Instrumentation for electrochemical performance characterization of neural electrodes

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In an effort to determine the chronic stability, sensitivity, and thus the potential viability of various neurochemical recording electrode designs and compositions, we have developed a custom device called the *Voltammetry Instrument for Neurochemical Applications* (VINA). Here, we describe the design of the VINA and initial testing of its functionality for prototype neurochemical sensing electrodes. The VINA consists of multiple electrode fixtures, a flowing electrolyte bath, associated reservoirs, peristaltic pump, voltage waveform generator, data acquisition hardware, and system software written in National Instrument's LabVIEW. The operation of VINA was demonstrated on a set of boron-doped diamond neurochemical recording electrodes, which were subjected to an applied waveform for a period of eighteen days. Each electrode's cyclic voltammograms (CVs) were recorded, and sensitivity calibration to dopamine (DA) was performed. Results showed an initial decline with subsequent stabilization in the CV current measured during the voltammetric sweep, corresponding closely with changes in electrode sensitivity to DA. The VINA has demonstrated itself as a useful tool for the characterization of electrode stability and chronic electrochemical performance. *Published by AIP Publishing.* [<http://dx.doi.org/10.1063/1.4993796>]

I. INTRODUCTION

Neurochemical measurement has many applications for medical research, such as efforts to understand the underlying basis of various behavioral and disease states, including essential tremor, Parkinson's disease, and major depression, that are linked to abnormal extracellular neurochemical concentrations.^{1,2} Several methods have been developed to measure neurochemical concentration in the brain: enzymatic biosensors, amperometry, cyclic voltammetry, and microdialysis.^{3–6} Of these, cyclic voltammetry has demonstrated distinct advantages in temporal and spatial resolution compared to other neurochemical measurement techniques.⁷ Fast-scan cyclic voltammetry (FSCV) is a well-established electroanalytical technique that can detect and measure electroactive neurochemicals *in vitro*^{8–11} and *in vivo*^{12–18} by imposing a voltage waveform that ramps through the oxidation and reduction potentials of the species of interest while monitoring nanoampere scale electrical currents that are generated by redox reactions at specific voltage characteristics of certain chemical species. However, despite the advantages of FSCV, its use with conventional electrodes has drawbacks that affect chronic recording stability.

Conventional carbon fiber microelectrodes (CFM) are capable of recording neurochemical release in acute or limited-use applications, but their life-cycle can be limited by oxidation of carbon when the CFM is operated outside the

narrow range of voltage within which the electrochemical behavior of the carbon fiber is stable.^{19,20} This oxidation can occur with many of the extended waveforms that are commonly used in order to obtain improved sensitivity.^{21–23} Given this life-cycle limitation, we are working to develop durable neurochemical recording electrodes that demonstrate uniform operating characteristics throughout their useful life and could potentially support chronic neurochemical recordings. We have created several promising electrode candidates and found that optimization of their neurochemical sensitivity varies with their active material composition and fabrication process. However, to assess their long-term durability and sensitivity, a means of testing electrode performance over time was needed.

The *Voltammetry Instrument for Neurochemical Applications* (VINA), described here, was created to expand electrode evaluation capabilities beyond the traditional flow cell²⁴ and data acquisition systems that are routinely used to assess electrochemical sensor performance. Thus, the VINA was designed as a complete package that would include provisions for temperature control, electrode handling, fluid control and storage, and multi-channel data acquisition. The goal for the VINA is to enable accelerated development and optimization of neurochemical sensing electrodes by allowing multiple electrodes to be characterized simultaneously and multivariable process optimization studies to be performed.

Here, we describe in detail the components and function of the VINA, along with a proof of principle experiment that was carried out with eight boron-doped diamond (BDD) electrodes

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over an eighteen day period. The cyclic voltammograms (CVs) and sensitivity to dopamine (DA) were recorded to characterize the changes in electrode performance over time. Results illustrated how the VINA can be used to characterize electrode stability and sensitivity over time.

