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A fast scan cyclic voltammetric digital circuit with precise ohmic drop compensation by online measuring solution resistance and its biosensing application

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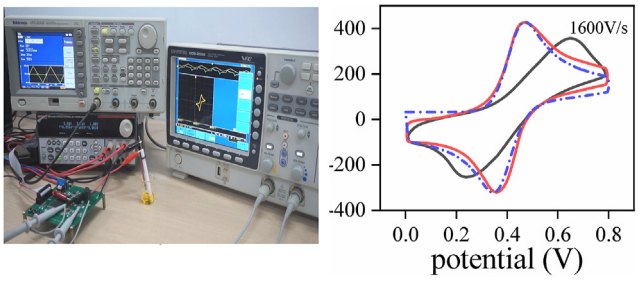
HIGHLIGHTS

- A digital circuit for fast scan cyclic voltammetry (FSCV) was developed.
- Precise ohmic drop compensation through online measuring solution resistance first.
- Ohmic drop compensation was realized automatically without signal oscillation.
- Hg^{2+} could be detected with a LOQ of 1 pmol/L, using a biosensor based on FSCV.

GRAPHICAL ABSTRACT



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ABSTRACT

In this work, a novel fast scan digital circuit for voltammetric analysis with precious ohmic drop compensation is developed, which is achieved through online measuring solution resistance first and then proportionally feedbacking the output signal to potentiostat's in-phase input through a potentiometer. It mainly consists of a solution resistance measurement module based on AD5933 chip, an ohmic drop automatic compensation module and a STM32F103ZET6 microcontroller. The performance of the circuit is checked successively using pure resistances, RC dummy cells, RC dummy cells incorporating a pseudo-faradaic component, and the ferrocene redox system. Results show that, precise ohmic drop compensation can be realized online and automatically, affording fast scan cyclic voltammetric (FSCV) analysis for theoretical electrochemical cells at 2000 V/s and that for practical electrochemical system using conventional electrodes at 1600 V/s. Based on this circuit, a very simple DNA biosensor for ultrasensitive detection of mercuric ions was explored. Benefitting from the high sensitivity brought by the high scan rate, the limit of quantitation (LOQ) can reach 1 pmol/L, demonstrating the application potential of FSCV in the field of ultrasensitive electrochemical detection.

1. Introduction

Cyclic voltammetry (CV) is one of the simplest and most classic

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electrochemical techniques [1]. It mainly investigates electrochemical and thermodynamic properties of the redox system by changing the potential scan rate, and obtains some kinetic information which other electrochemical technologies cannot [2,3]. Fast scan cyclic voltammetry (FSCV) is cyclic voltammetry with a high scan rate [4,5], which has two significant advantages: (1) Improving the time resolution. The higher the potential scan rate used is, the smaller the kinetic time window can be distinguished. That is, faster heterogeneous or homogeneous reactions can be studied, and shorter-lived intermediates can be tracked, bringing better understanding of electron transfer and chemical reaction kinetics [6–8]. (2) Improving detection sensitivity [9,10]. The peak current i_p of CV is proportional to the square root of the scan rate $v^{1/2}$ in diffusion-controlled electrochemical reaction, and is proportional to the scan rate v in adsorption-controlled electrochemical reaction [11]. Obviously, increasing the scan rate can increase the Faradaic current i_f. Although the background charging current i_c is also proportional to the scan rate v, it is a stable plateau value equal to vC_{dl} where C_{dl} is the double layer capacitance, so it can be easily deducted [10]. Therefore, increasing the scan rate helps improve the detection sensitivity, which is especially beneficial when analyzing low-concentration research targets [12,13]. Due to above two characteristics, FSCV is widely used for in-vivo detection of neurotransmitters such as dopamine, guanosine, adenosine, and 5-hydroxytryptamine, etc. [14–18]. However, the increase in scan rate brings serious solution ohmic drop as well.

Ohmic drop refers to the potential drop iR_u which is produced when the current i flows through the uncompensated solution resistance R_u between the surface of the working electrode and the potential reference point [19,20]. At high scan rate, the ohmic drop can reach tens or even hundreds of mV, which will severely distort the voltammograms, making it difficult to extract correct thermodynamic and dynamic information. Various methods have been tried to eliminate the ohmic drop, including AC conductance voltammetry, current interruption compensation, and applied potential iterative correction, etc. [21–27]. Though reducing iR_u to some extent, none of them can online eliminate ohmic drop thoroughly and the ensuing voltammogram distortion [28,29]. At present, the most successful solution to online eliminate ohmic drop is still the positive feedback compensation technique [30].

