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A 3-electrode electrochemical cell on CMOS and application for amperometric measurement of dopamine

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An overview of CMOS-integrated dopamine sensors - in which the working electrode(s) are monolithically integrated on the CMOS chip - is presented with a focus on key advantages of such monolithic integration, namely, the scalability and high spatial and temporal resolutions. We highlight that a key current limitation of such integrated microsystems is their lack of autonomy: (i) external off-chip reference and counter electrodes are still needed to carry out a measurement; and (ii) post-CMOS processing for electrode development requires clean-room-based techniques (e.g., lithography) or benchtop electrochemical workstations. This work addresses both limitations by fully integrating all three electrodes on a CMOS chip. We also demonstrate how simple on-chip circuits can be used for electrode development. An array of gold and silver/silver chloride (Ag/AgCl) microelectrodes was developed using a simple, scalable, and low-cost electroless and electroplating process. An on-chip current generator circuit is used for *in situ* control of the electrodeposition and an amperometric readout circuit is designed to read the sensor current. The circuits are designed and fabricated in a standard 180-nm CMOS process. The on-chip 3-electrode sensor has been successfully used for amperometric dopamine measurement.

KEYWORDS

amperometric readout, CMOS sensor fabrication, dopamine, gold microelectrode, potentiostat

1 Introduction

Dopamine (DA) is a central neuromodulator involved in reward learning, motivation, movement control, and cognition (Zablocka et al., 2019). Dysregulated dopaminergic signalling is implicated in major neurological and psychiatric disorders, including Parkinson's disease, addiction, and schizophrenia-spectrum conditions (Xu et al., 2015). Experimentally, DA is challenging to measure because it is released in brief, spatially localized events and coexists with electroactive interferents and structurally related catecholamines. Conventional electrochemical approaches, such as carbon-fiber microelectrodes (CFEs) coupled with fast-scan cyclic voltammetry (FSCV) or amperometry, provide excellent temporal resolution but are typically limited to single-site measurements, require labor-intensive fabrication, and are susceptible to noise and parasitic effects associated with long interconnects (Zachek et al., 2008). These limitations have motivated the development of complementary Metal-Oxide-Semiconductor (CMOS)-integrated dopamine sensor arrays, in which microfabricated sensing interfaces are coupled directly to on-chip readout circuitry to enable miniaturized, scalable, and high-performance measurement platforms that allow cell-level spatial resolutions.

Moreover, by directly sensing and amplifying the sensor output on the same chip, the signal channel is reduced to the micrometer level, reducing interferences and improving the signal-to-noise ratio of measurements (Yu et al., 2023).

Notable examples of CMOS-integrated sensors are optical imagers that use CMOS image sensors with arrays of photodiodes, and DNA analysers which use an array of ion-selective field effect transistors (ISFETs) (Kim et al., 2017; Merriman et al., 2012; Moser et al., 2022). The latter requires the exposure of the CMOS passivation layer (on the surface of the CMOS-integrated sensor array) to the biological fluid in order to initiate a field-effect transistor (FET)-based transduction of the measurand. These do not involve any direct charge exchange between the sensor and the electrolyte.

However, a wide range of electrochemical sensors, such as those that involve reduction and oxidation (redox) reactions, or those that are based on nanopores, require direct electric charge transfer between the sensor electrode and the electrolyte (Carminati et al., 2018) followed by amperometric readout electronics to measure the electrical current produced. An amperometric sensor typically has three electrodes: the working, counter and reference electrodes (WE, CE, and RE).

A number of CMOS-integrated working electrodes, on the exposed top metal layer (i.e., pad), have been developed for amperometric measurement of biological substances such as small biomolecules, neurotransmitters, and hormones (Moser et al., 2022; Stefan et al., 2000; Dorta-Quinones et al., 2018; Baj-Rossi et al., 2014; Bhadra et al., 2013). However, to form a complete three-electrode sensor, existing systems use external reference and counter electrodes, located outside the CMOS chip, limiting scalability.

In a standard CMOS process, the exposed top metal layer is nearly pure aluminum (Al), an electroactive material not suitable for electrochemical sensing (Tedjo and Chen, 2020). The first crucial step in sensor development is, therefore, to cover this layer with an appropriate metal film. Gold (Au) is favored for the biosensors' working and counter electrodes, due to its conductivity and biocompatibility (Limo et al., 2018), but it is excluded from the standard CMOS manufacturing process to prevent contamination (Niitsu et al., 2015; Kurita et al., 2019). To achieve a suitable gold surface on Al pads, CMOS chips undergo post-processing steps, such as photolithography and lift-off, gold bumping, electroless and electrodeposition. Despite successful demonstrations of these techniques in literature, progressing to commercial products has been hindered due to challenges in developing robust electrodes. Critically, the nature of direct electrode-electrolyte interaction has been shown to cause various forms of electrode decay and failure mechanisms (Zhang and Ghoreishizadeh, 2024; Zhang et al., 2025), limiting the lifetime and reliability of the sensing platform.

In our previous work (Li et al., 2025), we demonstrated a low-cost, rapid, scalable, and reproducible method to deposit a layer of gold directly on CMOS Al pads. The method is based on electroless and electrochemical deposition and achieves excellent control over the layer thickness and surface roughness of the deposited Au. In this work, we extend this line of research, addressing the long-standing dependence of CMOS amperometric sensors on external RE and CE, through monolithically integrating all three electrodes—WE, RE, and CE - on the same CMOS chip. Using

this fully integrated three-electrode platform, we demonstrate amperometric measurement of dopamine and benchmark the on-chip configuration against systems employing external CE/RE.

Furthermore, to enhance the autonomy and scalability of the post-CMOS electrode-development step, this work replaces the benchtop potentiostat conventionally used for electrodeposition with integrated on-chip circuits capable of generating high-fidelity deposition waveforms for *in-situ* electrodeposition. The proposed platform monolithically integrates all three electrodes required for electrochemical sensing on the CMOS chip and uses on-chip circuits to control the key electrodeposition process. Building on our previously reported circuit architectures (Li et al., 2022a; b), this work provides experimental measurements showing that the integrated electrodeposition circuit maintains a comparable level of control over the gold morphology with minimal waveform distortion. This integration reduces equipment overhead and process complexity, thereby removing an important barrier to scalable post-CMOS electrode fabrication and improving the autonomy of CMOS-based electrochemical sensing platforms.

This paper is organized as follows. Section 2 provides a brief overview of CMOS-integrated dopamine sensors presented to date, covering their unique features and application scenarios, performance and limitations. Section 3 introduces the overall system architecture and details the design of key circuit blocks: the current generator circuit and amperometric readout within the CMOS chip. Section 4 evaluates the electrical performance of the key circuit blocks. Section 5 presents the CMOS post-processing for Au microelectrode development. Section 6 presents experimental analysis of stability of the CMOS-integrated WE and RE. Finally in Section 7, we present key characteristics of the three electrodes, all developed using on-chip circuits, and demonstrate its suitability for amperometric electrochemical measurement of dopamine.

2 CMOS-integrated dopamine sensors

2.1 Measurement mechanism

CMOS-integrated dopamine sensors reported in the literature can be broadly classified according to their signal transduction mechanism as (i) electrochemical sensors (Xu et al., 2025; Nasri et al., 2017b; White et al., 2018a; Huang et al., 2018; White et al., 2025; Massicotte et al., 2016), (ii) capacitive sensors (Wang et al., 2009; Lu et al., 2010), and (iii) FET-based sensors, including open-gate ISFETs and hybrid silicon nanowire/CMOS platforms (Qian and Yan, 2026; Li et al., 2010; Sessi et al., 2022).

CMOS electrochemical sensors quantify dopamine by measuring faradaic currents generated during its oxidation and reduction. These devices typically operate using fixed-potential amperometry or FSCV, where the resulting peak current is proportional to dopamine concentration according to the Randles–Ševčík equation (Equation 1):

$$i_p = (2.69 \times 10^5) n^{3/2} A D^{1/2} C v^{1/2} \quad (1)$$

where i_p is the peak current, n is the number of electrons transferred, A is the electrode area, D is the diffusion coefficient, C is the analyte concentration, and v is the scan rate.

