Integrated Potentiostat for Neurotransmitter Sensing

A High Sensitivity, Wide Range VLSI Design and Chip

BY KARTIKEYA MURARI, MILUTIN STANAĆEVIĆ, GERT CAUWENBERGHS, AND NITISH V. THAKOR

Sensing and measurement of neurotransmitters such as nitric oxide and dopamine may be invaluable in the basic research on neurochemistry of the nervous system and its role in neurological disorders. Certain neurochemicals can be detected using electrochemical principles but require a highly sensitive measurement device, i.e., a potentiostat. A very-large-scale-integrated (VLSI) potentiostat design with 16-channel current measuring circuitry and multiple ranges from picoamperes to microamperes is presented. The analog input current is digitized using an A/D converter design that employs a current-mode, first-order single-bit delta-sigma modulator architecture with a digitally configurable oversampling ratio (OSR) for controlling the conversion scale. The potentiostat achieves superior sensitivity (in picoampere range) along with low power (in hundreds of microwatts) and low voltage (3.3 V) operation in a 3 mm × 3 mm package. An integrated prototype is fabricated in complementary metal oxide semiconductor (CMOS) technology and experimentally characterized. The real-time acquisition of dopamine concentration in vitro is performed. Applications of the device include implantable neurochemical detection and neuroprosthetic devices.

Most of the communication in the nervous system is via electrical impulses. However, between two neurons there are nonconductive regions, synapses, across which conduction takes place through the release and uptake of chemicals called neurotransmitters, as shown in Figure 1.

Detection and measurement of these molecules is of great importance in unraveling how information is carried and processed by the nervous system. Mechanisms of several neurological disorders, like Parkinson's disease and epilepsy, are also linked to neurotransmitters [1], [2]. Several methods have been reported in the literature for analyzing neurotransmitters. Some of these are optical and chromatographic methods, positron emission tomography (PET) and single photon emission computerized tomography (SPECT) [3]–[5]. These methods are mostly indirect, detecting products of reactions involving the neurotransmitter, rather than the neurotransmitter itself. Electrochemical detection is a direct analytical method that can be applied to a subset of neurotransmitters that are electrochemically active [6], [7]. The measurement of neurotransmitters from multiple sites rather than a single site holds great potential in that it can lead to the knowledge about how the release of neurotransmitters affects the surrounding cells and tissue. This is particularly important for highly diffusive, gas-phase neurotransmitters like nitric oxide. Since the electrochemical sensors transduce concentration into current, specialized multichannel instrumentation is required to obtain readouts. This article presents novel ultrasensitive instrumentation developed by our group for this purpose. We give an introduction to integrated neurochemical sensing and electroanalysis. This is followed by the description of our design and the characterization of the fabricated device. Finally, we present experimental results with our device interfaced to electrochemical neurotransmitter sensors along with conclusions and directions for future work.

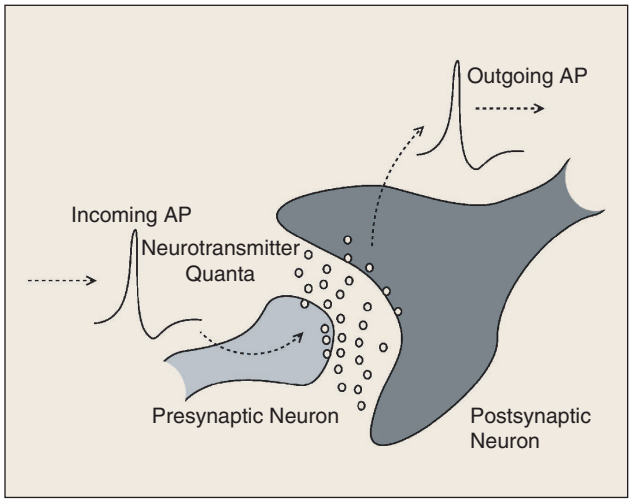

Fig. 1. A schematic of a synapse. Incoming action potential (AP) causes release of a neurotransmitter from the presynaptic cell, inducing an AP in the postsynaptic cell.