II. METHODS

A. Reagents

Chemicals were acquired from Sigma-Aldrich (St Louis, MO) and VWR (Radnor, PA) and used as received. All solutions were made using deionized (DI) water. All experiments were conducted in phosphate buffered saline (PBS) (137 mM sodium chloride, 2.7 mM potassium chloride, and 10 mM phosphate buffer), pH 7.4. For electrode sensitivity testing, 5 mM dopamine stock solution was prepared in DI water immediately prior to each sensitivity experiment and diluted to the desired concentration in PBS buffer.

B. Electrode fabrication

BDD microelectrodes were prepared by co-crystallization of boron and carbon to form polycrystalline diamond films on electrolytically tapered tungsten wires (250 μm in diameter, A-M systems, Carlsborg, WA) using hot-filament chemical vapor deposition (CVD) techniques as previously described.¹⁹ After CVD BDD deposition, the electrode wires were coated with $\sim 30\ \mu\text{m}$ parylene-C using a low pressure polymerization chamber (Specialty Coating Systems, Indianapolis, IN). The first $\sim 100\ \mu\text{m}$ of the parylene coating was selectively ablated from the tapered tip using a pulsed femtosecond ultraviolet laser (Photomachining, Inc. of Pelham, NH), exposing the underlying boron-doped diamond coating for electrochemical detection.

C. Data acquisition system

A National Instruments NI USB-6363 (Austin, TX) data acquisition (DAQ) system is interfaced with the VINA. It is programmed to generate an arbitrary voltage waveform, applied uniformly to each electrode distributed across 16 channels. Additionally, the DAQ measures and records the voltage output from the transimpedance amplifier circuit which is

equated to the current measured at the electrode tip. The NI USB-6363 is controlled through the use of NI LabVIEW™ software communicated through a Universal Serial Bus (USB) interface.

D. Electrode testing

Eight boron-doped diamond (BDD) electrodes were subjected to a continuous triangular waveform of holding potential $-0.4\ \text{V}$, peak potential $1.5\ \text{V}$, with a scan rate of $200\ \text{V/s}$, and frequency of $10\ \text{Hz}$ for a period of 18 days. Although higher scan rates are typically used for neurochemical detection, a slower scan rate allows more time for reactions to occur at the electrode surface, thereby aggravating any electrode dissolution that may occur. The electrodes were submerged in PBS in the fluid path at an elevated temperature of $37\ ^\circ\text{C}$ (human body temperature). Electrodes were removed from the VINA at regular intervals (days 0, 4, 8, 11, 15, and 18) to measure sensitivity to dopamine (DA) with the Wireless Instantaneous Neurochemical Concentration Sensing (WINCS) system^{25,26} in a separate beaker setup. The same FSCV waveform was used with WINCS as in the VINA with the exception of a $400\ \text{V/s}$ scan rate. Sensitivity to concentrations of 0.5 , 1.0 , and $1.5\ \mu\text{M}$ DA was measured in a two-electrode electrochemical cell with a chlorinated silver wire (Ag/AgCl) serving as the reference electrode. These concentrations were selected to reflect dopamine concentrations that are expected in the brain in response to stimulation and are comparable to concentrations used by other groups for the calibration of carbon fiber microelectrodes.^{23,27}

III. RESULTS

A. System architecture

To facilitate long-term test-cycle throughput, the VINA was designed to test and record multiple electrodes simultaneously. It was also designed to be highly configurable in the following key areas: (1) user-defined test liquids and fluid flows; (2) user-defined test waveforms (voltage vs. time); (3) automated data collection and recording during extended operation. An image of the entire operating device is shown in Fig. 1, which highlights the main components: temperature controller, transimpedance amplifier, NI DAQ, power supply, and fluid path.

FIG. 1. Photo of the instrumentation setup: (a) Omega CN7223 temperature controller; (b) VINA transimpedance amplifier; (c) National Instruments USB-6363 data acquisition; (d) Keysight Technologies EM31A power supply; (e) fluid path; and (f) workstation running LabVIEW software.