CMOS capacitive sensors detect dopamine through non-faradaic changes in interfacial capacitance. The electrode surface is functionalized with boronic-acid receptors, which selectively bind the catechol group of dopamine. This binding alters the surface charge and potential, producing a measurable change in capacitance (Wang et al., 2009; Lu et al., 2010).

FET-based CMOS sensors also use non-faradaic, charge-based transduction. Dopamine binding at the functionalized oxide surface modulates the surface potential, causing a shift in the transistor threshold voltage, according to Equation 2:

$$V_{th} = E_{ref} - \Psi + \chi_{sol} - \frac{\phi_{si}}{q} - \frac{Q_{ox} + Q_{ss} + Q_B}{C_{ox}} + 2\phi_F \quad (2)$$

where E_{ref} is the reference electrode potential, Ψ is the chemical input potential, χ_{sol} is the solvent surface dipole potential, Q_{ox} , Q_{ss} , and Q_B are the oxide, interface-state, and depletion charges, respectively, and C_{ox} is the gate-oxide capacitance per unit area.

Molecular recognition is achieved either intrinsically through the electrochemical oxidation of dopamine at a particular applied potential, or through selective receptors, such as boronic acid derivatives and aptamers, that bind dopamine at the sensor surface.

2.2 Main advantages and achievements

High-density CMOS-integrated microelectrode arrays enable electrochemical imaging of dopamine diffusion and release across large fields of view. By simultaneously recording from hundreds to thousands of microelectrodes, these platforms generate spatial maps of neurotransmitter dynamics in tissue and model systems. For example (White et al., 2025), developed a 1024-pixel electrochemical imaging platform that achieved real-time imaging of dopamine diffusion at 40,000 frames per second, the highest frame rate among the electrochemical imaging systems, enabling visualization of rapid dopamine diffusion with high spatiotemporal resolution. Moreover, dual-mode arrays have enabled simultaneous chemical and electrical recording, allowing neurochemical measurements to be correlated directly with neuronal activity (Xu et al., 2025).

Similarly, monolithic CMOS bioelectronics combined with microfabricated cell traps have enabled cell-level specificity together with high-throughput single-cell amperometry. By positioning individual cells directly above the sensing electrodes, these platforms enable simultaneous monitoring of vesicular dopamine release from 76 SH-SY5Y cells and capture 7,147 exocytotic events within a recording window of 42 s (White et al., 2018b; Huang et al., 2018). Acquiring a comparable dataset using conventional single-electrode/cell amperometry would have required months of sequential measurements, highlighting the unique advantage offered by CMOS integration.

CMOS integration has also been exploited to improve multi-site FSCV measurements in (Nasri et al., 2017a). By placing the readout circuitry in close proximity to the sensing electrodes, a hybrid CMOS-graphene platform was developed to provide a scalable architecture for multi-site dopamine detection (Nasri et al., 2017a). Notably, an on-chip background current subtraction is utilized in this work to reduce the large non-faradaic currents that dominate FSCV measurements, thereby lowering the dynamic range requirements of the analog-to-digital converter, leading to a theoretical dopamine detection limit of 6 nM (Nasri et al., 2017a).

Capacitive CMOS sensors also benefit from monolithic integration, which reduces parasitic effects between the sensing interface and the readout circuitry, enabling statistically distinguishable responses down to 0.1 fM (Lu et al., 2010). Hybrid silicon nanowire/CMOS platforms such as those reported in (Sessi et al., 2022) further demonstrate that CMOS is compatible with affinity-based FET biosensors for ultrasensitive dopamine detection.

Overall, these studies demonstrate that the advantages of CMOS integration extend well beyond miniaturization. By co-integrating sensing interfaces with dedicated readout and signal-processing circuitry, CMOS platforms enable high-throughput measurements, high temporal resolution, exceptionally low detection limits, and scalable sensor architectures that are difficult or impossible to achieve using conventional non-integrated electrochemical sensors.

2.3 Key challenges

Despite these advances, several challenges remain before CMOS dopamine sensors can be translated into robust platforms for physiological measurements. Here we highlight three main challenges.

(i) Selectivity- Fixed-potential amperometry cannot inherently distinguish dopamine from other electroactive species. Although cyclic voltammetry and FSCV improve chemical discrimination, they increase circuit complexity and data-processing requirements (Nasri et al., 2017b; White et al., 2025). Alternatively, molecular recognition can be introduced through biorecognition elements such as aptamers, which provide improved selectivity towards dopamine.

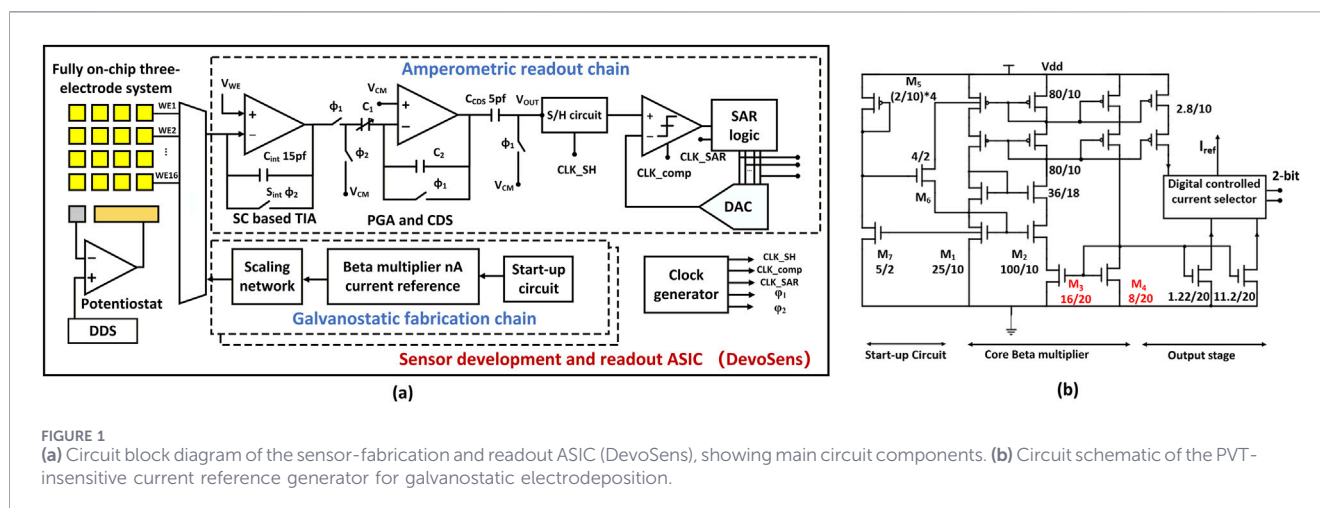
(ii) Post-CMOS electrode fabrication- As briefly mentioned in Section 1, as the top metals available in standard CMOS processes are generally unsuitable for electrochemical sensing, most reported platforms rely on post-CMOS integration of gold, platinum, graphene, or silicon nanowires. While these approaches enable high-performance sensing, they introduce additional fabrication steps, increase cost, and may affect fabrication yield and reproducibility (White et al., 2018b; Nasri et al., 2017b; White et al., 2025; Sessi et al., 2022). Furthermore, the different fabrication methods offer varying levels of scalability and compatibility with large-scale manufacturing.

(iii) lack of autonomy - due to reliance on external RE together with specialized wet-environment packaging (White et al., 2018b; Nasri et al., 2017b; White et al., 2025). These requirements complicate miniaturization and deployment, while making accurate measurements across large sensor arrays more challenging.

The CMOS platform presented in this work addresses challenges (ii) and (iii).