Integrated Neurochemical Sensing

Traditionally, neurological measurements have been taken using single or multiple microelectrodes. Multisite recording and stimulating probes have been developed with the associated integrated electronics for this purpose [8]. However, apart from electrical conduction of action potentials (APs) by

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neurons, such neuronal activity also involves neurochemical transmission. The electrical and chemical activities are not exclusive but modulate each other. Neurochemical sensing is thus a different paradigm for studying neural pathways. This alternate paradigm is similar to traditional patch clamp measurements. Both techniques use current sensing. In patch clamping, a voltage is applied to create a potential gradient across the membrane. In neurochemical sensing, a voltage is applied to stimulate an oxidation-reduction (redox) reaction [9]. Thus, the electronics needed for driving the electrochemical reaction must apply the redox potential and measure the current produced at the electrode surface. Usually, surface modifications of electrodes enable them to measure chemical activity. It may also be desirable to measure neurochemical activity at multiple electrode sites. The advantage of making multisite measurements is that simultaneous distributed measurements of diffusible neurochemicals are made possible. With miniaturization and advances in microfabrication, electrode arrays can be made for high spatial resolution sensing [10], [11]. Completely integrated, self-contained implantable systems can now be envisaged. These would be of significant research potential, giving us, for example, the ability to record from live, awake, and behaving animals while they are undergoing a neurological event like a stroke or a seizure. Such a probe requires the development of electronics for processing the transduced chemical sensor data to be integrated with the sensor itself. The electronics required depends in part on the kind of chemical analysis being done. The following section discusses the preferred method of electrochemical analysis and the kind of instrumentation needed for doing such a measurement and analysis.

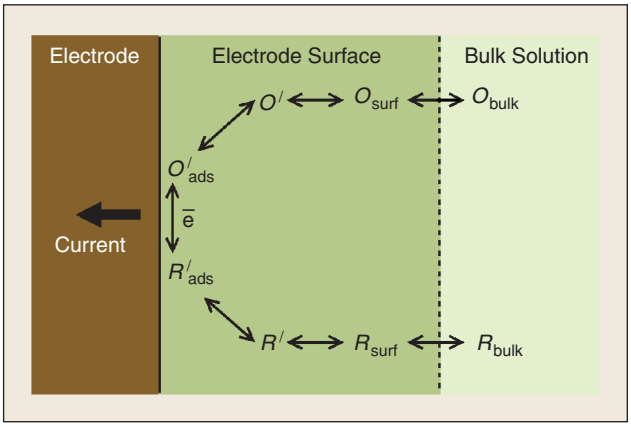

Fig. 2. A schematic showing an electrochemical reaction. The species exists in the bulk solution in the oxidized (O_{bulk}) or reduced (R_{bulk}) state. Following diffusion to the electrode, a chemical change, and adsorption, the electron transfer takes place.

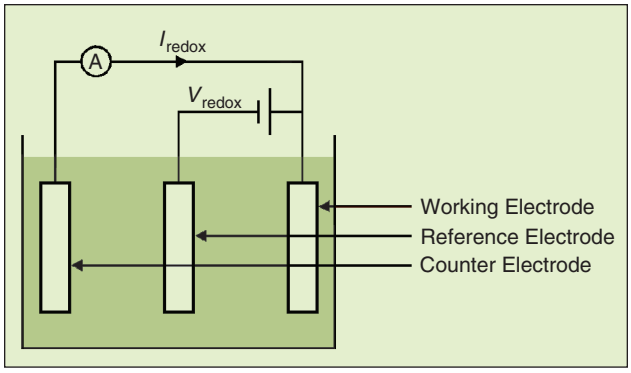

Fig. 3. A schematic of the electroanalysis setup. A redox potential V_{redox} is applied between the working and the reference electrode, and the resulting electrochemical current is measured between the counter and working electrodes.

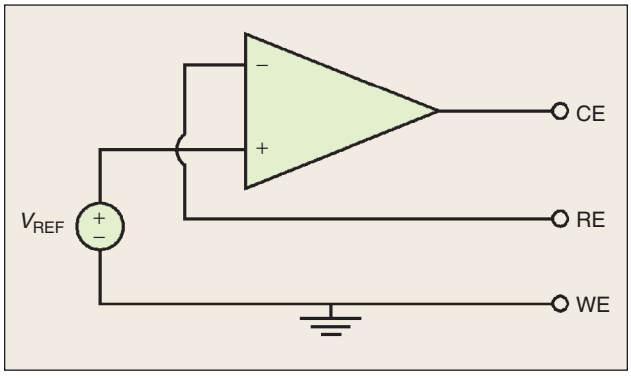

Fig. 4. A schematic of a simple potentiostat circuit using an opamp.

Electrochemical Analysis

Electrochemical analysis is based on testing the redox properties of the substance under measurement at the electrode surface [9]. Basically, these are the properties of electron-transfer reactions involving the chemical being analyzed. The reaction is a multistep process, as shown in Figure 2.

