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Highly sensitive FET sensors for cadmium detection in one drop of human serum with a hand-held device and investigation of the sensing mechanism

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ABSTRACT

As the heavy metal contamination is becoming worse, monitoring the heavy metal content in water or human body gets more and more important. In this research, a cadmium ion-selective field effect transistor (Cd-ISFET) for rapidly detecting cadmium ions has been developed and the mechanism of the sensor is also investigated in depth. Our Cd-ISFET sensor exhibits high sensitivity beyond the ideal Nernst sensitivity, wide dynamic range, low detection limit ($\sim 10^{-11}$M), which is comparable with inductively coupled plasma mass spectrometry, and easy operation enabling people to detect cadmium ion by themselves. From the analysis of electrical measurement results, this Cd-ISFET is preferred to operate at the bias with the maximum transconductance of the FET to enhance the sensor signal. The AC impedance measurement is carried out to directly investigate the mechanism of an ion-selective membrane (ISM). From impedance results, the real part of the total impedance, which is the resistance, was shown to dominate the sensor signal. The potential drop across the ISM is caused by the heavy metal ion in the membrane, which is employed to the gate of the FET via an extended gate electrode. Cadmium ion detection in one drop of human serum with this sensor was demonstrated. This cost-effective and highly sensitive sensor is promising and can be used by anyone and anywhere to prevent people from cadmium poisoning.

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I. INTRODUCTION

Heavy metal pollution has been a public concerned issue in recent years. As modern technologies are rapidly developing, heavy metal pollution is also increasing sharply. Among the list of major heavy metals, cadmium is one of the most commonly seen heavy metals existing in our daily lives.[1–3] Cadmium is a soft and ductile element with silver color. It is widely utilized in nickel–cadmium battery, plastic production, edible pigment, electroplating process, and paint production. People may ingest cadmium from food, air, water, herbal medicine, or cigarette.[4] The U.S. Environment Protection Agency (EPA) sets the up-limit for drinking water as 0.005 mg/l (5 ppb) for cadmium. In Germany, the regulation up-limit in drinking water is the same as in the USA.[5] The permissible cadmium level in blood is in the range of 0.3–1.2 μg/l (0.3–1.2 ppb = 2.67×10^{-9}–1.07×10^{-8} M), which was suggested by WHO in 1996.[6] Many cases were reported for cadmium pollution around the world previously.[7–14] Because cadmium is odorless, and it may be ingested by people without consciousness. Cadmium is difficult to be metabolized by human body and will accumulate in several organs like kidney, liver, skeleton, lung, and reproductive system.[15–20]

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Cadmium poisoning may cause osteomalacia, itai-itai disease, and lung cancer.[21] Therefore, monitoring of the cadmium level daily in water or human blood is extremely critical to our health.

Currently, typical instruments used to detect cadmium are laboratory-based, including inductively coupled plasma mass spectrometry (ICP-MS), inductively coupled plasma atomic emission spectroscopy (ICP-AES), and atomic absorption spectroscopy (AAS).[22–23] The most sensitive instrument is the ICP-MS, which has a detection limit of 0.5 ng/l = 0.5 ppt (4.5×10^{-12}M) for cadmium.[24] However, the sample pretreatment for ICP-MS is complicated and the operation needs well trained personnel. It is time-consuming and the cost of tests is high. Potentiometry has been developed for a long time. The system of potentiometry can be small and cost-effective. The apparatus is constructed with an ion-selective electrode (ISE), a reference electrode, and a voltammeter, as shown in Fig. 1(a). The ion-selective electrode uses an ion-selective membrane (ISM) as a filter to allow only the target ion to pass through. The principle of potentiometry is based on the Nernst equation, which originated from the equation of free energy in thermodynamics, defining the ideal Nernst sensitivity of this method.[25–27] Although the apparatus of the potentiometry is much smaller than the above-mentioned laboratory-based instruments, its sensitivity is not as good as those of typical laboratory-based instruments. The detection limit of potentiometry is near 0.5 ppm for cadmium,[28] which is higher than the cutoff value for water quality regulated by EPA. In the 1970s, Bergveld developed a model for a pH sensor using ion-sensitive field effect transistors (ISFETs). His model predicts the ideal sensitivity of the pH sensor (59.2 mV/pH), which is the same as the ideal Nernst sensitivity.[29] For most ISFET sensors reported, the sensitivity is indeed either comparable[30,31] or lower than the ideal Nernst sensitivity.[32–35] Conventional ISM-coated FETs (ISMFETs) for ion detection were