The positive feedback compensation technique, which proportionally feedbacks the output signal to potentiostats in-phase input through a potentiometer, increases the electric double layer's potential difference to compensate the solution ohmic drop in real-time [31,32]. The criterion for judging whether the solution ohmic drop has been fully compensated is the self-excited oscillation of the circuit [30]. However, the self-excited oscillation of the circuit does not necessarily occur when the solution ohmic drop is 0, but is influenced by plenty of factors such as the overall design of the circuit, Printed circuit board (PCB) wiring, component layout, and solution system, etc. [14,33–35]. That is to say, it is likely to occur when the solution ohmic drop compensation >105%. Supposing i is 1 mA and R_u is 1 kΩ, a 5% compensation error brings a peak potential shift of 50 mV. It could reach several hundred mV in some cases, even the redox peaks disappear completely, meaning that the redox reaction has not yet occurred though the working electrode potential has reached the very edge of the potential window. In this case, it is impossible to extract any valuable electrochemical information. Apparently, an absolutely precise ohmic drop compensation could be achieved only if R_u could be measured accurately and then online compensated by positive feedback technique [32]. To our best knowledge, there is no relevant report about it in the design of digital circuits for FSCV.

In this work, a novel FSCV digital circuit with automatic and precious ohmic drop compensation is developed based on the combination use of AD5933 chip and STM32F103ZET6 microcontroller, which can precisely measure R_u first and then perform online iR_u compensation in real-time through positive feedback. The FSCV circuit can be applied to fast scan voltammetric analysis at 1600 V/s. It was successfully tried for ultrasensitive detection of mercuric ion Hg^{2+} at the level of pmol/L basing on an DNA biosensor.

2. Designs and methods

2.1. System architecture

As shown in Fig. 1A, the novel fast scan circuit for voltammetric analysis with automatic ohmic drop compensation by in-situ detection of solution resistance consists of a solution resistance measurement module, an ohmic drop automatic compensation module and a microcontroller. The microcontroller is the core of the circuit and controls it overall, which has four main functions: (1) measuring the solution resistance; (2) adjusting the tap of the digital potentiometer to realize automatic compensation of ohmic drop; (3) controlling the analog switch to realize the free switching between the solution resistance measurement module and the electrochemical cell, thus to avoid mutual interference between the solution resistance measurement module and the ohmic drop automatic compensation module; and (4) controlling the magnification of the programmable gain amplifier. The working principle of this circuit is as follows. First, the microcontroller completes the measurement of the solution resistance. Then, after switched to the electrochemical cell, redox reaction will occur when a potential waveform is implemented by the signal generator. Next, ohmic drop is automatically compensated. Finally, the output waveform of the circuit is displayed on an oscilloscope. Printed circuit board (PCB) of this circuit is shown in Fig. 1B, the actual connection of the fast-scan voltammetric detection system is shown in Fig. 1C, and the detailed design including the circuit board design, electronic parts list and firmware source code, are provided in the supporting information. In addition, some specific operations are uploaded in the formation of video still.

2.2. Solution resistance measurement module

The solution resistance measurement module consists of an attenuation circuit and an AD5933 chip, V_{OUT} and V_{IN} pin of which connect with the two electrodes of the electrochemical cell (Fig. 1D). The AD5933 chip is a high-precision impedance measurement chip, integrated by a 12-bit analog-to-digital converter (ADC) with a sample rate up to 1 MSPS, a frequency generator, a digital signal processor (DSP) and so on. First, a sine signal generated by the frequency generator is used to excite the external impedance caused by the solution in the electrochemical cell, and the response signal is collected by the ADC. Second, the real part and the imaginary part can be calculated by means of Discrete Fourier Transform (DFT) through the DSP, the values of which are transmitted to the microcontroller by serial communication. Third, the mode and phase difference of the impedance are calculated by the microcontroller according to real part and the imaginary part. The specific measurement steps are as follows.