The species to be detected exists in the bulk of the solution in either the oxidized (O_{bulk}) or reduced (R_{bulk}) state. The species diffuses to near the surface of the electrode (O_{surf} or R_{surf}), following which it undergoes a chemical change (O' or R') and gets adsorbed on the electrode (O'_{ads} or R'_{ads}). The electron transfer takes place in this adsorbed state. Finally, the products desorb from the surface and diffuse away into the bulk of the solution. The loss of electrons is called reduction, and the gain is called oxidation. Simultaneous occurrence of reduction and oxidation is called a redox reaction. The experimental setup involves three electrodes inserted into a solution containing the species under analysis. Thermodynamically, redox reactions can either be spontaneous or need to be driven. The electron transfer in a spontaneous reaction sets up a characteristic potential across the two electrodes. This characteristic potential is called the redox potential. A preferred redox potential, suited for the species to be detected, needs to be applied across the electrodes to optimally drive a nonspontaneous redox reaction. In such a case, the current flow caused by the electron transfer is directly proportional to the concentration of the reactant. This is the principle behind detecting and mapping out neurotransmitters electrochemically. The particular redox potential favored for a given neurotransmitter is applied across the electrodes. The resulting current is also measured with the same set of electrodes. The instrument needed, a potentiostat, requires the ability to measure current at a fixed potential. Figure 3 shows a schematic of the setup.

Since physiological concentrations of various neurotransmitters are of the order of nanomolar and lower, the potentiostat needs to be able to measure currents of the order of nanoamperes or even picoamperes. Potentiostats have been around for a very long time. Traditionally, these instruments have been

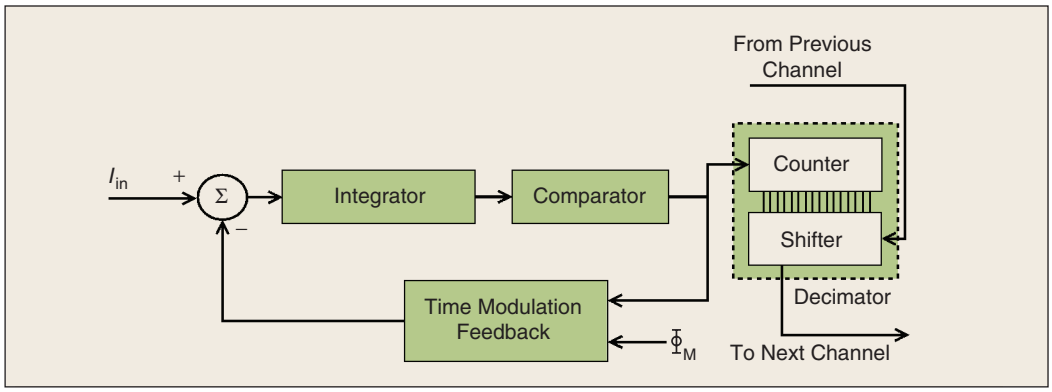

Fig. 5. A block diagram of one channel of the detection system. The potentiostat current I_{in} is digitized by the delta-sigma converter and stored in the output register, which is cascaded to the next channel.

large benchtop instruments with functionality beyond what their name signifies—keeping a static potential. A potentiostat is a three-terminal device. It has a working, a reference, and a counter electrode. The electrical potential between the working and reference electrodes is maintained at a preset value. This is done by forcing some required current through the counter electrode, such that the desired potential is maintained. This is the potentiostatic current we are interested in measuring. Figure 4 shows the circuit diagram of a basic potentiostat.

The output voltage of an opamp with an open loop gain A is given by

$$e_{OUT} = A(e_+ - e_-). \tag{1}$$

Let V_{Cell} denote the drop between the counter and working electrodes and the subscripts CE, WE, and RE denote the counter, working, and the reference electrodes, respectively. Since WE is grounded, single-ended potentials are referred to it. Therefore, $e_+ = V_{REF}$, $e_- = V_{RE-WE}$ and $e_{OUT} = V_{CE-WE} = V_{Cell}$. Substituting in (1)

$$V_{Cell} = A(V_{REF} - V_{RE-WE}) \tag{2}$$

$$V_{RE-WE} = V_{REF} - \frac{V_{Cell}}{A}. \tag{3}$$

For an ideal opamp, $A \to \infty$. Thus

$$V_{RE-WE} \approx V_{REF}. \tag{4}$$

The reference electrode must not carry any current to prevent an ohmic drop across the solution due to current in that branch of the circuit. If present, this drop superimposes on the set potential between the reference and the working electrodes, thereby changing it. Since the potentiostat for our application is expected to deal with very small currents, the ohmic drop would be negligible. Thus, for our purpose, a potentiostat would be used in the two terminal mode with the reference electrode being short-circuited to the counter electrode.