FIG. 2. VINA block diagram of the main components and their connectivity: (a) mechanical and fluid components, which consist of the fluid path, electrode holders, heater elements, peristaltic pump, and fluid reservoirs, all held within a liquid containment tray; (b) main electrical components of the system, the front and back panels of the TIA case, USB-6363 data acquisition, temperature controller, and Keysight Technologies EM31A power supply.

FIG. 3. Circuit schematic for the transimpedance amplifier channel pairs showing the serial-to-parallel shift register, the analog switch modules for selecting and indicating the gain status, the transimpedance amplifier, and the difference amplifier. The *Channel #2* on the right is intended to point out that the serial-to-parallel shift register actually controls 2 separate TIA/Diff amplifier pairs. This circuit is then copied 8 times on the printed circuit board to produce 16 channels.

FIG. 4. Diagram of the main fluid containment vessel and electrode holder. The primary components indicated are (a) individual electrode cartridge; (b) electrode mounted in the cartridge, arrow indicating the sensing tip; (c) serial serpentine fluid path with 16 individualized wells for each electrode; (d) Luer lock fittings for the liquid feed and return lines; (e) heater elements mounted in the thermally conductive aluminum heater block; (f) resistance temperature detector (RTD) for temperature control; (g) reference electrode rod; and (h) pre-heated fluid path prior to entry into the serpentine fluid path (c).

fluid path, and workstation. A block diagram of the system, detailing the connectivity of the main components, is shown in Fig. 2. The mechanical and fluid components in Fig. 2(a) consist of the fluid path, electrode holders, temperature controller, heater elements, peristaltic pump, and fluid reservoirs all held within a liquid containment tray. The primary electrical components are shown in Fig. 2(b), which include the VINA transimpedance amplifier, NI DAQ, and power supply.

B. Transimpedance amplifier

A low-noise precision operational amplifier (op amp) (OPA140, Texas Instruments, Dallas TX) and a switchable network of feedback resistors comprise the first stage of each transimpedance amplifier. The transimpedance amplifier (TIA) op amp not only converts a current input into a voltage output but also applies the FSCV waveform to the working electrode. The DAC-produced FSCV waveform is directly applied to the TIA op amp's non-inverting input; feedback action causes the same waveform to be impressed on the op amp's inverting input, which is wired to the working electrode for that channel. The FSCV waveform also appears on the output of the TIA op amp and must be removed. The subtraction is performed by an INA132 difference amplifier (Texas Instruments) which serves as the second stage of the TIA. The resulting voltage

signal is equal to the working electrode current multiplied by the selected gain resistance. Various combinations of four gain resistors can be engaged for each TIA by an ADG1412 analog switch module (Analog Devices, Norwood MA), controlled by an HEF4015 serial-to-parallel shift register (NXP Semiconductors, Eindhoven, Netherlands), which receives its serial input from the NI USB-6363 DAQ. The TIA gain selections are indicated by light emitting diodes on the front panel. A circuit diagram of the amplifier stage pair is shown in Fig. 3. The main components illustrated are the serial-to-parallel shift register, the analog switch modules for selecting and indicating the gain status, the transimpedance amplifier, and the difference amplifier.

Flexible cables allow for ease of use when connecting electrodes to the transimpedance amplifier. In order to minimize electromagnetic interference that may be picked up by the cabling, leads with internal shielding (AS155-28-2SJ; Cooner Wire, Chatsworth, CA) were selected and grounded to the amplifier printed circuit board (PCB).

C. Waveforms and current specifications

For maximum experimental flexibility, the VINA was designed to accommodate a range of ± 10 V and waveforms at any frequency including sine, square, triangle, and other arbitrary signal shapes defined by the end user limited by the sampling rate and resolution of the DAQ.

The electrode-electrolyte interface is often represented by a parallel combination of a resistor and a capacitor, and when a time-varying voltage waveform is applied, current is produced. For typical voltammetry electrode sizes and materials, currents are in the range of 1–10 μ A, but currents can vary depending upon the waveform voltage amplitude, scan rate, and electrode impedance. For this reason, three different gain resistors were selected for the TIA that can accommodate various current ranges, with a fourth option available for an additional gain setting, if desired. The lowest current range measures up to 2.0 μ A with a nominal resolution of 61.0 pA, the second range provides for currents up to 20 μ A with a nominal resolution of 610 pA, and the third range measures up to 200 μ A with a nominal resolution of 6.10 nA. The input-referred rms noise for these current settings was measured to be 444 pA, 828 pA, and 3.88 nA, respectively.