3 Sensor development and readout system

The top-level block diagram of the sensor development and readout system (DevoSens) is shown in Figure 1. The DevoSens chip consists of four key functional blocks: an amperometric readout chain for sensing-current acquisition, current-reference generators for galvanostatic electrodeposition, a potentiostat with a Direct



digital synthesizer-based waveform-generator for electrochemical excitation, and a multiplexed microelectrode array for channel selection and interfacing. Together, these blocks enable selective electrode functionalization and electrochemical sensing on a single platform, with the measured current signals digitized by an analog-digital converter (ADC) and transmitted off-chip via a serial-parallel interface (SPI). The design and simulation results of the circuits have been previously reported in Li et al. (2022a); Li et al. (2022b). These are briefly explained here followed by measurement results.

3.1 Amperometric readout chain

A switched-capacitor (SC)-based transimpedance amplifier (TIA) is employed for amperometric readout because it supports bidirectional current measurement and simultaneously attenuates the low-frequency electrochemical noise through charge integration (Ghoreishizadeh et al., 2017). Furthermore, by exploiting the switching frequency as an additional control dimension, the SC topology enables programmable scaling of the input current range (Li et al., 2026). Accordingly, the readout front-end consists of a capacitive-feedback SC-TIA for bidirectional current integration, followed by an SC programmable-gain amplifier (PGA) with correlated double sampling (CDS) to provide gain programmability and suppress flicker noise and offset, as illustrated in Figure 1a. The output voltage of the readout circuit (Equation 3) can be calculated as follows.

$$V_{OUT} = V_{CM} - \frac{C_1}{C_2} \frac{I_{in}}{C_{int} f_s} \quad (3)$$

A single-stage folded-cascode amplifier architecture is employed in the potentiostat, PGA, and integrator blocks due to its favorable tradeoff among dc gain, input common-mode range, power efficiency, and closed-loop stability. In addition, the single-stage topology alleviates frequency-compensation requirements and facilitates robust analog operation. In addition, all timing signals required by the readout chain are derived from a fully integrated non-overlapping clock generator as adopted from (Martin et al., 1987), which ensures proper phase separation in the switched-capacitor operation and minimizes charge-injection-induced signal corruption.

3.2 Current generator

A current reference generator based on a modified beta-multiplier architecture is designed to generate currents at the nA level. The circuit is shown in Figure 1b, where all transistors except two operate in the subthreshold region, thereby limiting the power consumption to a few microwatts. Further details on the operation of the circuit, including circuit simulations reported in our previous work (Li et al., 2022b).

3.3 Direct digital synthesizer

An on-chip, multi-mode direct digital synthesizer (DDS) generates both the sub-hertz triangular waveforms required for cyclic voltammetry and the fixed potentials used in chronoamperometry, with programmable amplitude (potential window) and frequency (scan rate). The DDS comprises an 8-bit bidirectional counter, an 8-bit digital-to-analog converter (DAC), and a voltage-buffer stage. A resistor-ladder DAC is employed due to its low complexity and power efficiency and is followed by a programmable inverting operational amplifier that provides both gain boosting and output buffering.

The counter step size is programmed by a 4-bit tuning word, which controls the update rate of the counter and therefore sets the frequency of the generated triangular waveform. The waveform amplitude is independently adjusted through the programmable gain of the buffer stage, thereby enabling flexible tuning of the potential window and scan rate while preserving a compact and low-power implementation.

3.4 Microelectrode array and multiplexing

A 4×4 array of exposed top metal layers are designed in the middle of the chip, each with a dimension of $66 \mu\text{m} \times 66 \mu\text{m}$. The spacing between the on-chip microelectrode and the peripheral pads is set to $200 \mu\text{m}$ to allow sufficient margin for subsequent epoxy encapsulation. At any given time, one WE is selected and connected to either the readout circuit or the electrodeposition circuits (current generators) through a 16-to-4 multiplexer. N-channel Metal-Oxide-Semiconductor (NMOS)-only switches are adopted in the multiplexer to minimize leakage current.

A single pad with the same dimensions as above, located on top of the array, forms the base of the reference electrode. The counter electrode consists of four pads, electrically connected to allow a larger total electrode size.

4 Electrical measurements

The chip has been fabricated in a 180 nm CMOS standard process (at Taiwan Semiconductor Manufacturing Company, TSMC) with six metal layers, where the uppermost metal is aluminum. The entire chip occupies an area of $1.7 \text{ mm} \times 1.7 \text{ mm}$ and consumes an average power of 0.21 mW from a supply voltage of 1.8 V.

4.1 Readout chain

A current source generator (Keithley 6,221) is used to source or sink current into I_{in} the readout circuit. The microcontroller provides the sampling clock f_{CLK} to the clock generator, which in turn generates the synchronized clock phases required by the switched-capacitor TIA and the ADC. The microcontroller also transfers the digitized ADC output to a PC via SPI. The gain setting is controlled by a 3-bit word and can be programmed from 1 to 7.

The measured I - V characteristics of the readout circuit were evaluated at $f_{\text{CLK}} = 2, 10, 100$, and 180 kHz. The readout circuit exhibits excellent linearity ($R^2 = 0.998$) up to $\pm 4 \mu\text{A}$ at $f_{\text{CLK}} = 180 \text{ kHz}$ with the PGA gain set to 1, indicating that the input current range can be extended by increasing the clock frequency. However, the dynamic input current range determined by the sampling frequency is ultimately limited by the conversion speed of the subsequent successive-approximation (SAR) ADC.

The measured input leakage current is less than 0.1 nA, which causes saturation of the readout circuit when $f_{\text{CLK}} < 5 \text{ Hz}$. Nevertheless, the readout chain maintains high linearity when operated at $f_{\text{CLK}} > 10 \text{ Hz}$. This low leakage current is attributed to the use of NMOS-only switches in the multiplexer instead of complementary transmission gates.

4.2 Current references

To evaluate the current reference under process, voltage, and temperature (PVT) variations, six IC samples were characterized using a Keithley 6,485 current meter. Two resistor-loaded branches tied to V_{DD} and ground were used to sense the currents from the P-channel Metal-Oxide-Semiconductor (PMOS) and NMOS current-mirror branches, respectively. Table 1 summarizes the measured reference current I_{ref} as a function of temperature from 0 °C to 80 °C at $V_{\text{DD}} = 1.8 \text{ V}$. An average temperature coefficient of 216 ppm/°C is obtained among six chips. In addition, the measured results show a maximum chip-to-chip current variation of 9.5%, indicating the impact of process variation. Across the six samples, the temperature coefficient ranges from 168 ppm/°C to 312 ppm/°C. For V_{DD} ranging from 1.1 to 2.2 V, the current reference exhibits a line regulation of 1.8%/V. When V_{DD} exceeds 2.4 V, the output current increases due to leakage from the start-up circuit, which remains active and injects additional current into the bias-voltage generation branch.

TABLE 1 Measured performances of the current references.

Process	180-nm
Temperature range	0 °C–80 °C
V_{DD} range	1.2–2.2 V
Reference currents (uA)	0.1; 0.3; 2.2; 4; 8
Temperature coefficient	261 ppm/°C
Process variation	9.5%
Line regulation	1.8%

5 CMOS post-processing for Au microelectrode development

A carefully designed 7-step process, including both electroless and electrodeposition, was adopted to cover the Al pad surfaces within the CMOS electrode array with an Au surface. The optimization process, along with surface morphology characterization are presented in our recent work (Li et al., 2025), where a bench-top potentiostat was used for the electrodeposition step. In this work, we employ the on-chip current reference circuit to generate and apply the current profile.

5.1 Materials and setup

5.1.1 Chemicals and electrodes

The Au electroplating solution (NB Au Semi100) and Ag electroplating solution (NB Ag Semi100) were purchased from NB Technologies Ltd. Bright Au electroless plating solution, sulfuric acid ($\geq 95\%$, ACS grade), sodium hydroxide, dopamine hydrochloride, nickel sulfate hexahydrate ($\geq 99\%$), sodium hypophosphite, and phosphate-buffered saline (PBS) were purchased from Sigma-Aldrich. Nitric acid ($\geq 65\%$), acetone ($\geq 99\%$, GC grade), and isopropyl alcohol (IPA, $\geq 99\%$, HPLC grade) were used without further purification. Ultrapure deionized water (18.2 MΩcm) was obtained from a Millipore purification system.