First, a known calibration impedance Z_0 is connected, the real part value R_0 and the imaginary part value I_0 of the DFT are obtained,

$$A_0 = \sqrt{{R_0}^2 + {I_0}^2} \quad (1)$$

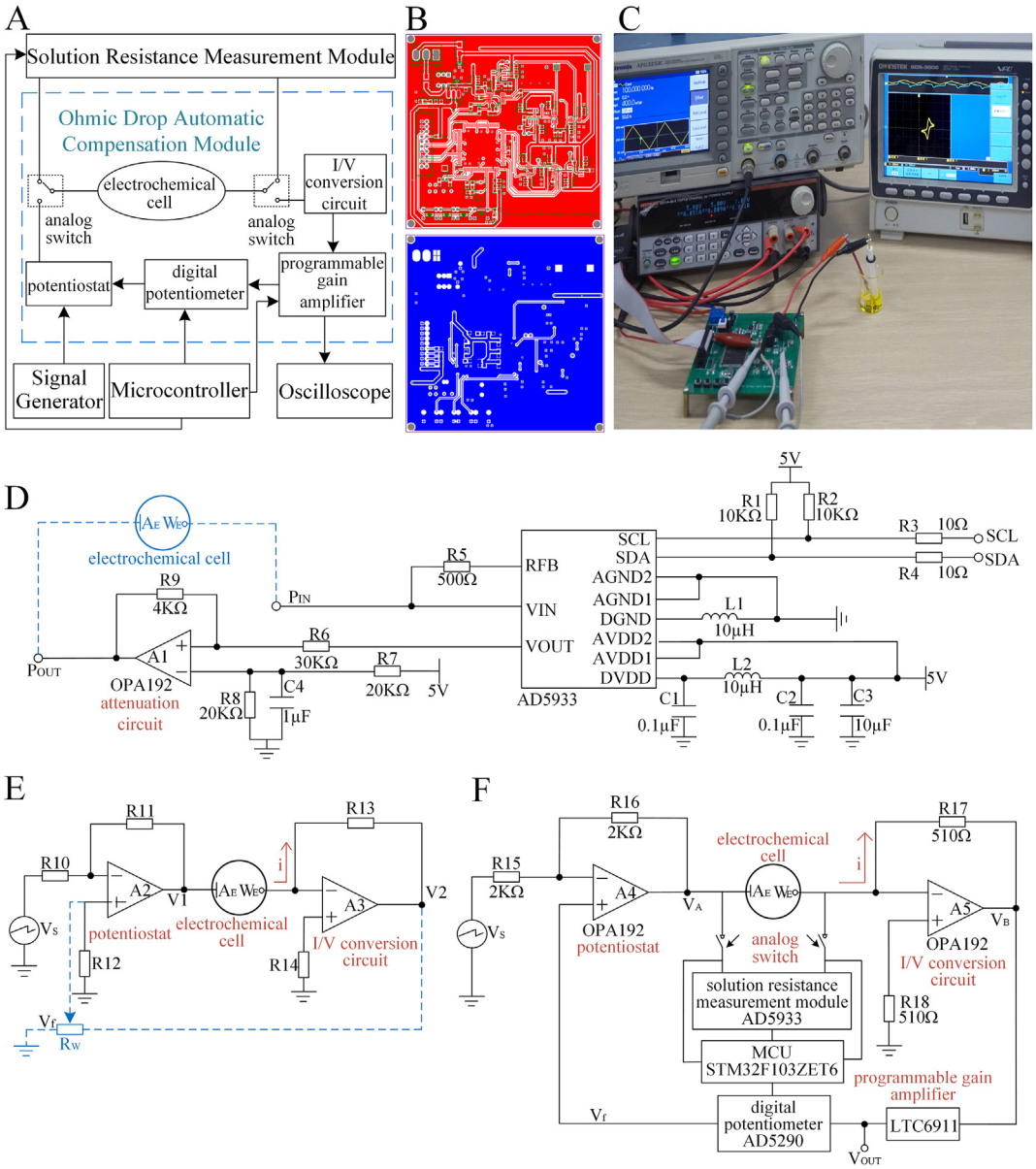

Fig. 1. (A) Block diagram of the circuit. (B) PCB of the circuit. (C) Actual connection of the fast scan detection system. (D) Solution resistance measurement module. (E) Ohmic drop automatic compensation module. (F) Actual design of the fast scan circuit for voltametric analysis.

$$Gain = \frac{(1/Z_0)}{A_0} \tag{2}$$

$$\varphi_0 = \tan^{-1}(I_0 / R_0) \tag{3}$$

where A_0 is DFT magnitude of Z_0, *Gain* is the gain factor, and Φ_0 is the phase of the system.

Second, an unknown impedance Z is connected, the real part value R and the imaginary part value I of the DFT are obtained,

$$A = \sqrt{R^2 + I^2} \tag{4}$$

$$\varphi = \tan^{-1}(I / R) \tag{5}$$

where A is DFT magnitude of Z, and Φ is the overall phase.