D. Fluid flow control

A peristaltic pump (6K, Boxer, Ottobereun, Germany) is used to drive fluid through the VINA. The fluid input and

FIG. 5. Screenshots of the LabVIEW software interface and flow diagram. (a) waveform input, (b) gain select, and (c) data display and collection. Adjustable parameters include sampling rate, frequency (Hz), gap (sample), pulse repetition, index, multiplier, and offset. Additionally, the user can select the save duration, interval, and filename output for data collection needs.

TABLE I. Summary of verification tests and results confirming conformance to design specifications.

Verification activity	
Name/description	Results
Arbitrary voltage slew rate (10-10 000 V/s increasing and decreasing from triangle peak)	Slew rates of 10-100 000 V/s demonstrated
Amplifier designed to accommodate input/output waveforms to ± 10 V	10.2 and -10.4 V max/min recorded for sawtooth waveform inputs
Minimum allowable frequency range of stimulus to be between 0 and 1 kHz (adjustable)	Frequency capabilities of 0-20 000 Hz demonstrated
Ability to generate arbitrary waveform	Sawtooth, square, sine, triangle, and DC inputs demonstrated
Confirm that current for all channels are within $\pm 5\%$ of the average current output across all channels	Current outputs measured across 16 channels measured were measured to be within $\pm 2.5\%$ of overall channel average current output

output sources are manually selected through the positioning of the three-way stopcock valves shown in Fig. 2(a). The fluid is drawn from the source reservoir and cycles through the heated aluminum block. Then, it is directed into the left side of the fluid path where it flows serially through 16 wells that contain the sensing tips of the electrodes. Finally, the fluid exits the right side of the fluid path and is returned to the selected reservoir. The flow source reservoir and waste tank bottles are 1-L Pyrex®. The fluid path itself was constructed of clear acrylic sheet stock, which is a relatively inert and electrically nonconductive material. This component was fabricated by computer numerical control (CNC) milling of two separate pieces which were then bonded together with solvent cement to form a closed channel. After the two pieces were bonded, fluidic connections were machined into the assembly. Detailed schematics of these pieces may be found in the [supplementary material](#). Fluid flow through the fluid path is laminar, with a Reynolds number at maximum flow rate calculated to be 213 for distilled water. At lower flow rates or with increased viscosity (as would be seen with isotonic fluids), the Reynolds number would be smaller (i.e., further from turbulent flow).

The valve configuration allows the pump to recirculate, flush, and/or fill desired fluids for calibration and cleaning purposes. The fluid path and related components were designed to limit exposure to air and minimize evaporation. Fluid loss due to evaporation was measured at 4 ml/24 h at an operating temperature of 37 °C. With a total electrolyte volume of 1000 ml, the liquid needs to be topped off periodically during longer test cycles.

E. Electrodes

The electrodes are mounted on cartridges milled from acetal sheet stock [Fig. 4(a), detailed schematics in the [supplementary material](#)], which attach to the fluid path back plate with a dove-tail tongue and groove design. They are individually removable for easy loading and safe handling. Each cartridge allows mounting flexibility for a wide range of electrode lengths and diameters. A final adjustment ensures that all the electrodes have uniform depth in the test liquids. The reference electrode is a 1/8th in. diameter rod that runs the length of the fluid path and is exposed to the test fluid in each

individual well, shown in Fig. 4(g). Any electrode material can be used for the reference electrode, but for initial testing, a 316L stainless steel rod was utilized.

F. Heater block

The electrolyte fluid circulating through the fluid path is heated by passing the fluid through a thermally conductive aluminum block containing dual heater elements. A temperature sensor in the aluminum block signals the temperature controller which switches the heater elements on and off to maintain the desired temperature. The temperature sensor is a 3-wire Pt100 (PR-23, Omega, Stamford) and the temperature controller is an Omega Engineering, Inc CN7223 Proportional-Integral-Derivative (PID) controller (Stamford, CT). An expanded view of the thermal heater block is shown in Fig. 4(e).