The electroless nickel (Ni) plating solution was freshly prepared by mixing equal volumes of nickel sulfate hexahydrate solution (28 g/L in ultrapure water) and sodium hypophosphite solution (27 g/L in ultrapure water). Silver conductive epoxy (8331D) was purchased from MG Chemicals, and non-conductive epoxy (EP41S-5) was obtained from Master Bond.

The CMOS chip was fabricated using the TSMC 180 nm CMOS process. A platinized titanium counter electrode was purchased from Ti-shop.

5.1.2 Equipment

Scanning electron microscopy (SEM) and energy-dispersive X-ray spectroscopy (EDX) were performed using a JEOL IT100 SEM system to characterize the surface morphology and elemental composition. EDX analysis was conducted at an accelerating voltage of 15 kV, corresponding to an estimated analysis depth of approximately 0.5 μm from the microelectrode

surface. Atomic force microscopy (AFM) was carried out using a NaioAFM system (Nanosurf) for surface roughness and thickness analysis. A potentiostat (PGSTAT204, Metrohm) was used for electrodeposition and electrochemical measurements.

5.2 Electroless deposition

An electroless deposition process was employed to obtain an initial, thin layer of Au on the electrodes. The detailed optimisation process for the electroless plating process is described in our previous paper (Li et al., 2024) and is briefly explained here.

The process starts with the preparation of the chip through surface cleaning with acetone and IPA. It is then etched slightly with 10% sodium hydroxide (NaOH) for 2 min at room temperature to remove Al oxide from the Al microelectrodes. A double zincation process was carried out to activate the aluminium layer, with each zincation step performed by immersing the chip in the Zinc (Zn) electroless plating solution for 1 min at 45 °C. The chip was then immersed in the electroless Ni plating solution for 25 min at 85 °C to form a Ni layer on the electrode surface. Finally, an electroless Au layer was deposited on the Ni-coated microelectrodes through a displacement reaction by exposing the chip to the Au plating solution for 15 min at 90 °C.

After electroless Au plating, the chip was glued to a carrier printed circuit board (PCB) using silver conductive epoxy, and the peripheral pads were connected to PCB pads to allow electrical connections to the potentiostats. The wires were encapsulated using non-conductive epoxy such that the circuits, peripheral pads and wire bonds are protected while the microelectrodes in the middle of the chip remain exposed. The epoxy was left to cure overnight. A plastic or a glass ring was glued on the PCB on top of the chip using the same non-conductive epoxy to form a reservoir to contain fluids during the following Au electrodeposition and electrochemical tests and measurements.

5.3 Au electrodeposition

The pulsed galvanostatic deposition (PGD) method was adopted here due to its potential to achieve a smoother, harder, and more uniform surface compared with applying direct current (DC) (Umrana and Shukla, 2022). The method involves applying a pulsed current between the electrode to be covered and a second counter electrode.

A pulsed current with an average of 1.5 mA/cm², frequency of 100 Hz with a 50% duty cycle was found to achieve optimum results (Li et al., 2024). This was generated on-chip, as explained below and applied between the electroless Au-coated microelectrode and an external platinized titanium (Ti) electrode in the presence of the Au electroplating solution.

An individual microelectrode within the array was selected for Au electrodeposition via the multiplexer, as shown in Figure 2a. A current reference multiplier with the output current closest to the optimized current amplitude (312 nA) was selected and its output gated using a clock signal generated externally (through a Keysight 33600 A) at 100 Hz and a 20% duty cycle, to achieve an average current density of 1.5 mA/cm².

5.3.1 Characterization

5.3.1.1 Layer thickness, roughness, and comparison with bench-top potentiostat

The thickness of each deposited layer was determined from the AFM's Nanosurf Easyscan measurements by recording the step height between the plated microelectrode surface and the surrounding passivated CMOS surface before and after each deposition step. The layer thickness was then calculated from the difference between these height profiles. Surface roughness was calculated as the arithmetic mean deviation of the AFM height data from the mean surface plane following plane correction.

The surface roughness and Au-layer thickness of the microelectrodes fabricated using the on-chip circuits are presented in Figure 3 for different electrodeposition times. Three CMOS microelectrodes were used at each electrodeposition time, with error bars indicating the corresponding variation. For comparison, similar characteristics from electrodes that were electrodeposited using the benchtop potentiostat are also presented in Figure 3. The latter were previously reported in (Li et al., 2025).

Compared with the benchtop potentiostat, the on-chip current-source-based electrodeposition achieves lower thickness and surface roughness variations. For thickness, the standard deviations were 0.016, 0.068, and 0.083 μm at 300, 600, and 900 s, respectively, compared with 0.030, 0.045, and 0.188 μm for the benchtop method, with a particularly significant reduction at 900 s, indicating improved deposition repeatability and controllability under prolonged electrodeposition.

The difference between the on-chip technique and Autolab in the thickness of the Au layer with an electroplating time of 900 s may be due to leakage contribution from the electrostatic discharge (ESD) diodes that are connected to the path from the electrode to Autolab, but not from the electrode to the on-chip current generators. Another reason is that the higher peak current (312 nA compared to 128 nA) with a lower duty cycle (20% compared to 50%) may lead to a different nucleation rate and crystal size.

5.3.1.2 Crystallinity

To assess the crystallinity of the surface of the electrodeposited Au layer, cyclic voltammetry measurements were carried out in sulfuric acid (0.5 M) with a scan rate of 100 mV/s, followed by analysis of the location of the oxidation peaks. An Au-electrodeposited WE developed using the benchtop potentiostat was used in the crystallinity analysis.

The voltammogram obtained along with the SEM image of the electroplated Au microelectrode are shown in Figure 4a, where two distinct oxidation peaks are observed. These peaks indicate regions on the surface where Au atoms are arranged in a crystalline pattern, likely corresponding to all three orientations: Au (100), Au (110), and Au (111), as suggested in the literature (Zamani et al., 2022; Hamelin, 1996; Jeyabharathi et al., 2016; Zukauskas et al., 2023). Based on this, it can be concluded that the Au microelectrodes exhibit the characteristics of a polycrystalline gold surface (initially reported in (Li et al., 2025)). Crystalline gold surfaces are more suitable than amorphous gold for the development of biosensors that require recognition elements such as antibodies and aptamers