Third, the magnitude of the unknown impedance $|Z|$ and the phase difference Φ_Z which is actually the phase of Z can be obtained,

$$|Z| = \frac{1}{Gain \cdot A} = \frac{Z_0 \cdot \sqrt{R_0{}^2 + I_0{}^2}}{\sqrt{R^2 + I^2}} \tag{6}$$

$$\varphi_z = \varphi - \varphi_0 \tag{7}$$

Finally, the value of resistance R_s can be obtained,

$$R_s = |Z|\cos(\varphi_z) = \frac{Z_0 \cdot \sqrt{R_0{}^2 + I_0{}^2}}{\sqrt{R^2 + I^2}} \cos(\varphi - \varphi_0) \tag{8}$$

However, in case of impedances <1 KΩ, the current flowing through the impedance will become too large to be provided by the V_{OUT} pin of the AD5933 chip. Therefore, the attenuation circuit is formed by amplifier A1, resistances R6 and R9, which could reduce

the current flowing through the impedance and allow the measurement of impedances <1 KΩ.

2.3. Ohmic drop automatic compensation module

A typical circuit of two-electrode system is shown in Fig. 1E, which mainly consists of a potentiostat and a I/V conversion circuit. In case of a high scan rate, the ohmic drop must be eliminated because the voltammetric curve would be distorted too severely to be ignored. To eliminate the ohmic drop, the positive feedback method is the most widely used due to its simplicity, by replacing the resistor R12 with a potentiometer Rw. It is noting that, because the solution resistance is not accurately known, the criterion for judging whether 100% compensation of ohmic drop is achieved is based on the occurrence of self-excited oscillation. Obviously, it is not an accurate standard, because self-oscillation will only occur when more than 100% is compensated. If Rw is adjusted back to eliminate the self-oscillation to complete the measurement, the ohmic drop is difficult to be exactly 100% compensated, being a bit over-compensated or insufficiently compensated. At high scan rates, the current is usually at the level of mA. Assuming the solution resistance is about 1KΩ, the 5% uncompensated or over-compensated ohmic drop would bring an error of tens of mV or even hundreds of mV, which is obviously unacceptable for electrochemical measurement. Evidently, in order to obtain accurately 100% compensation of ohmic drop, it is necessary and feasible to accurately measure the solution resistance first and then compensate it according to the measured result by positive feedback. The principle is as follows.

Ohmic drop V_c is:

$$V_c = i \cdot R_s \tag{9}$$

Where i is the current through the electrochemical cell, and R_s is the solution resistance. In order to eliminate ohmic drop, positive feedback compensation is introduced. In Fig. 1E,

$$V_1 = -V_s + 2V_f = -V_s + 2\beta V_2 = -V_s + 2\beta i R_{13} \tag{10}$$

Where V_1 is the output potential of the potentiostat; V_s is the output potential of the signal source; V_f is the positive feedback potential; and β is the feedback proportional coefficient, i.e., the tap of the digital potentiometer. And, to compensate the ohmic drop, V_1 should be as follows.

$$V_1 = -V_s + V_c = -V_s + iR_s \tag{11}$$

According to equations (10) and (11), perfect ohmic drop compensation can be obtained if

$$\beta = \frac{R_s}{2 \cdot R_{13}} \tag{12}$$

Therefore, R_s and β are calculated by the microcontroller, β is automatically adjusted by a digital potentiometer, and then the online perfect automatic ohmic drop compensation could be realized.

2.4. Actual design of the fast scan circuit for voltametric analysis

Actual design of the fast scan circuit for voltametric analysis is shown in Fig. 1F. The potentiostat is composed of an inverting amplifier A4 and resistances R15 and R16, to control the potential of the working electrode. I/V conversion circuit is formed by the amplifier A5 and resistance R17, which amplifies a weak current signal and convert it into a voltage signal easy to measure. The voltage signal is boosted by the programmable gain amplifier LTC6911 to increase the detection sensitivity. R_s is measured by the solution resistance measurement module, β is calculated by the microcontroller, the tap of the digital potentiometer is automatically adjusted, and then perfect online ohmic drop compensation is achieved.

2.5. Reagents

Ferrocene, tetrabutylammonium tetrafluoroborate (NBu_4BF_4), tris(2-carboxyethyl) phosphine (TCEP) and mercury nitrate monohydrate ($Hg(NO_3)_2 \cdot H_2O$, ≥99.99% trace metals basis) were purchased from Sigma-Aldrich (St. Louis, MO, USA). HPLC-grade acetonitrile was purchased from Aladdin Bio-Chem Technology Co., Ltd. (Shanghai, China). Other chemicals used were of analytical reagent grade at least and used as received. The DNA aptamer for mercuric ion Hg^{2+} was synthesized by Sangon Biotech Co., Ltd. (Shanghai, China) with the sequence as follows: 5′−SH−**TTT**CGAACGACG**TTT**-3′. Milli-Q ultrapure water was used throughout the experiment.