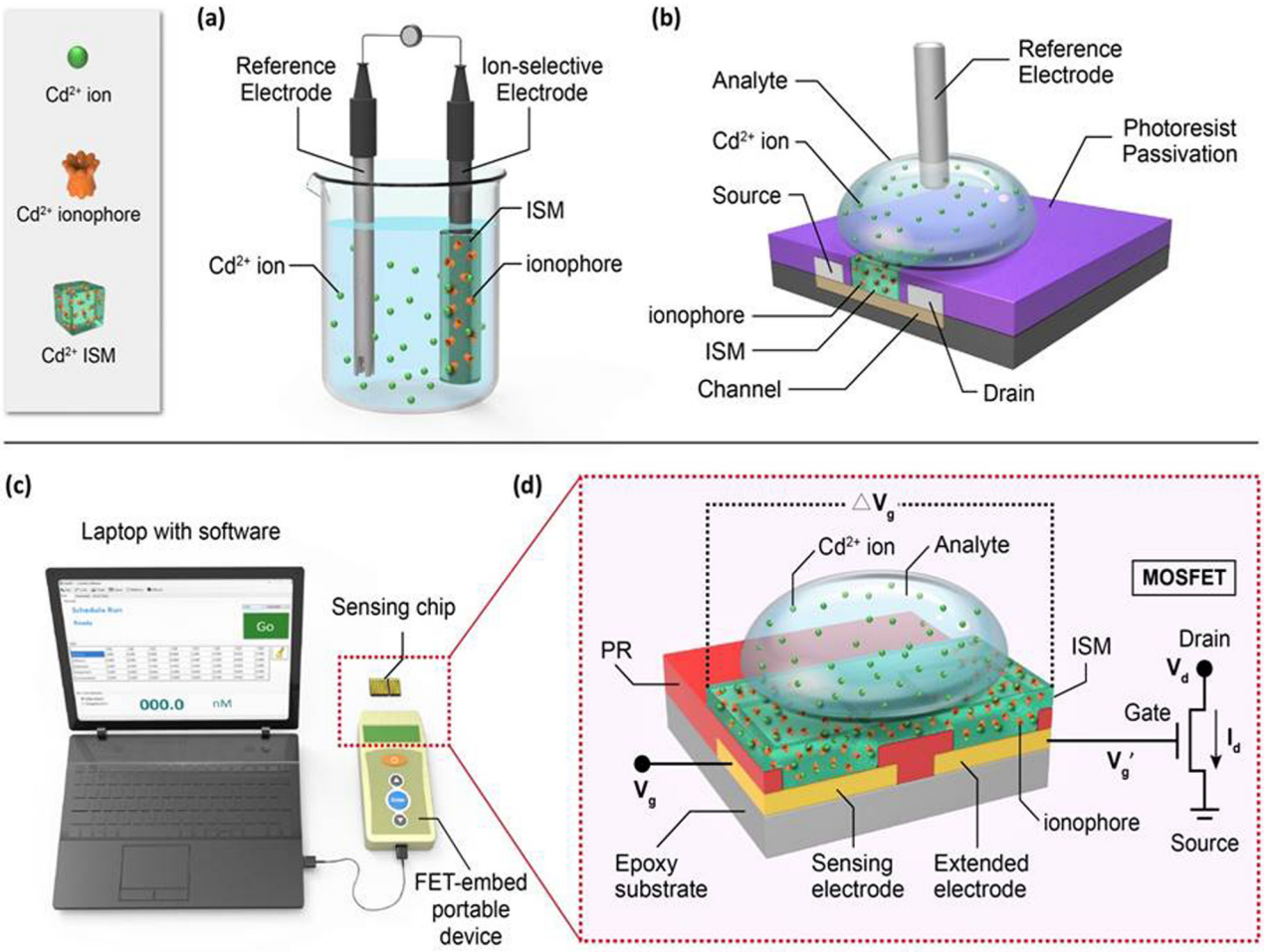

FIG. 1. The schematic of (a) the apparatus of the conventional potentiometry, including an ion-selective electrode, a reference electrode, and a voltmeter, (b) the conventional ion-selective membrane-coated FET sensor, (c) the portable measurement system, and (d) the ion-selective membrane conductivity-modulated FET sensor.

