. Andreou, K. A. Boahen, P. O. Pouliquen, A. Pavasovic, R. E. Jenkins, and K. Strohbehn, "Current-mode subthreshold MOS circuits for analog VLSI neural systems," *IEEE Trans. on Neural Networks*, vol. 2, pp. 205–213, Mar. 1991.