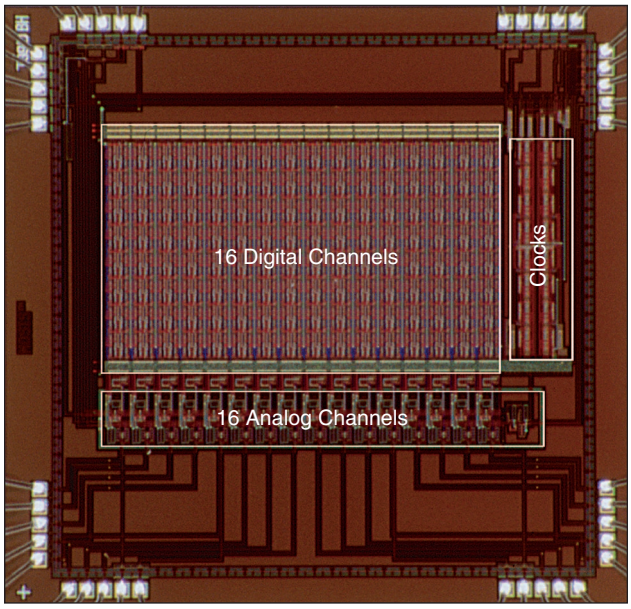

Fig. 6. A micrograph of the VLSI potentiostat. The die size is 3 mm × 3 mm. The transistor count is approximately 28,000 and the number of bondpads is 40.

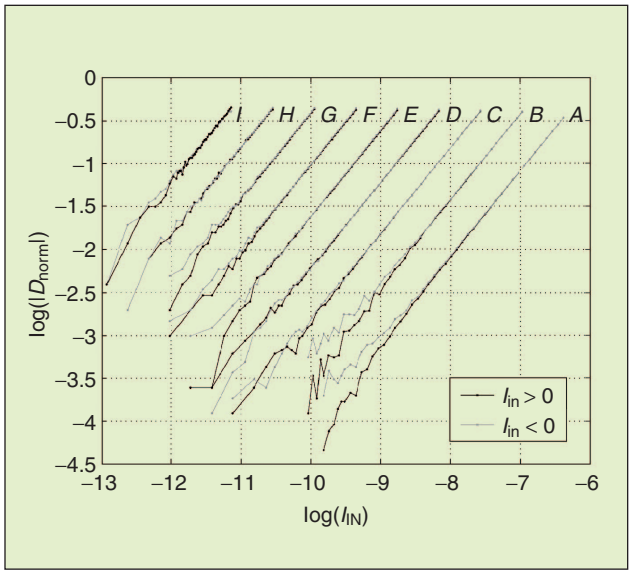

Fig. 7. The characteristics of the potentiostat at several scales and gains. Note that the potentiostat works in a linear regime over several decades. Gain selection (A–I, Table 1) makes it possible to sense the redox current over very wide ranges.

Detection and measurement of neurotransmitters is of great importance in unraveling how information is carried and processed by the nervous system.

Integrated VLSI Potentiostat

Traditional potentiostats are unsuited to our application of measuring neurochemicals. The problem with these instruments is their size (several inches; several tens of kilograms), complexity (capable of potentiostatic, galvanostatic, impedance, and other experiments) and cost (several thousands of U.S. dollars per channel). Basically, the instruments have been developed for electrochemical research, such as the study of corrosion involving large currents, and are a poor match for the current magnitudes, frequencies, and experimental requirements of biological sensing. VLSI potentiostat designs would be very attractive for our application. VLSI designs offer multichannel capability, very high sensitivity, low power consumption, and a very small footprint. They can be integrated with sensors and telemetry to develop self-contained implantable probes. VLSI potentiostats with a few parallel channels have been reported before. Turner et al. [12] use a direct current-to-voltage conversion with an opamp and a resistor. In another design, the input current is integrated on a capacitor and the voltage across the capacitor is sampled [13]. The design presented in [14] has a current amplification input stage followed by an A/D converter. In general, there are two stages in measuring an analog current. The current can be converted into an analog voltage and reported [12], [13], or this analog voltage can further be digitized by an A/D converter [14]. We chose the latter system, as it is more complete and robust and lends itself to easy collection and processing of data. The main challenge in either design is the ability to reliably convert very small currents into voltages. Most designs reported in literature use some kind of amplification to get the input currents into a more manageable range. The problem with current amplification is that it is an inherently nonlinear analog operation, and it distorts the current that is finally converted into voltage. The result is an imprecise measurement of the input current and, thus, of the concentration.