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then reported with a lower detection limit compared to the potentiometric method.[32] The ISM was coated on the gate region of the FETs and a reference electrode was immersed into the test solution, as shown as in Fig. 1(b). However, the detection limit (3.1×10^{-6}M) is still far beyond that of the regulation in drinking water (4.5×10^{-8}M) and the sensitivity is also limited to the ideal Nernst sensitivity.[32] Due to the limited sensitivity, the conventional ISMFETs were regarded as one type of potentiometric device.

In this study, we have proposed a new type of ISMFET sensor, based on the change of the membrane conductivity caused by cadmium ions, resulting in the gate voltage change of the extended FET. The sensitivity of the sensor is not limited to the ideal Nernst sensitivity. A portable measurement device was also developed to measure the sensor chips. The portable measurement device is controlled by application software in a laptop, as shown in Fig. 1(c). A MOSFET was deployed in the designed circuit of the measurement device. The cadmium-selective membrane was coated across two metal electrodes on the sensor chip. One electrode is defined as the sensing electrode and the other one is called the extended electrode. The gate voltage was applied on the sensing electrode and the extended electrode was connected to the gate of the MOSFET. The sensor chip was inserted into the measurement device through a typical PCI socket for measurement, as shown in Fig. 1(d). The cadmium-selective membrane is formed by a polyvinyl chloride (PVC) based matrix, which includes cadmium-specific ionophore, added anions, and plasticizer. As cadmium ions diffused into the membrane and were captured by the ionophore, the conductivity of the membrane changed. The change of the membrane conductivity leads to the change of the gate voltage drop in the membrane, resulting in the drain current change. Because the voltage drop of this sensor follows Ohm's law, instead of the Nernst equation, the sensitivity of this sensor is not limited and can be higher than the Nernstian one. The obtained sensitivity of the Cd-ISMFET in this study is 71 mV/decade, which is beyond