G. Software

The software to control the device was written in LabVIEW, a visual programming language. There are three main

FIG. 6. Channel current uniformity of the VINA with applied waveform of holding potential -0.4 V, peak potential 1.5 V, with a scan rate of 200 V/s, and frequency 10 Hz. The graph illustrates channel-to-channel current uniformity which was obtained using an identical resistor dummy load on each channel. The cyclic voltammogram currents were averaged from all 16 channels, and each individual channel was compared to the average where it was observed to be within $\pm 2.5\%$.

FIG. 7. Raw cyclic voltammograms and dopamine calibration data collected for 8 electrodes over a period of 18 days of applied triangle waveform: (a) each plot represents an individual electrode and shows a set of CVs collected, one from each day, over the 18-day experiment. Note that electrode 5 had an insulation leak during the experiment resulting in electrode failure and amplifier saturation at the 10 000 nA gain setting and was thus not included in the data analysis [plots (b) and (c)]; (b) plot of the average normalized background current at the switching potential 1.5 V and at the oxidation potential of dopamine 0.9 V; (c) averaged normalized electrode sensitivity calibration plots at time points $T = 0, 4, 8, 11, 15$, and 18 days for the detection of DA at concentrations of 0.5, 1.0, and 1.5 μM .

components to the virtual instrument (VI): Waveform Input, Gain Select, and Waveform Save as seen in Fig. 5. First, the user must input the desired waveform from a text file. Once the waveform is loaded, a few parameters can be adjusted to finalize the output. These parameters include sampling rate, frequency (Hz), gap (sample), pulse repetition, index, multiplier, and offset. The sampling rate defines the rate at which the VI samples data, affecting data resolution and waveform slew rate. The frequency (Hz) value changes the number of times the waveform is applied per second. Gap (sample) and pulse repetition (i.e., the number of pulse repetitions and the time gap between them) are optional, which enables the generation of multi-pulse waveforms. The index value defines the holding potential between waveforms, and the multiplier and offset alter the magnitude of the waveform and baseline potential. Once the waveform is selected, the next tab is activated, and the user can then choose the gain setting for the device. After the gain is selected, the final tab in which the raw CVs are displayed for each channel is shown. Additionally, the user can select the save duration, interval, and filename output for data collection needs.

H. Verification and validation

We conducted verification testing to confirm the functionality and conformance to our desired design specifications for the VINA. A summary of the verification tests

performed are shown in Table I. During the design of the amplifier, two of the most critical goals/specifications were to minimize the overall amplifier noise and match the channel-to-channel signal uniformity. A full plot of the uniformity for all 16 amplifier channels is shown in Fig. 6. The graph illustrates channel-to-channel uniformity which was obtained using an identical resistor dummy load on each channel. The cyclic voltammogram currents were averaged from all 16 channels, and each individual channel was compared to the average where it was observed to be within $\pm 2.5\%$.

I. Electrode testing

Each separate plot in Fig. 7(a) represents an individual electrode and shows a set of CVs collected in PBS, one from each day, over the 18 day experiment. A graph of the background current shift at the switching potential of 1.5 V and at the oxidation potential of DA of 0.9 V on the BDD electrodes is shown in Fig. 7(b). The average peak background current at the switching potential decreased 41% by day 4. However, the background current at the oxidation potential for DA decreased an average of 20% by day 4. The CVs began to show signs of stabilization after 4 days, with a remaining downward trend from days 4 to 18 of less than 9% at the oxidation potential of DA. The normalized electrode sensitivity calibration for the detection of DA is plotted in Fig. 7(c). Normalization