In our design [15], we use a novel mechanism by which the current is amplified by integration over a certain period. The distortion is much less because the gain is implemented as a precisely controllable digital number, which sets the duration of the integration period. The current is integrated on a capacitor for conversion into voltage. Following this circuit stage, we use a delta-sigma A/D converter with a novel time-

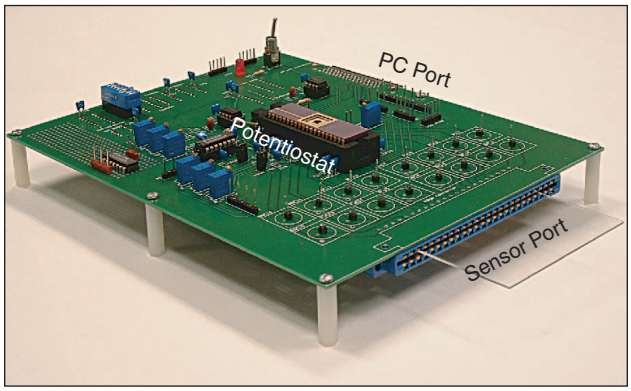

Fig. 8. A photograph of the setup showing the potentiostat chip and the custom PCB.

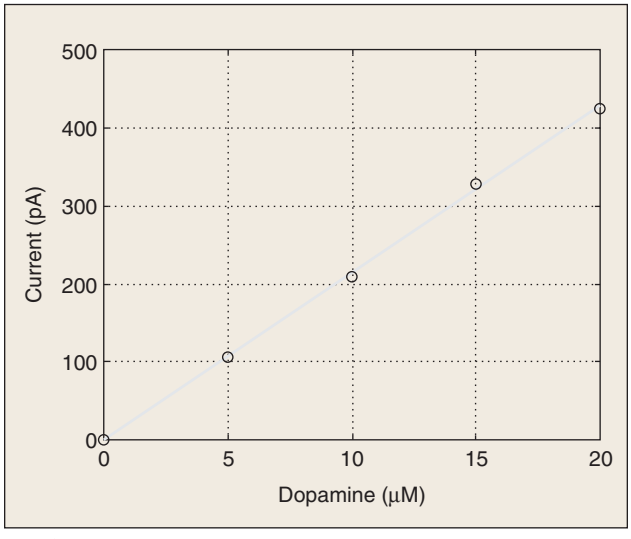

Fig. 9. The static current output of the potentiostat chip in response to additions of 5 μM dopamine.

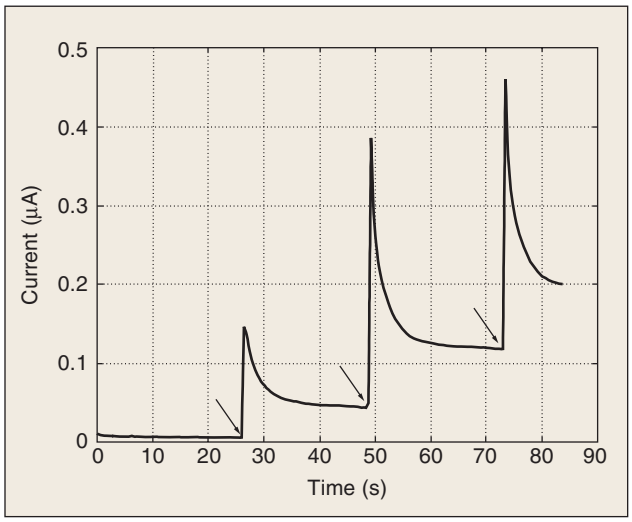

Fig. 10. The real-time acquisition of dopamine concentration. Boluses of millimolar concentrations of dopamine are added at times denoted by the arrows.