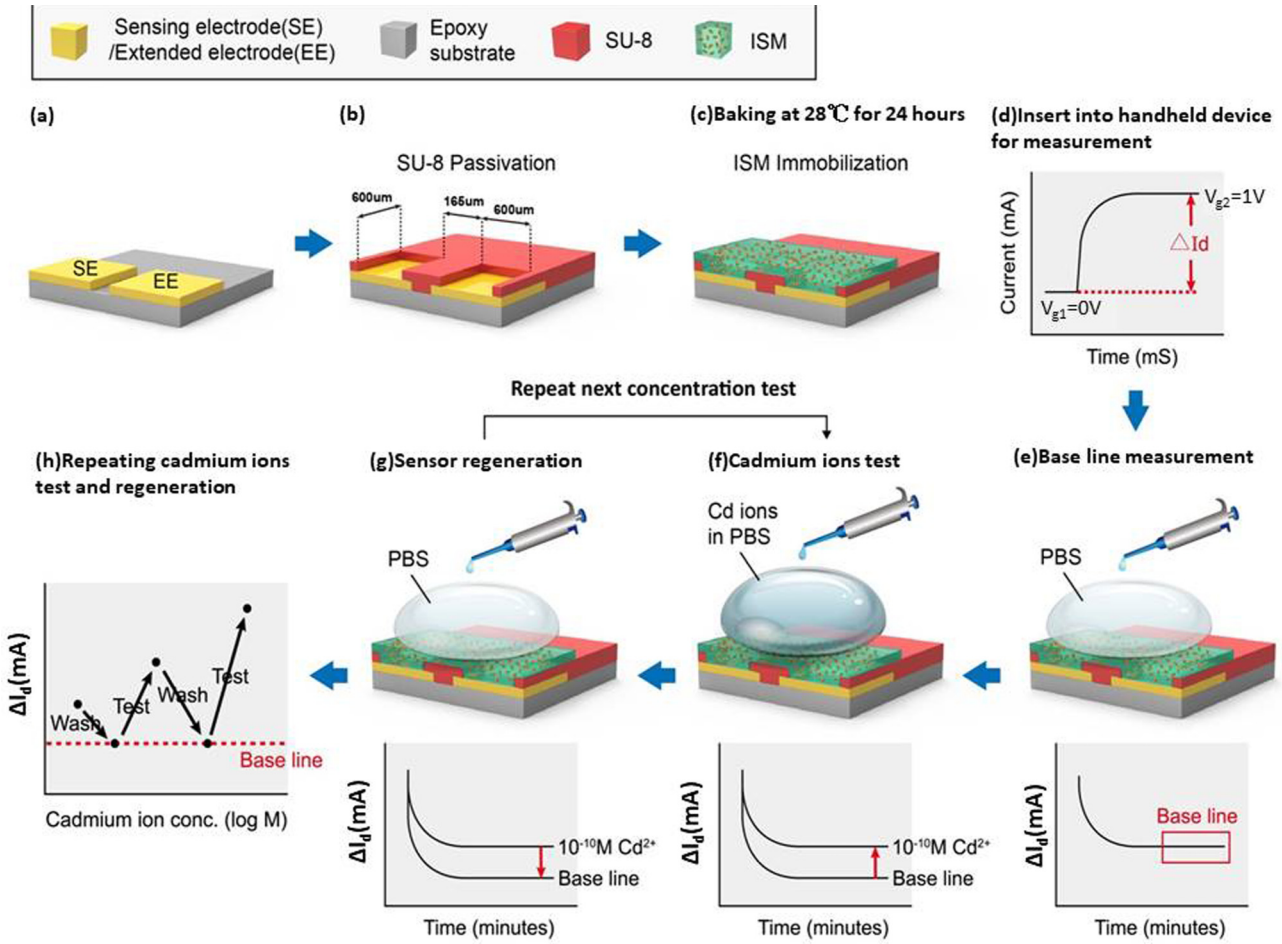

FIG. 2. Schematics of the experimental process. (a) Metal deposition for electrode pair. (b) Formation of the passivation layer. (c) ISM immobilization. (d) Sensor signal definition. (e) Baseline measurement in PBS. (f) Cadmium ion detection. (g) Regeneration process. (h) Multiple tests and regeneration of the cadmium ion FET sensor.

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the ideal Nernst sensitivity, 29.58 mV/decade. The AC impedance measurement of the membrane-coated chip (without FETs) was also conducted to support the proposed sensing mechanism. Not only the standard buffer solutions but also human serum samples were successfully demonstrated for cadmium detection with this sensor and the device. This Cd-ISMFET sensor has shown superior high sensitivity, low detection limit, simple operation, and low cost. This sensor is affordable and convenient for anyone at anytime and anywhere for personal healthcare.

II. EXPERIMENTAL

A. Extended gate chip fabrication

The extended gate chip is fabricated by the following method. First, we drill a poly(methyl methacrylate) (PMMA) mold into the shape of an extended gate chip by laser cutting. A silicon-based organic polymer, poly(dimethylsiloxane) (PDMS), is then pulled into the PMMA mold and baked at 65 °C for 2 h in the oven. PMMA mold and PDMS are separated after baking. Epoxy glue is then poured into the PDMS mold and cured at 125 and 165 °C for 90 and 60 min, respectively. This molding process was also reported previously in detail.[36] After peeling off the epoxy substrate from PDMS, the photolithography process is carried out, followed by metal deposition with E-gun evaporator and a lift-off process, to create an electrode pair, as shown in Fig. 2(a). Photoresist (SU-8) is coated as a passivation layer and the opening on the electrode pair is created. Each electrode pair contains a sensing electrode and an extended electrode. Gate voltage (V_g) is applied on the sensing electrode. The extended electrode is connected to the gate terminal of the FET. The gap between the electrode pair is 165 μm and the sensing area is $600 \times 600\,\mu m^2$ as shown in Fig. 2(b).