FIG. 8. Background-subtracted dopamine voltammograms for 3 of the diamond electrodes depicted in Fig. 7. All 3 electrodes are depicted at 0.5, 1.0, and 1.5 μM of dopamine, and all voltammograms were obtained at the end of a lifetime experiment after the electrodes had been subjected to 18 days of continuous FSCV scanning at 10 Hz in the “VINA” system. While VINA was used to stress-test and “age” the electrodes over the 18-day experiment, the voltammograms depicted here were acquired with the Mayo Clinic-designed “WINCS” system, not with the VINA electrode longevity-tester itself (as its long fluid-flow path and relatively large volume are not intended or well-suited for generating calibration curves). Also note that the oxidation peak of dopamine is shifted to a somewhat higher voltage with a diamond electrode (here, about 0.95 V) relative to standard carbon fiber electrodes (data not shown).

was conducted by dividing the background-subtracted peak oxidation current by the background current at the oxidation potential. Electrode sensitivity also showed signs of stabilization by day 4, and the average loss was 34% from start of the experiment.

Note that electrode 5 in Fig. 7(a) has a saturated background current starting at day 6. This was due to failure from physical impact during handling, and therefore the results from electrode 5 are not included in the data analysis in Figs. 7(b) and 7(c). However, we included it in Fig. 7(a) to demonstrate how an electrode insulation failure can be observed by monitoring the CVs over time.

With decreasing CV currents over the period of the experiment, electrode sensitivity was also expected to decrease, and this change was reflected in the electrode sensitivity plot shown in Fig. 7(c). The CVs showed a more stable pattern after 4 days, and this can be seen in Fig. 7(b) as the plots begin to plateau.

A selection of nine background-subtracted dopamine voltammograms is depicted in Fig. 8. This selection comprises three distinct diamond-based electrodes, each evaluated at three different dopamine concentrations after 18 days of continuous use in the VINA system. While the VINA was used to stress-test and “age” the electrodes over the 18-day experiment, the voltammograms depicted in Fig. 8 were acquired with the Mayo Clinic-designed “WINCS” system,^{25,28,29} not with the VINA electrode longevity-tester itself (as its long fluid-flow path and relatively large volume are not intended or well-suited for generating calibration curves).

IV. DISCUSSION

The VINA was capable of testing multiple electrodes simultaneously with user-defined test solutions, waveforms, and automated data collection during extended operation. The transimpedance amplifier circuitry design met our initial specifications for channel uniformity and waveform flexibility and allowed for adjustable gain configuration and light-emitting diode (LED) indication for all 16 channels. The fluid management components were adequate for providing elevated temperature fluids with a laminar flow through the fluid path, minimal fluid loss due to evaporation, and configurable valves for recirculation, flush, and/or filling desired fluids. The electrode cartridges were especially convenient for easy loading and safe handling, keeping the vulnerable tips secure for the duration of the experiment. The heater block design was sufficient for maintaining desired bath temperature throughout the fluid path with slight modifications that involved adapting a thin thermal insulation between the back plate and base to reduce unnecessary heat transfer. LabVIEW software allowed a simple interface for applying the waveforms, adjusting the gain settings, and saving the output data. In addition to the design and construction of the instrumentation, we were able to demonstrate its use in testing a set of BDD electrodes as a proof-of-principle. The trial experiment allowed observation of the shift and stabilization of the background current over an 18 day period. Most notably, the majority of stabilization occurred after 4 days of waveform application. This was

reflected in the plot of the background current at the switching potential and oxidation potential of DA in Fig. 7(b) along with the calibration curve grouping shown in Fig. 7(c).

The VINA was able to perform a proof of principle stability study of BDD neural electrodes over an 18-day period. It has addressed a means of testing the durability and viability of varying types of electrodes by facilitating temperature control, electrode handling, fluid control and storage, and multi-channel data acquisition. We plan to continue to use the VINA to help characterize electrode lifetimes and failure modes, moving us toward solving the challenge of designing a neurochemical recording electrode capable of functioning reliably on the order of years. Further experiments of similar design will be conducted using this device to evaluate and help optimize the sensitivity and durability of electrode designs and materials for the detection of neurochemicals.

SUPPLEMENTARY MATERIAL

See [supplementary material](#) for detailed schematics of the fluid flow path and electrode cartridges.

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