A preferred redox potential, suited for the species to be detected, needs to be applied across the electrodes to optimally drive a nonspontaneous redox reaction.

modulated feedback to digitize the voltage. The choice of the A/D converter is motivated by the low-frequency nature of the currents being measured. Neurotransmitter concentrations change fairly slowly, on the order of seconds. Delta-sigma A/D converters are particularly suited to such cases, as they involve a trade-off between speed of conversion and resolution [16]. Thus, because the input currents do not have to be sampled very often, we can increase the resolution of the measurements. The resolution and the dynamic range are also linked, with a higher resolution available for a smaller dynamic range. Measurements can be made across a wider dynamic range at the cost of losing resolution. This resolution versus dynamic range trade-off is necessary to measure a wide range of neurotransmitter concentrations. The same structure is duplicated on 16 parallel channels to implement the 16-channel VLSI potentiostat reported here. Figure 5 gives the block diagram of a single-channel implementation of our design.

Delta-sigma modulators require a reference current of a magnitude similar to the input current. The need for a wide dynamic range, with a fixed reference current, without the use of noisy current amplification, necessitates changing the standard delta-sigma architecture. This change has been implemented as a time modulation in the feedback loop shown in Figure 5, a block diagram of a single-channel implementation of our design. The parameters effecting the modulation are the gain and the OSR, which are both set digitally prior to the current conversion. The resolution, the dynamic range, and the conversion speed are also linked by the set gain and OSR.

The potentiostat was implemented on a 3 mm × 3 mm VLSI chip in 0.5-μm triple-metal, double-poly CMOS technology. The chips were fabricated through the MOSIS integrated circuit fabrication service (http://www.mosis.org). Figure 6 shows a micrograph of the fabricated potentiostat.

Characterization

For testing and characterizing the chip, we developed and fabricated a custom printed circuit board (PCB). The board was connected to a PC using a National Instruments data acquisition (DAQ) card. The board and the chip were powered by the DAQ card. All biases external to the chip were generated on the PCB using potentiometers and the analog outputs of the DAQ card. An oscillator and a divide-by-two counter provided a wide range of system clock speeds to test the system on. The digital I/O pins of the card were used to generate the control signals for the chip and for acquiring the serial bit-stream output of the chip. For testing purposes, the currents were sourced by a Keithley Instruments Model 6430 source/meter. This instrument was also connected to the PC and controlled via a National Instruments general purpose interface bus (GPIB) card to allow for easy and automated characterization. Both the GPIB and the DAQ cards were controlled on the PC using MATLAB. The external system clock, redox voltage reference, and the delta-sigma reference current were fixed at 2 MHz, 1.0 V, and 600 nA, respectively. Figure 7 shows the normalized digital output of the chip for several current ranges with corresponding gains and OSRs. The data is shown in Table 1.

The raw output of the chip needs to be normalized to compare characteristics across various scales and gains. The raw data is normalized thus. The expected number of bits of resolution in the A/D conversion depends on the OSR of the delta-sigma modulator (Table 1). This gives us the maximum digital output $(D_{\max})$ of the chip for a set gain and OSR. The digital output D_{raw} of the chip decreases as the current is swept from negative to positive. When $I_{\text{in}} = 0$, let $D_{\text{raw}} = D_{\text{lin}=0}$. If R is the expected number of bits of resolution, and D_{norm} is the normalized digital output of the chip:

$$R = \log_2(OSR) \tag{5}$$

$$D_{\max} = 2^R - 1 \tag{6}$$

$$D_{\text{norm}} = \frac{D_{\text{lin}=0} - D_{\text{raw}}}{D_{\max}}. \tag{7}$$

This normalization takes care of the fact that negative currents are also represented by the positive digital output range $(0 < D_{\text{raw}} < D_{\max})$. Ideally, zero input current should be represented by raw output $D_{\text{raw}} = D_{\text{lin}=0} = D_{\max}/2$. After normalizing, zero current is indicated by $D_{\text{norm}} = 0$, maximum positive current by $D_{\text{norm}} = -0.5$, and maximum negative current by $D_{\text{norm}} = +0.5$. These numbers are independent of the scale and the gain. As seen from Figure 7, we achieve

Table 1. Parameters for characterization traces shown in Figure 7. Note that the selection of the gain sets the range of the potentiostat and allows for multiple ranges spanning several decades.

Trace	Gain	OSR	Input Current Range
A	2^0	2^{16}	±500nA
B	2^2	2^{15}	±125nA
C	2^4	2^{14}	±30nA
D	2^6	2^{13}	±8nA
E	2^8	2^{12}	±2nA
F	2^{10}	2^{11}	±500pA
G	2^{12}	2^{10}	±125pA
H	2^{14}	2^9	±30pA
I	2^{16}	2^8	±8pA

picoampere sensitivity and a very wide dynamic range: six orders of magnitude from microamperes to picoamperes. The power consumption of the chip was analyzed by measuring the current drawn from the 3.3-V supply. There were two components to the power: an analog component and a digital component. The digital power drawn depends on the clock on which the digital part of the potentiostat is run and the set gain. For all 16 channels converting at 2 MHz, the analog power drawn was 53.1 μW, and the digital power was in the range of hundreds of microwatts, depending on the gain. Thus, the average power dissipation per channel was in tens of microwatts.