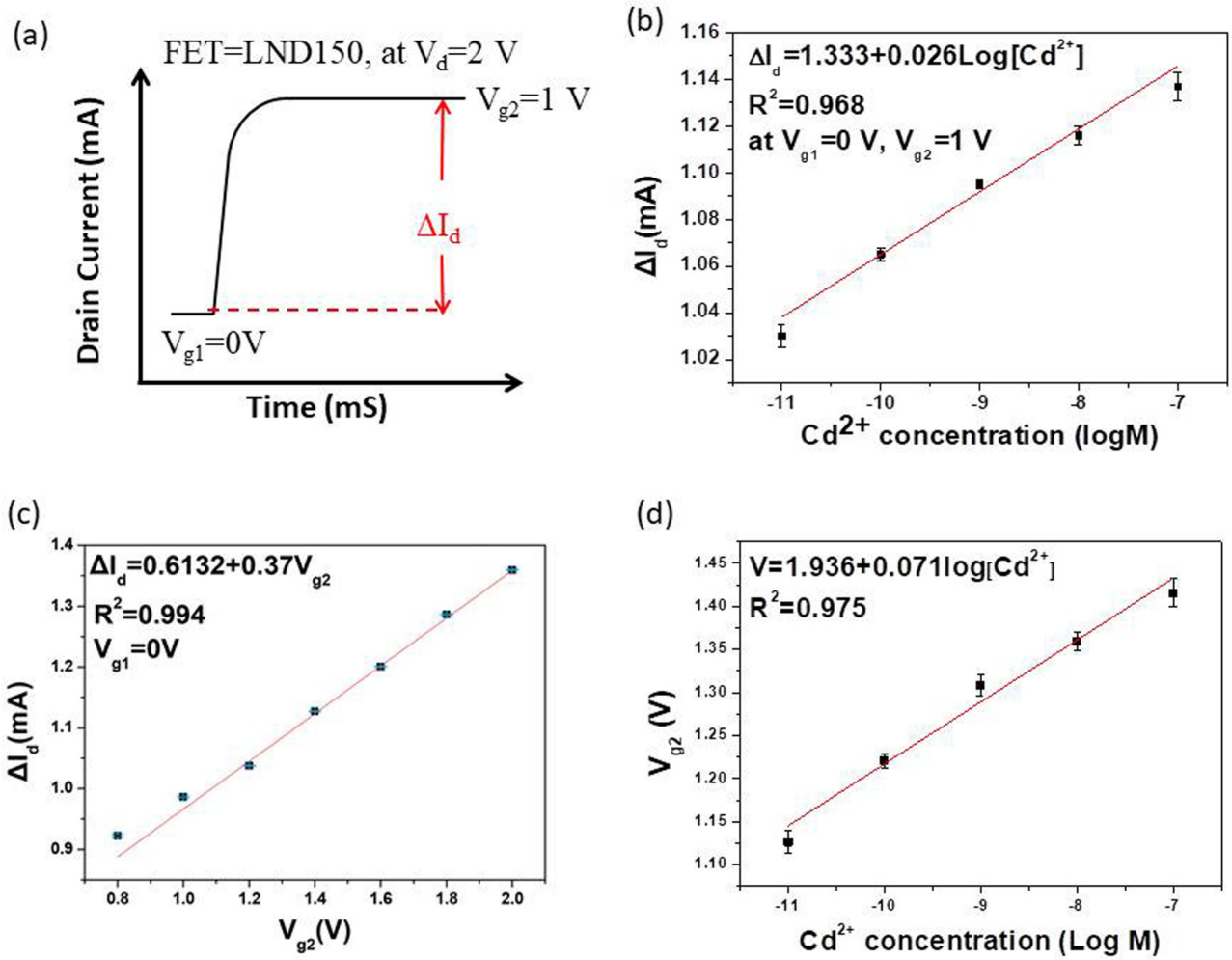

FIG. 3. (a) Definition of ΔI_d of the FET (LND150). (b) ΔI_d vs cadmium ion concentration. (c) ΔI_d vs V_{g2}. (d) V_{g2} vs cadmium ion concentration.