2.6. Biosensing detection of Hg^{2+}

A 5 μL of mixture solution containing 5 μmol/L DNA aptamer for mercuric ion Hg^{2+} and 1 mmol/L TCEP was dropped onto the surface of a polished gold electrode with a diameter of 2 mm, and incubated overnight at 4 °C. After rinsed with water to remove excess DNA that was not bound to the gold electrode, the electrode was incubated with 20 μL of sample solution containing Hg^{2+} at room temperature for 1 h. After cleaned, the electrode was ready for FSCV detection.

Parameters for FSCV detection were as follows. The electrolyte solution was 0.5 mol/L KNO_3 aqueous solution, the potential window was −0.2 V to +0.6 V, and the scan rate is 1600 V/s.

3. Results and discussion

3.1. Performance of solution resistance measuring

Obviously, accurate online measurement of solution resistance is the key for precise ohmic drop compensation. To evaluate the performance of solution resistance measuring, resistances obtained by this circuit R_m were compared with R_c obtained by a KEITHLEY digital multimeter with a measurement accuracy 0.012%. As shown in Fig. 2, there is a very good linear relationship between the two, and the linear regression equation is $R_m = 1.005 \times R_c - 1.94$ with a squared correlation coefficient $R^2 = 0.9996$. It indicates that this circuit could online measuring the resistance accurately.

3.2. Performance of ohmic drop compensation

3.2.1. Demonstration by RC dummy cells

Under ideal conditions, an electrochemical cell without redox substances is equivalent to a series connection of the uncompensated solution resistance R_u and the double layer capacitance C_{dl}. If the solution resistance is 100% compensated i.e. $R_u = 0$, the current response would be a square wave pulse equivalent to the charging current $i_c = vC_{dl}$. To demonstrate the ohmic drop compensation ability of this circuit, several RC dummy cells of 100 Ω + 1 μF, 240 Ω + 0.47 μF and 330 Ω + 0.33 μF were used to simulate conventional electrodes with a diameter of 1−3 mm in different solution systems. At scan rates of 400, 800, 1200, 1600 and 2000 V/s, current responses were recorded under three different situations, i.e., R_u was not compensated, R_u was compensated automatically by

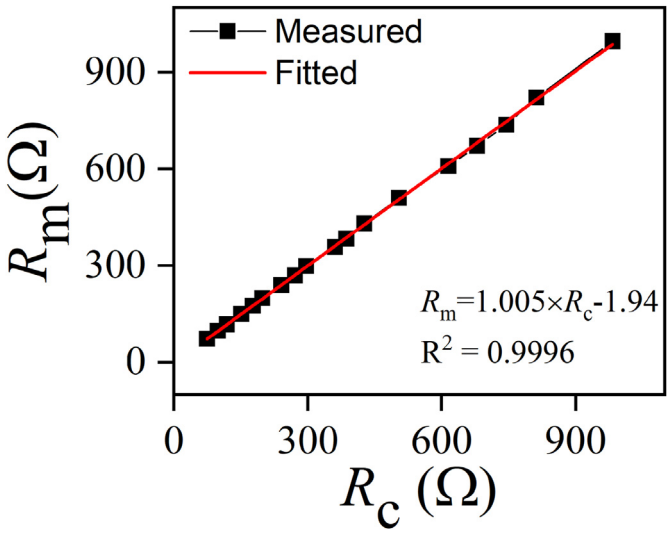

Fig. 2. Performance of solution resistance measuring.

this circuit, and R_u was 100% compensated according to the simulation by Multisim software. As shown in Fig. 3A, current responses are obviously distorted if R_u is not compensated, while there is no significant difference between those compensated automatically by this circuit and the simulated even at the scan rate of 2000 V/s. It indicates that this circuit can be applied to fast scan voltametric analysis for theoretical electrochemical cells with the scan rate up to 2000 V/s.