Neurotransmitter Sensing

Following the testing and characterization of the potentiostat, we performed some basic neurotransmitter measurements. Figure 8 shows a photograph of the setup with a port for various kinds of sensors.

We interfaced commercially available carbon fiber electrodes (CF30-250, WPI, Sarasota, Florida) to electrochemically detect the neurotransmitter dopamine. Dopamine is a catecholamine neurotransmitter in the brain. Lack of dopaminergic neurons in the basal ganglia is implicated as a cause of Parkinson's disease [1]. Two kinds of measurements were taken using the potentiostat. One was a static test where the digital output of the potentiostat was recorded for several known concentrations of dopamine. A stock solution of dopamine was prepared by dissolving 95 mg of dopamine hydrochloride (Alfa Aesar, Ward Hill, Massachusetts) in 99 mL of deionized water. One mL of perchloric acid (Alfa Aesar, Ward Hill, Massachusetts) was added to the solution to prevent the spontaneous oxidation of dopamine. The solution thus obtained is 5 mM dopamine. This solution was added to 100 mL phosphate buffered saline, pH 7.4 (Biofluids, Rockville, Maryland) in steps of 100 μL leading to final concentrations in steps of 5 μM. The solution was magnetically stirred to avoid effects of diffusion. A silver/silver chloride electrode (Bioanalytical Systems, West Lafayette, Indiana) was used as the reference electrode. The output of the potentiostat was allowed to equilibrate before recording. The gain and OSR were set to 2^7 and 2^{14}, respectively. The digital output was normalized for the gain and OSR. The normalized value multiplied by the reference current of 600 nA gives the measured current. Figure 9 shows the current measured by the potentiostat for various concentrations of dopamine.

The second measurement was a real-time acquisition of dopamine concentration as it was added to the phosphate buffer saline (PBS) solution. The experimental procedure consisted of adding boluses of dopamine to the base solution of PBS at regular time intervals. The electrochemical current is measured constantly. Figure 10 shows the real-time monitoring of dopamine concentration. Arrows denote the times of dopamine addition.

The solution is not stirred, and the current is not allowed to equilibrate, showing the transient effects of diffusion. In this experiment, the dopamine concentrations are in the millimolar range, so we expect redox currents that are orders of magnitude higher than in Figure 9. Thus, the gain was set to a much lower 2^0 and the OSR was set to 2^{14}. The reference current was maintained at 600 nA. The measurements of micromolar to millimolar concentrations of dopamine demonstrate the wide range of the potentiostat made possible by the gain implemented by the time modulation feedback.

Conclusions and Future Work

We have presented a chemical analysis paradigm for neurochemical studies, as opposed to the traditional electrophysiological regime. We described electrochemical analysis and the instrumentation involved in doing such analysis. The article presents the design and characterization of a 16-channel, high-sensitivity, wide-range VLSI potentiostat. We demonstrate the use of this potentiostat in real-time in vitro monitoring of the neurotransmitter dopamine.

Further improvements and enhancement are possible, and such work is underway. As with any circuit, there can always be incremental advances in the capabilities of the potentiostat chip. Possible areas are improving the robustness, improving current detection sensitivity, and reducing the minimum feature size for higher density integration, leading to more parallel channels. Additional circuitry for other kinds of electrochemical analysis like cyclic voltammetry can be incorporated. The dynamic power consumption can be reduced by using optimized low-power digital design. New fabrication technologies like silicon on insulator (SOI) or silicon on sapphire (SOS) can be used to reduce parasitic capacitance and leakage effects. Apart from modifications to the existing circuit, there is also the possibility of changing the design itself. We are currently working in the analog subthreshold region for high sensitivity and low power. Since the release of neurotransmitters is actually quantal in nature [17], it makes sense to move from an analog front-end design to some kind of digital detection. Statistical techniques like stochastic resonance could be used to pull out digital data buried in analog noise. Another practical addition would be the introduction of modules for telemetry and wireless power transfer to the potentiostat [18]. The serial output of the current potentiostat design has been designed to make it amenable for telemetry. A long-term goal of this work is to develop a self-contained, implantable, fully integrated, continuous neurotransmitter monitoring probe. Such a probe would be useful in neuroscience research involving the role of neurochemicals such as dopamine, glutamate, and nitric oxide in the nervous system and would complement electrophysiological measurements for a holistic picture of neural signal analysis. Neurochemical detection using integrated systems would be useful in conducting research on animal models of disorders like epilepsy and stroke. Ultimately, using microfabricated sensors and VLSI circuits in an integrated device could also be useful in implantable neural prosthetic devices.