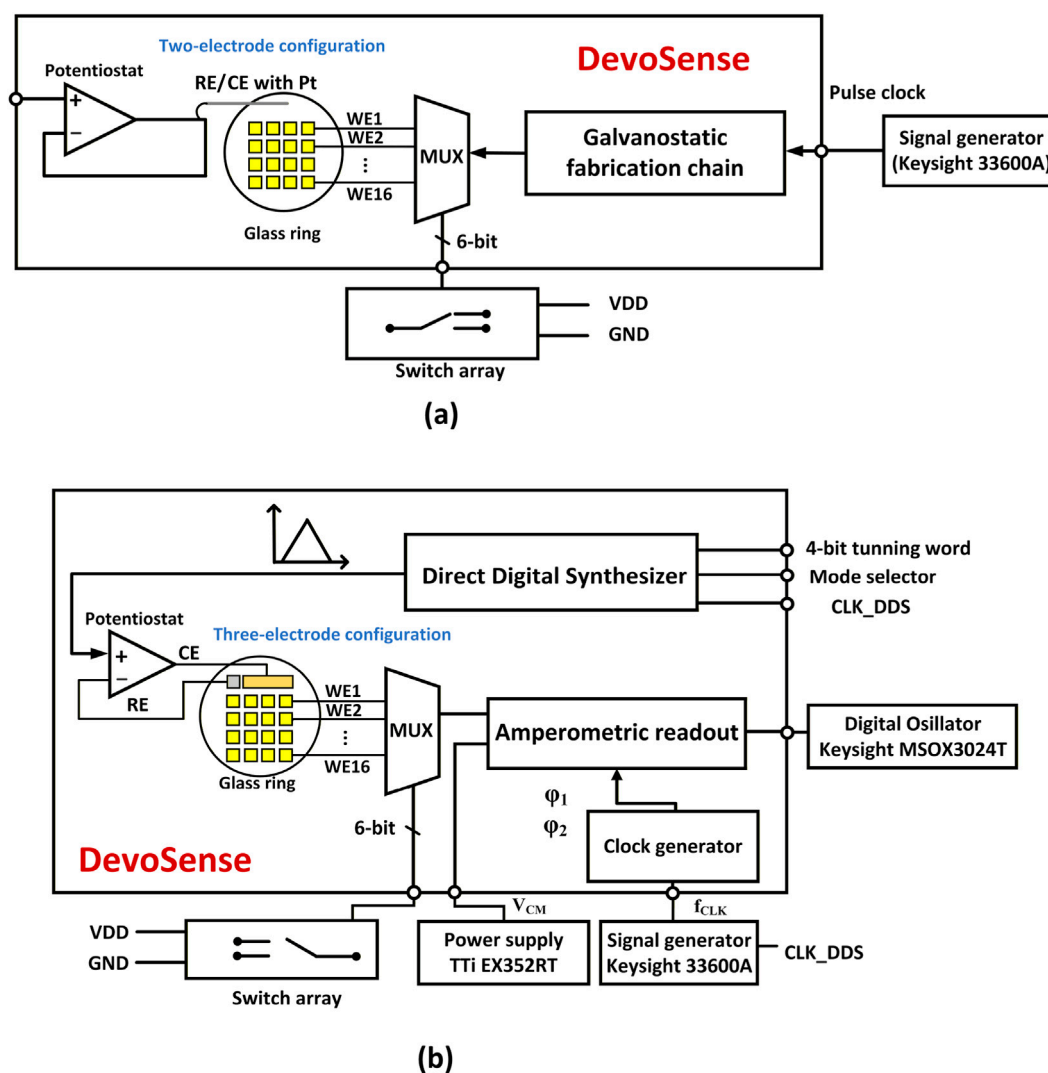


FIGURE 2 Experimental setups showing the chip connections both inside and outside of it for (a) electrodeposition of microelectrodes; and (b) the readout of the microelectrode current.

(Zamani et al., 2022), as well as for nonenzymatic electrochemical sensors (Dutta et al., 2021). Figure 4b shows the EDX profile of the microelectrode after Au electrodeposition, confirming complete Au coverage of the electrode surface.

5.4 Ag/AgCl electrode development

An electroless Au-plated microelectrode within the on-chip array was further developed to achieve an Ag/AgCl pseudo-reference electrode. Ag was first electrodeposited on Au using a pulsed electrodeposition technique. A pulsed current with amplitude, frequency and duty cycle of 2 μ A, 100 Hz and 50% was applied between the Au electrode and a platinised Ti reference electrode in the presence of an Ag electroplating solution. The chlorination was carried out by immersion in 1 M iron (III) chloride (Sigma-Aldrich) for 60 s, similar to (Keeble et al., 2024). The EDX spectra obtained after the Ag electroplating and

chlorination steps are presented in Figures 5a,b, respectively. These results confirm that, after Ag electroplating, the electrode surface is predominantly covered by Ag, with a measured composition of 85.2%. After chlorination, the Ag levels reduce to 73.3% Ag, and a 12.3% Cl appears on the surface while the Au percentage remains unchanged at 14.3% Au, confirming the formation of Ag/AgCl. Two chips were fabricated for subsequent measurements: one for open-circuit potential (OCP) testing and the other for on-chip dopamine detection.

6 Electrode stability

6.1 WE stability

To investigate the stability of the Au microelectrodes, continuous cyclic voltammetry (CV) was performed on three

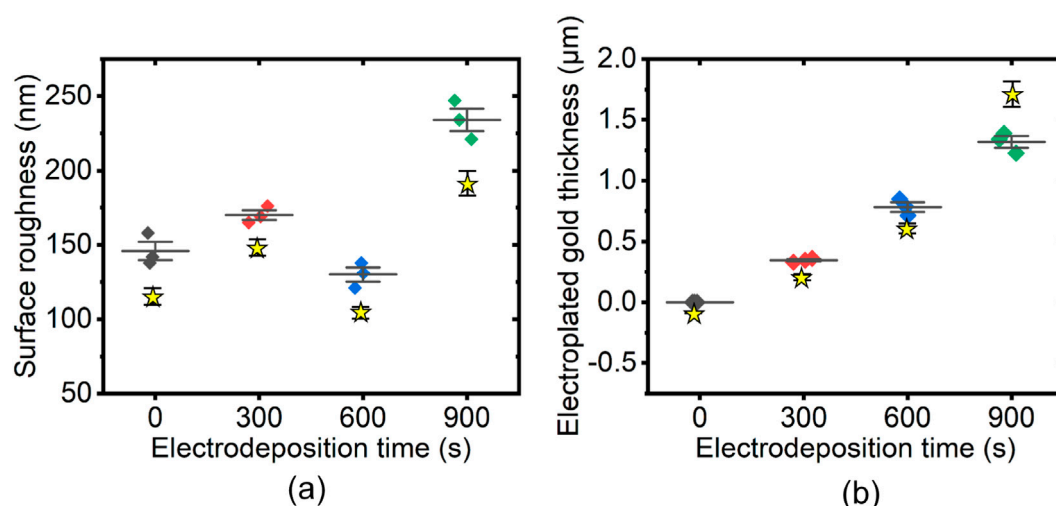


FIGURE 3

(a) Surface roughness ($n = 3$) of electrodeposited Au layer versus the electrodeposition time. (b) Thickness ($n = 3$) of the electrodeposited Au layer versus electrodeposition time. All electrodes were electrodeposited using the on-chip current generator circuits, except those marked with asterisks, which correspond to electrodes that were electrodeposited using the benchtop potentiostat and previously reported in (Li et al., 2025). Error bars represent standard deviation.

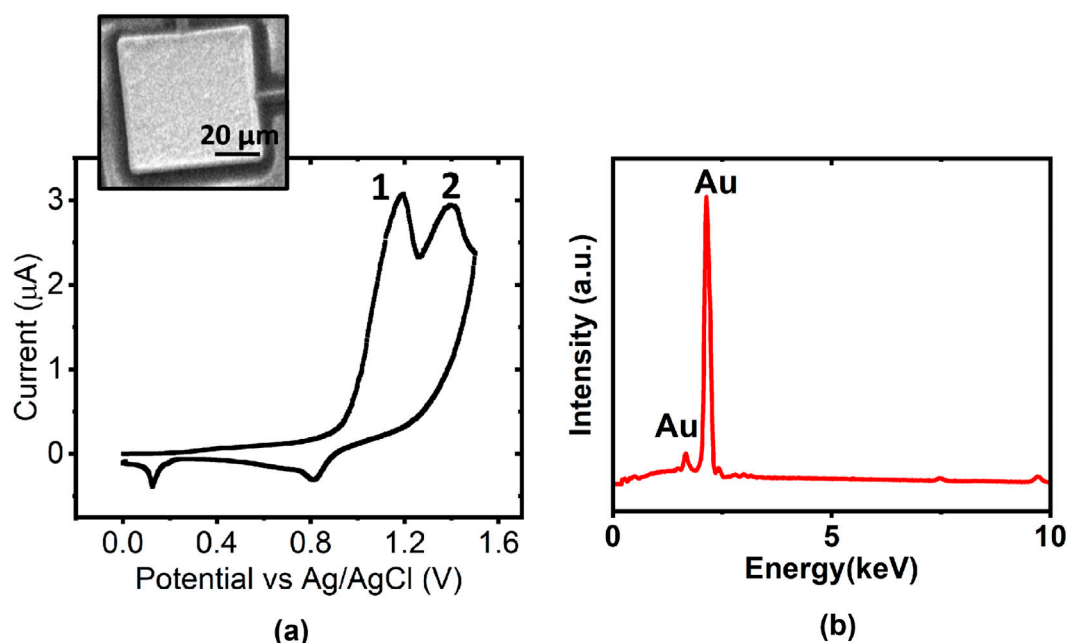


FIGURE 4

(a) Cyclic voltammetry with CMOS Au microelectrode in 0.5 M sulfuric acid with a scan rate of 100 mV/s showing anodic peaks that indicate a polycrystalline Au surface, as we presented in (Li et al., 2025). The inset shows the SEM image of the microelectrode surface. (b) EDX of the microelectrode after Au electrodeposition, confirming complete Au coverage of the electrode surface.

electrodes on three different CMOS chips. Freshly prepared electrodeposited Au microelectrodes were tested in PBS solution using off-chip RE and CE at a scan rate of 100 mV/s to determine how many consecutive voltammograms could be obtained before any observable instability occurred. The overall results from this experiment have been reported in our previous work (Li et al., 2025).