3.2.2. Demonstration by RC dummy cells incorporating a pseudo-faradaic component

To demonstrate the ohmic drop compensation ability of this circuit further, RC dummy cells incorporating a pseudo-faradaic component were also tested. It is well known that, when a forward voltage is applied to a diode to a certain value, the current would suddenly increase, similar to the phenomenon in the electrochemical system when the electrode potential reaches the potential of the redox couple studied. Therefore, a pseudo-Faradaic impedance could be formed using a resistor 1 kΩ in series with a diode 1N4148. Then, RC dummy cells incorporating a pseudo-faradaic component were used to imitate the electrochemical behavior, which were constructed using the pseudo-Faradaic impedance connected in parallel with C_{dl} and then in series with R_u. As shown in Fig. 3B, current responses are severely distorted if R_u is not compensated, while those compensated automatically by this circuit are almost identical to the simulated ones when the scan rate is high as 2000 V/s. Thence, this circuit could manage fast scan voltametric research on electrochemical cells at 2000 V/s theoretically.

3.2.3. Demonstration by the ferrocene redox system

The ferrocene redox system [36,37], an actual electrochemical system, was used to demonstrate the performance of ohmic drop compensation of the circuit finally. The working electrode was a conventional glassy carbon electrode with a nominal diameter of 0.5 mm, and the auxiliary electrode was a Pt wire. The concentration of ferrocene solution was 4.5 mmol/L, and the supporting electrolyte solution was acetonitrile containing 0.9 mol/L NBu_4BF_4. A set of voltammograms uncompensated, voltammograms compensated by this circuit and voltammograms simulated based on a self-established simulation program of our group [38] are displayed in Fig. 3C. In the simulation, Butler-Volmer kinetics were observed [39], and following parameters simulation were adopted: standard electrode potential E_0 = 0.4 V versus the Pt reference, reaction rate constant k_0 = 0.95 cm/s, electron transfer coefficient α = 0.5, diffusion coefficient $D_O = D_R = 1.0 \times 10^{-5}$ cm^2/s, initial potential V_i = 0.8 V, reverse potential V_r = 0 V, solution temperature T = 20 °C, electrode area A = 0.00196 cm^2, double layer capacitance C_{dl} = 0.02 μF, uncompensated solution resistance R_u = 0 (precise 100% compensation, without any ohmic drop), scan rate v from 200 V/s to 1600 V/s. It could be found that, voltammograms uncompensated are severely distorted by the ohmic drop and no correct electrochemical information could be extracted. On the contrary, voltammograms compensated by this circuit are approximately same as voltammograms simulated, demonstrating again that the performance of the ohmic drop compensation of the proposed circuit is excellent and voltammetric distortion originated from the increased scan rate is effectively eliminated. In general, fast scan voltametric research about practical electrochemical system at the scan rate of 1600 V/s on conventional electrodes are available.

3.3. Ultrasensitive biosensing of Hg^{2+}

The detection principle of this biosensor is shown in Fig. 4A. The DNA aptamer for Hg^{2+} is immobilized onto the electrode surface through the sulfhydryl group at 5′ end. In presence of Hg^{2+}, a stem-loop structure is formed through T-Hg^{2+}-T mismatch. In this situation, Hg^{2+} ions are captured and fixed on the electrode surface, ready for detection by FSCV.

As shown in Fig. 4B, when Hg^{2+} concentration was 1.000×10^{-9} mol/L, the peak current was about 1.7 μA at 0.1 V/s, while it was approximately 0.39 mA at 1600 V/s which was 230 times higher than the former, showing a great advantage of FSCV in improving detection sensitivity. In addition, the peak current increases with the increment of Hg^{2+} concentration (Fig. 4C), and there is a good linear relationship between peak current (y) and the logarithm of Hg^{2+} concentration (x) (Fig. 4D). The regression equation is y (mA) = 0.113 × log$x$ (mol/L) + 1.41 with R^2 = 0.999. The peak current of Hg^{2+} solution at the concentration of 1.000×10^{-12} mol/L was 62 μA which was about 10 times higher than the noise 5–6 μA. According to signal-to-noise ratio (S/N) = 10, the limit of quantification (LOQ) could be roughly estimated as 1 pmol/L.

Inductively coupled plasma atomic emission spectrometer (ICP-AES) was used to verify the reliability of this biosensor based on the fast scan circuit, detecting tap water samples spiked with Hg^{2+} standard solution simultaneously. It could be found that (Table 1), ICP-AES and this biosensor could both detect 1.000×10^{-8} mol/L Hg^{2+}, and there is no significant difference between the two methods according the inter-group t-test. And, this biosensor could detect 1.000×10^{-10} mol/L and 1.000×10^{-12} mol/L Hg^{2+} yet, but ICP-AES could not, indicating the biosensor based on FSCV has an excellent sensitivity. In addition, satisfied accuracy and precision were obtained with recoveries 92.8%–113.4% and RSDs 6.8%–11.1%, due to the extremely simple biosensor construction and stable circuit performance.