Acknowledgments

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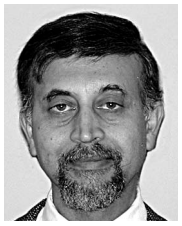
Kartikeya Murari received the B.Tech. degree in electrical engineering from the Indian Institue of Technology, Madras, India, in 2002 and the M.S. degree in biomedical engineering from Johns Hopkins University, Baltimore, Maryland, in 2004. He is currently working towards the Ph.D. degree in biomedical engineering at Johns Hopkins School of Medicine. His research interests include

mixed-signal VLSI design for biomedical applications, neuromorphic systems, and the study of the micro-/nanoscale interface between living tissue and sensors.

Milutin Stanaćević received the B.S. degree in electrical engineering from the University of Belgrade, Serbia and Montenegro, in 1999 and the Ph.D. degree in electrical and computer engineering from Johns Hopkins University, Baltimore, Maryland, in 2005. He is currently an assistant professor of electrical and computer engineering at the State University of New York at Stony Brook. His research interests include mixed-signal VLSI circuits, systems, and algorithms for parallel multichannel sensory information processing with an emphasis on real-time acoustic source localization and separation and micropower implantable biomedical instrumentation and telemetry.

Gert Cauwenberghs received the Ph.D. degree in electrical engineering from California Institute of Technology in 1994. He is a professor of electrical and computer engineering at Johns Hopkins University, Baltimore, Maryland, and in 2005 he joined the University of California, San Diego where he is a professor neurobiology. His research covers VLSI circuits, systems, and algorithms for parallel signal processing, adaptive neural computation, adaptive optics, and biomedical instrumentation. He received the National Science Foundation Career Award in 1997, the Office of Naval Research Young Investigator Award in 1999, and the Presidential Early Career Award for Scientists and Engineers (PECASE) Award in 2000. He serves as an associate editor for *IEEE Transactions on Circuits and Systems I* and *IEEE Sensors Journal*. He was a distinguished lecturer of the IEEE Circuits and Systems Society and chaired its Analog Signal Processing Technical Committee.



Nitish V. Thakor received the B.Tech. degree in electrical engineering from the Indian Institute of Technology (IIT), Bombay, in 1974 and the Ph.D. degree in electrical and computer engineering from the University of Wisconsin, Madison, in 1981. He served on the faculty of electrical engineering and computer science of Northwestern University, Illinois, between 1981 and 1983; since then, he has been with the Johns Hopkins University, School of Medicine, Baltimore, Maryland, where he is currently serving as a professor of biomedical engineering. He teaches and conducts research in the field of neuroengineering in various areas, including neurological instrumentation, neural signal processing, micro- and nanotechnologies, and their clinical applications in brain injury monitoring, diagnosis, and therapy. He has authored more than 150 peer-reviewed articles on these subjects. He serves on the editorial boards of *IEEE Transactions on Biomedical Engineering* and the *Journal of Nanomedicine,* and he will be the editor in chief of *IEEE Transactions on Neural Systems and Rehabilitation Engineering* beginning January 2006. He has recently established a center for neuroengineering at Johns Hopkins University with the aim of carrying out interdisciplinary and collaborative engineering research for basic and clinical neurosciences. He is actively interested in developing international scientific programs, collaborative exchanges, tutorials, and conferences on neuroengineering and medical microsystems. He is a recipient of a Research Career Development Award from the National Institutes of Health and a Presidential Young Investigator Award from the National Science Foundation. He is a Fellow of the IEEE, a fellow of the American Institute of Medical and Biological Engineering, and a founding fellow of the Biomedical Engineering Society. He is also a recipient of the Centennial Medal from the University of Wisconsin School of Engineering, of honorary membership from the Alpha Eta Mu Beta biomedical engineering student honor society, and of a Distinguished Service Award from IIT.

Address for Correspondence: Kartikeya Murari, 720 Rutland Ave., Room 710, Traylor Building, Baltimore, MD 21205 USA. Phone: +1 410 955 0077. E-mail: kartik@jhu.edu.

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