For one representative electrode, 23 stable CV cycles were obtained before signs of instability appeared in the 24th cycle, as shown in Figure 6. During the stable cycling period, the relative variation of the peak current was within 5.2%, indicating good (short-term) electrochemical stability of the Au-plated CMOS microelectrode. The other two electrodes showed signs of instability in the 26th and 20th cycles, respectively. Based on

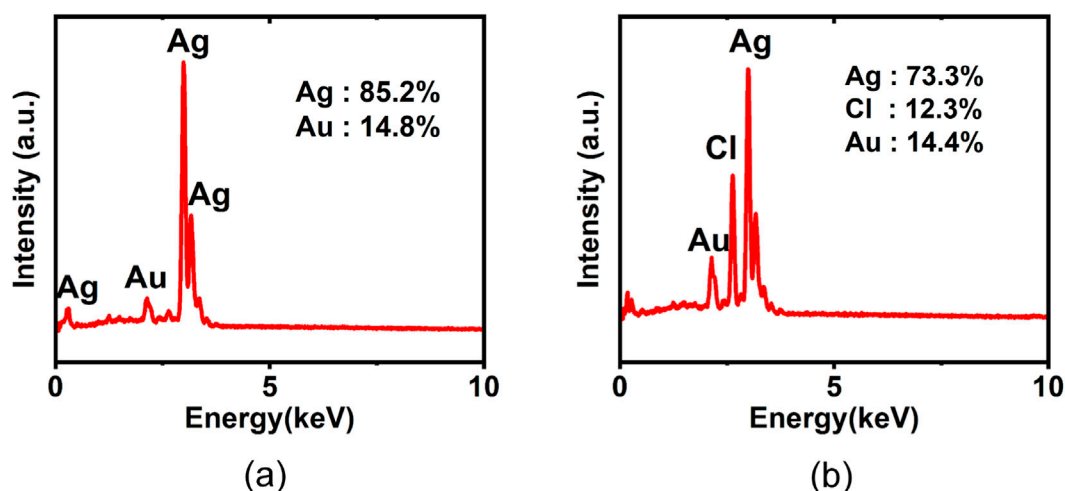


FIGURE 5
EDX spectra of the CMOS microelectrode obtained after (a) silver electrodeposition and (b) silver chlorination, with the percentages of the major elemental components indicated.

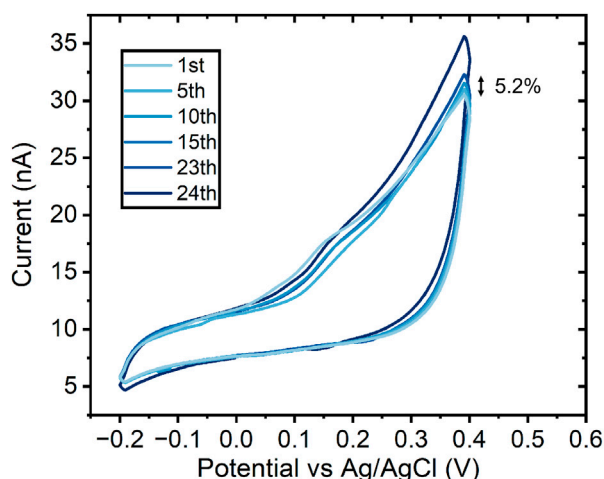


FIGURE 6
Continuous cyclic voltammetry in PBS at one electrodeposited Au microelectrode with a scan rate of 100 mV/s, showing Au electrode stability during repeated voltammograms.

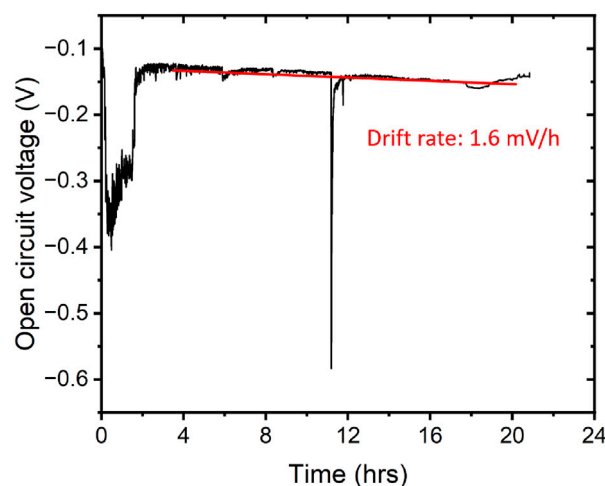


FIGURE 7
The OCP versus time for the developed CMOS Ag/AgCl electrode measured against a commercial Ag/AgCl electrode in 1 M KCl solution.

these results, the electrodes exhibited an average stable operation window of approximately 23 CV cycles.

6.2 RE stability

The open circuit potential (OCP) between the developed Ag/AgCl electrode on CMOS and a commercial Ag/AgCl was measured in 1 M potassium chloride (KCl) solution. The results are shown in Figure 7, indicating OCP changes between -0.123 V and -0.159 V over 22 h of measurement, with an overall drift rate of 1.6 mV/h after the initial 3-h period. These indicate that the integrated reference electrode can provide a sufficiently stable reference potential over the time scale used.

7 On-CMOS dopamine measurement

7.1 Measurement setup

The developed microelectrodes, without any further modifications or external electrodes, were used for the measurement of dopamine. The Ag/AgCl electrode developed using the above technique was used as a pseudo-reference electrode, an electroless-plated Au microelectrode was used as a counter electrode, and an Au-electroplated electrode (with 600 s deposition time) was used as a working electrode, as shown in Figure 8. The surface area of CE was designed to be a few times larger than that of WE to reduce CE polarization and prevent it from

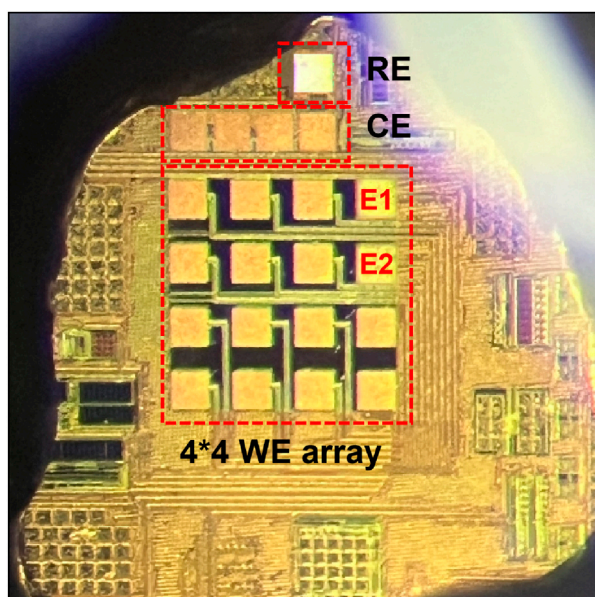


FIGURE 8
Optical microphotograph of the microelectrode array on the CMOS chip. All electrodes were first coated with Au using an electroless deposition technique. For the RE, Ag was then electroplated and converted to Ag/AgCl by conditioning in iron (III) chloride. For the WE, the two electrodes (E1 and E2) received additional Au electroplating for 600 s each.

limiting the cell current, thereby maintaining stable potential control at the WE.