4. Conclusions

In summary, we have developed a novel digital circuit for FSCV with precious ohmic drop compensation. Compared with fast scan voltametric circuits previously reported [32,40,41], this one has some special characteristics and advantages as follows. (1) The ohmic drop can be compensated precisely, because the solution resistance is directly and accurately measured in advance and then compensated by positive feedback technology. (2) Ohmic drop

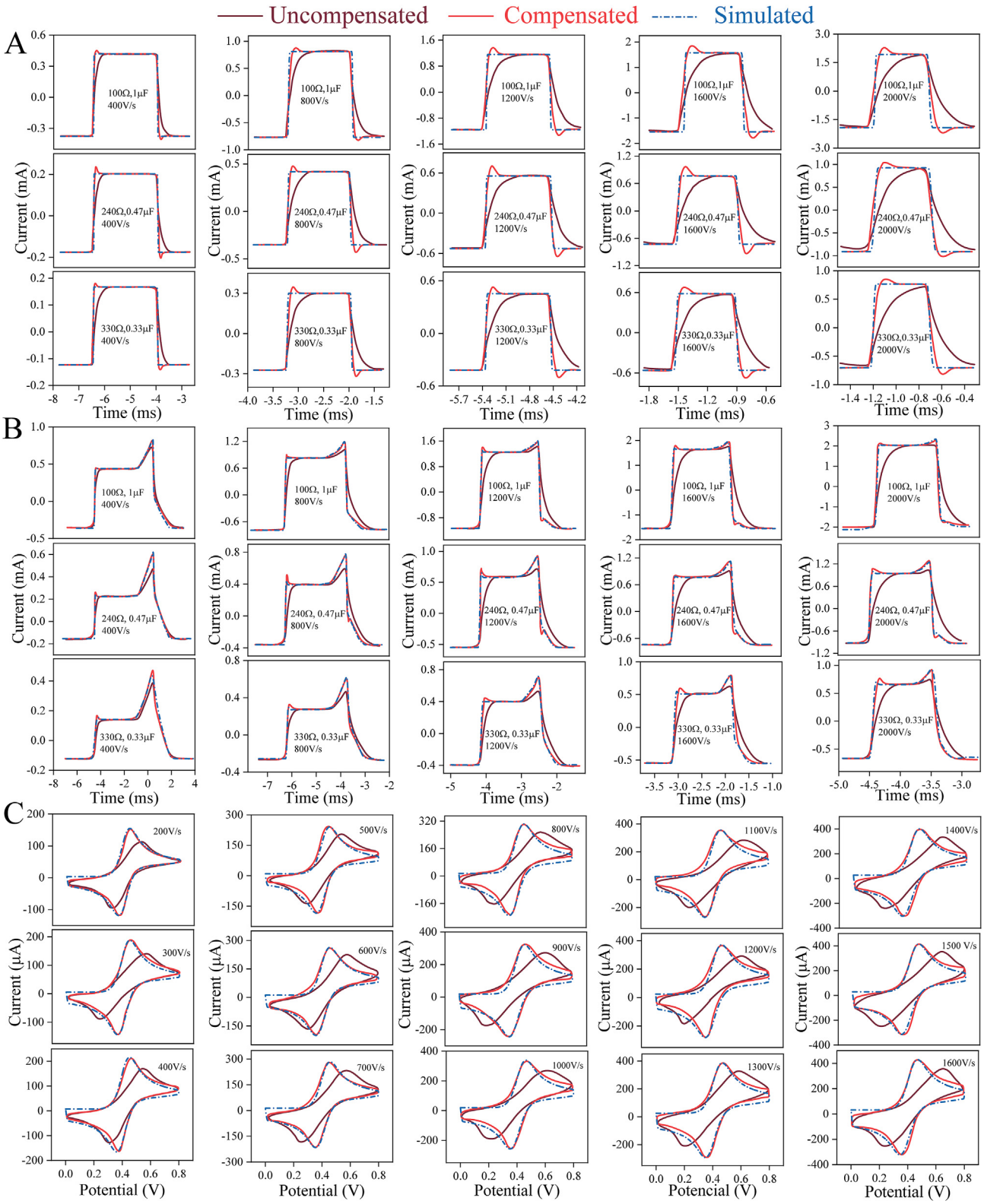

Fig. 3. Performance of ohmic drop compensation demonstrated by (A) RC dummy cells, (B) RC dummy cells incorporating a pseudo-faradaic component, and (C) ferrocene redox system.