The on-chip waveform generator generated a triangular voltage waveform ranging from 0.4 V to 1.2 V at a scan rate of 100 mV/s and applied it between the WE and RE. The multiplexer connected the electrodes to the readout circuit, while a clock from a signal generator (Keithley 33600 A) was fed into the on-chip clock generator to produce synchronous clocks for the readout circuit. The f_{clk} of the switched capacitor TIA is chosen to be 20 kHz to obtain a dynamic input current range of ± 400 nA while the PGA gain is set to 1. The outputs of the readout chain and DDS are connected to a digital oscilloscope (Keysight MSOX3024T) for data logging and display. The block diagram of the test bench is shown in Figure 2b. The data was processed offline using MATLAB code to filter out noise using a 50-point moving average filter and converted into a voltammogram.

Cyclic voltammetry was carried out in PBS and again in the presence of dopamine with concentrations of 100 μM , 200 μM , and 400 μM in PBS. The measured output potential of the readout circuit was divided by the I-V gain of the readout chain to calculate the sensing current. The voltammogram was formed by plotting the current versus the triangular voltage applied to the sensor.

7.2 Sensor performance

The measured voltammograms, all acquired using a single CMOC chip ($n = 1$) with all three electrodes embedded as well as the readout circuit, are shown in Figure 9a, indicating oxidation peak of dopamine is consistently located at about 0.27 V. The peak oxidation currents, extracted from the voltammograms in Figure 9a

are plotted versus dopamine concentration in Figure 9b indicate a linear response ($R^2 = 0.994$) over the tested dopamine range.

The sensitivity of the sensor to dopamine, calculated by dividing the slope of the trend-line in Figure 9b by the geometric surface area of the working electrode, is 12.35 $\text{mA mM}^{-1} \text{cm}^{-2}$. The limit of detection (LOD) is calculated to be 4.9 μM based on Equation 4.

$$\text{LOD} = 3\delta/m \quad (4)$$

Where m is the slope of the trend-line. To determine σ , cyclic voltammetry was repeatedly performed in the dopamine-free PBC blank (i.e., blank) solution. The current at cell voltage of 0.27 V, corresponding to the dopamine oxidation potential, was then extracted from each blank voltammogram, and σ was calculated as the standard deviation of these current values. Detection below the LOD level is mainly limited by the electrode/interface noise, possible dopamine adsorption or fouling on the electrode surface, the absence of a dedicated surface-modification layer for dopamine enrichment for sensitivity and selectivity enhancement, and the input-referred noise of the readout circuit (1.5 nA rms, corresponding to an equivalent of 2.8 μM dopamine concentration).

To extend the platform toward lower-concentration dopamine detection, potential approaches include increasing the effective electroactive area of the working electrode through nano-structuring, introducing catalytic coatings or selective membranes to enhance dopamine response and suppress interference and reducing the noise of the readout circuit.

7.3 Redox peak analysis

The dominant oxidation peak at 0.27 V is attributed to the two-electron oxidation of dopamine to dopamine-o-quinone. The absence of an obvious reduction peak may be attributed to the depletion of dopamine-o-quinone before the reverse scan through intramolecular cyclization and diffusion or desorption from the electrode surface (Kim et al., 2014).

Interestingly, voltammograms obtained during similar measurements carried out with on-chip WE and off-chip CE/RE reported in (Li et al., 2025) exhibit extra reduction and oxidation peaks that correspond to the cyclization (which are not observed here). Compared with the off-chip CE/RE configuration, the on-chip CE/RE has a much smaller geometric area and adopts a different spatial arrangement. As a result, the faradaic current associated with such secondary dopamine oxidation products might be weaker in the on-chip RE/CE/WE configuration and therefore obscured by background charging current.

7.4 Interferences

Ascorbic acid (AA) may cause interference in dopamine measurements due to its close oxidation potential to dopamine. To determine sensitivity to AA, cyclic voltammetry was performed with on-chip Au microelectrodes and off-chip RE and CE in solutions containing varying ascorbic acid concentrations at a scan rate of 100 mV/s. The results (initially reported in (Li et al., 2025)) shown in Figure 10 indicate a sensitivity of 0.26 $\text{mA mM}^{-1} \text{cm}^{-2}$, to AA, approximately 47.5-fold lower than that obtained for dopamine.

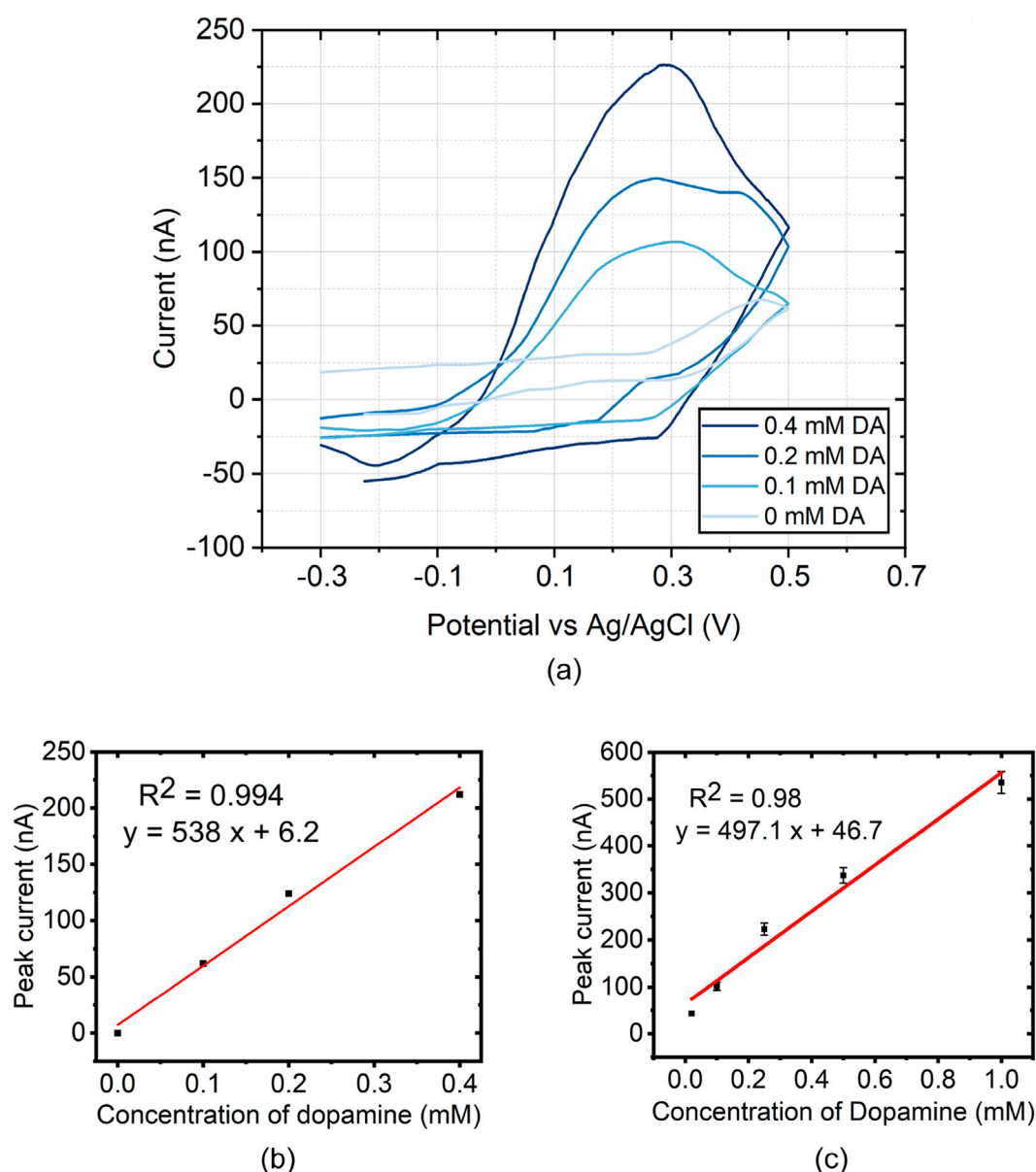


FIGURE 9

(a) Cyclic voltammograms obtained using a single CMOS chip with completely embedded electrodes and readout circuit at different dopamine concentrations in PBS, with a scan rate of 100 mV/s. (b) Corresponding calibration plot ($n = 1$) showing peak oxidation current versus concentration of dopamine using the fully on-chip electrodes (RE, WE, CE). (c) Calibration plot (initially reported in (Li et al., 2025)) using three CMOS chips ($n = 3$), each with an on-chip WE and off-chip/commercial CE and RE. error bars represent standard deviation from the three CMOS chips.

7.5 Comparison with off-chip RE/CE configuration

The calibration line obtained using the fully integrated three-electrode system shows strong agreement with those obtained using the off-chip RE/CE configuration, shown in Figure 9c ($n = 3$; previously reported in (Li et al., 2025)). The close match in sensitivity, linearity, and the consistency of peak position across dopamine concentrations demonstrates that the on-chip electrochemical cell preserves the essential oxidation kinetics of dopamine and supports reliable quantitative analysis. This functional equivalence confirms the feasibility of replacing

external electrodes with a fully on-chip implementation without sacrificing analytical performance.

Despite the overall agreement, small differences between the two calibration curves are observed and can be attributed to several factors. First, the on-chip reference electrode typically exhibits greater potential variability than a commercial Ag/AgCl electrode due to its smaller geometry, thinner Ag/AgCl layer, and stronger dependence on local ionic composition. Such variations can cause slight shifts in the effective oxidation potential during amperometric measurements. Second, the confined geometry of the integrated electrochemical cell alters the diffusion field compared with the macroscale commercial setup, introducing differences in mass-

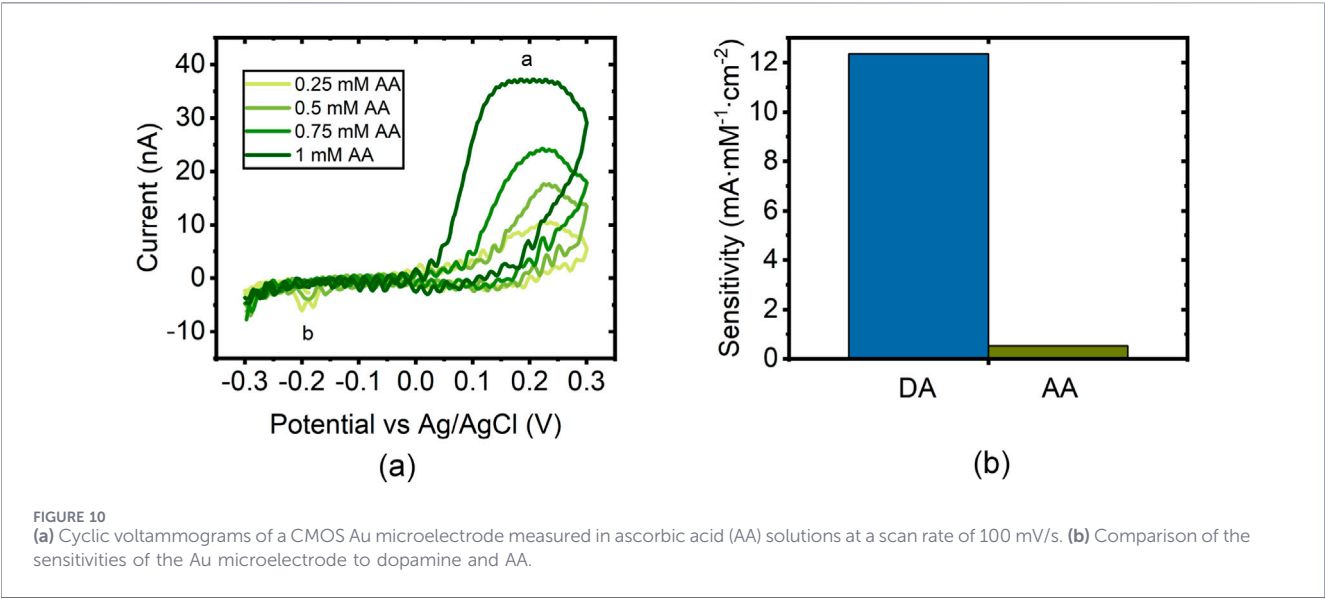


TABLE 2 Comparison with state-of-the-art integrated CMOS circuits with on-chip microelectrodes for amperometric measurement. Glu: Glutamate; Fc: Ferrocene; ELD: electroless deposition; ED: electrodeposition; PVD: physical vapour deposition; Cu: copper; CNT: carbon nanotube; Pd: Palladium; N.A.: not available. *The power consumption only accounts for the readout circuits.

Specifications	This work	(Xu et al., 2025)	(White et al., 2018a)	Dragas et al. (2017)	Jafari et al. (2023)	Giagkoulovits et al. (2018)
Target analyte	DA	DA	DA	DA	DNA	Fc
WE development method	ELD + ED	PVD + lift-off	Lift-off	PVD	N.A.	PVD
WE structure	Al/Zn/Ni/Au	Ti/Au	Al/Cu/Au	Al/Pt	Au	Al/Ti/Pd/Au
RE and CE location	On-chip	Off-chip	Off-chip	Off-chip	On-chip	Off-chip
On-chip ED circuit?	Yes	N.A.	N.A.	N.A.	N.A.	N.A.
Technology (nm)	180	N.A.	250	180	130	350
Sensitivity (mA mM ⁻¹ cm ⁻²)	12.35	N.A.	N.A.	N.A.	N.A.	5.3
Detection range (μM)	100–400	0.5–1	N.A.	200–500	N.A.	1,000–5,000
LoD (μM)	4.9	N.A.	N.A.	N.A.	N.A.	N.A.
Power (mW)	0.21*	N.A.	N.A.	0.22*	0.05/Channel	42.9
Pixel size (μm ²)	66 × 66	10 × 10	20 × 20	N.A.	N.A.	20 × 20

transport behavior that may subtly affect the current amplitude. Finally, variations in electrode surface chemistry—including roughness, active site density, and fabrication-related microstructure—can lead to minor deviations in charge-transfer kinetics between the two configurations.

The ability of the fully integrated system to reproduce the calibration characteristics of the hybrid setup highlights not only its analytical validity but also its broader technological advantages. Integration of all three electrodes on chip minimizes solution volume, reduces parasitic wiring resistance and external noise pickup, and enables compact, multi-site arrays that are challenging to achieve with discrete electrodes. These features position the integrated electrochemical cell as a scalable sensing

platform that can be extended beyond dopamine to other neurochemical or metabolic analytes through appropriate modification of the working-electrode surface.

7.6 Comparison with state-of-the-arts

Table 2 compares this work with previously reported amperometric electrochemical sensing platforms incorporating CMOS microelectrodes. This work uniquely integrates the Au working electrode, Au counter electrode, Ag/AgCl reference electrode, and electrodeposition circuits on the same chip, whereas most prior implementations rely on off-chip reference and counter electrodes as well as external electrode-fabrication

equipment. This high level of integration enables a self-contained sensing platform with improved system autonomy, scalability, and potential for low-cost mass production. In addition, the proposed platform achieves a high dopamine sensitivity of $12.35 \text{ mA mM}^{-1} \text{ cm}^{-2}$, a low limit of detection (LoD) of $4.9 \text{ }\mu\text{M}$, and a low power consumption of 0.21 mW .

8 Conclusion

This work presents the first on-chip electroplating circuit enabling *in situ* modification of integrated electrodes, thereby simplifying device preparation. The feasibility of the electroplated electrodes was verified using a fully integrated three-electrode system for dopamine sensing, which produced calibration behavior consistent with a conventional hybrid configuration. These results demonstrate the reliability of the on-chip electrochemical platform and highlight its advantages in system miniaturization, reduced sample volume, and suitability for scalable and implantable biosensing applications.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

ML: Data curation, Formal Analysis, Validation, Visualization, Writing – original draft, Writing – review and editing. AN: Formal Analysis, Methodology, Writing – original draft, Writing – review and editing. SG: Conceptualization, Formal Analysis, Funding acquisition, Supervision, Writing – original draft, Writing – review and editing.

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