compensation can be realized automatically by only one keystroke without any manual adjustment, so it is simple and easy to operate, avoiding errors from different compensation levels caused by manual operation. And (3), the signal oscillation owing to the over-compensation formed by manual adjustment that often occurs in traditional positive feedback compensation will not occur, as this circuit compensates precisely without any over-compensation and ensuing signal oscillation. Due to the high sensitivity originated

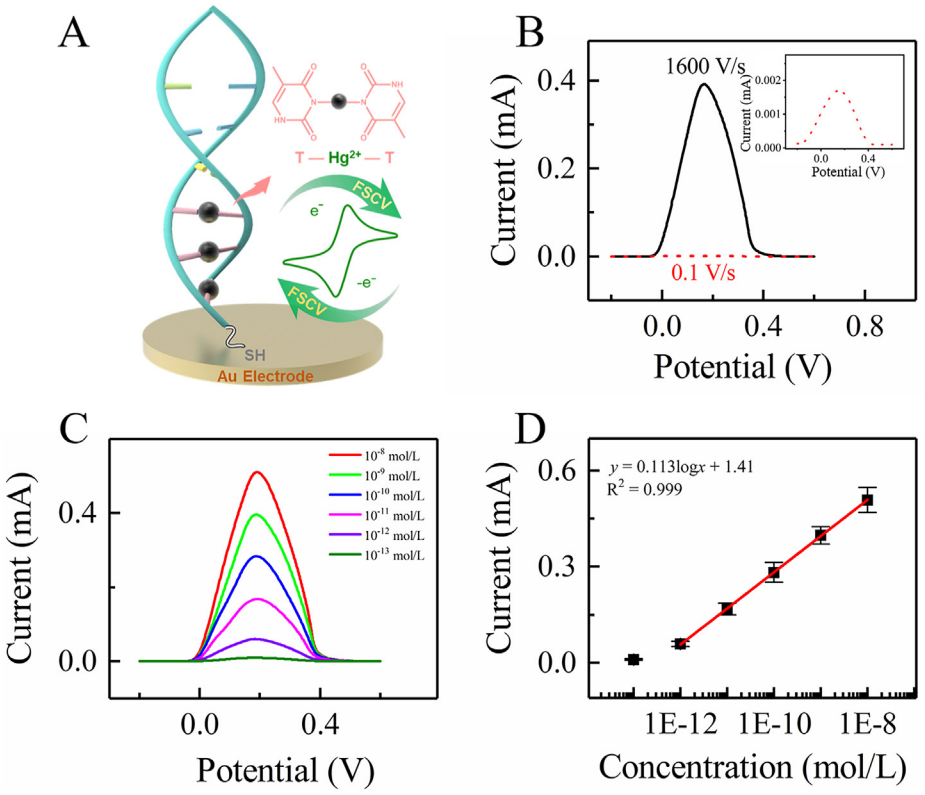

Fig. 4. (A) Detection principle of the biosensor. (B) Voltammograms of 10^{-9} mol/L Hg^{2+} at scan rates of 0.1 V/s (dashed line) and 1600 V/s (solid line). (C) Voltammograms of Hg^{2+} at different concentrations. And (D), linear relationship between the peak current and the logarithm of Hg^{2+} concentration.

Table 1
Detection of Hg^{2+} in spiked tap water samples using ICP-AES and FSCV ($\bar{x}\pm s$, $n = 5$).

Samples	Spiked (mol/L)	ICP-AES (mol/L)	FSCV (mol/L)	FSCV RSD (%)	FSCV Recovery (%)
1	1.000×10^{-8}	$(1.035 \pm 0.037) \times 10^{-8}$	$(1.069 \pm 0.073) \times 10^{-8}$	6.8	106.9
2	1.000×10^{-10}	ND[a]	$(0.928 \pm 0.087) \times 10^{-10}$	9.4	92.8
3	1.000×10^{-12}	ND[a]	$(1.134 \pm 0.126) \times 10^{-12}$	11.1	113.4

[a] Not detected.

from the high scan rate, Hg^{2+} at the level of pmol/L could be detected with a LOQ of 1 pmol/L, suggesting a great application potential of FSCV in the field of high-sensitivity biosensing.

CRediT authorship contribution statement

Fengming Xiao: Data curation, Writing – review & editing. **Huiqian Zhou:** Data curation, Writing – review & editing. **Han Lin:** Data curation, Writing – review & editing. **Hongze Li:** Data curation. **Tinglang Zou:** Data curation. **Yangbo Wu:** Supervision, Conceptualization, Funding acquisition, Writing – review & editing. **Zhiyong Guo:** Supervision, Conceptualization, Funding acquisition, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aca.2021.338744.

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