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B. Ion-selective membrane (ISM) preparation and immobilization

The ISM is composed of four constituents: ionophore, added anion, polyvinyl chloride (PVC), and plasticizer. Cadmium ionophore I (5% by weight) is used to capture target ions. Potassium tetrakis(4-chlorophenyl)borate (0.35% by weight) is used as an added anion to adjust the conductivity of ISM. 2-nitrophenyl octyl ether (2-NOE) (63.65% by weight) acts as a plasticizer in the ISM. The amount of PVC used in this ISM fabrication is 31% by weight. These constituents are dissolved in THF. As shown in Fig. 2(c), 0.15 μl ISM is dropped on the sensing platform and kept at 28 °C for 24 h in an oven to make sure that the solvent evaporates completely. After 24 h, the immobilization finishes and the measurements can be done. All the ingredients were purchased from Sigma.

C. Cadmium ion samples

The cadmium ion solution is prepared by using cadmium nitrate [$Cd(NO_3)_2$]. The stock solution contains 0.02× phosphate-buffered saline (PBS). 2.364 mg cadmium nitrate powder is dissolved in 10 ml 0.02× PBS. This makes the stock solution concentration to be 10^{-3}M cadmium ions. We then diluted the stock solution to get working concentrations from 10^{-11} to 10^{-7}M cadmium ions using 0.02× PBS.

The human serum is provided by a healthy person and the cadmium level of the human serum is lower than the detection limit of the laboratory-based instrument (ICP-MS). Before the measurement, we added 10 μl cadmium ion solution into 90 μl serum sample to prepare different cadmium ion concentrations in serum.

D. The measurement system

In this research, we used two measurement systems. One is the laboratory-based instrument, Agilent B1500A/B1530 semiconductor analyzer, and the other one is a portable measurement system. The portable measurement system is utilized to measure the sensor with a FET. The product numbers of the FETs are LND150 and VN10LP, respectively. LND150 is a depletion mode FET and provided by Microchip Technology. VN10LP is an enhancement mode FET and supplied by Diodes Incorporated. The prototype is connected to a laptop through a USB port and the measurement parameter can be set by software in the computer. The software was developed by us and it can set all the measurement parameters for the prototype device such as the gate bias, the duration time, the drain voltage, and the drain current. In the measurement, a steady 2 V of drain voltage (V_d) is applied on the FET. Gate bias (V_g) at V_{g1} is first applied on the sensing electrode for 100 μs. Following this, V_{g2} is applied on the sensing electrode for 2 ms. Figure 2(d) elucidates the definition of ΔI_d, which is the drain current difference between the V_{g1} and V_{g2}. After PBS is dropped on the sensing membrane, the ΔI_d is recorded every minute until it gets steady. The sensor signal is sampled at a steady state, as shown in Fig. 2(e). The PBS droplet is then removed and the low concentration of Cd^{2+} solution is then dropped on the sensor, leading to increasing ΔI_d, as shown in Fig. 2(f). The Cd^{2+} solution is then replaced with PBS solution and the ΔI_d moves back to the original baseline, as shown in Fig. 2(g). The Cd^{2+} solution and the PBS are repeatedly tested, resulting in Fig. 2(h).

The AC impedance measurement results are measured by Agilent B1500A/B1530A semiconductor analyzer. In the AC impedance measurement, the sensing chip is removed from the FET. We directly probe on the sensing electrode and the extended electrode in order to the ISM impedance. The AC frequency is 1 kHz and a 3 V DC bias is applied on the sensing electrode while giving a 100 mV of AC signal.

III. RESULTS AND DISCUSSION

Figure 3(a) defines the drain current measured for the FET, LND150, at $V_d = 2$ V, $V_{g1} = 0$ V, and $V_{g2} = 1$ V, respectively. The ΔI_d

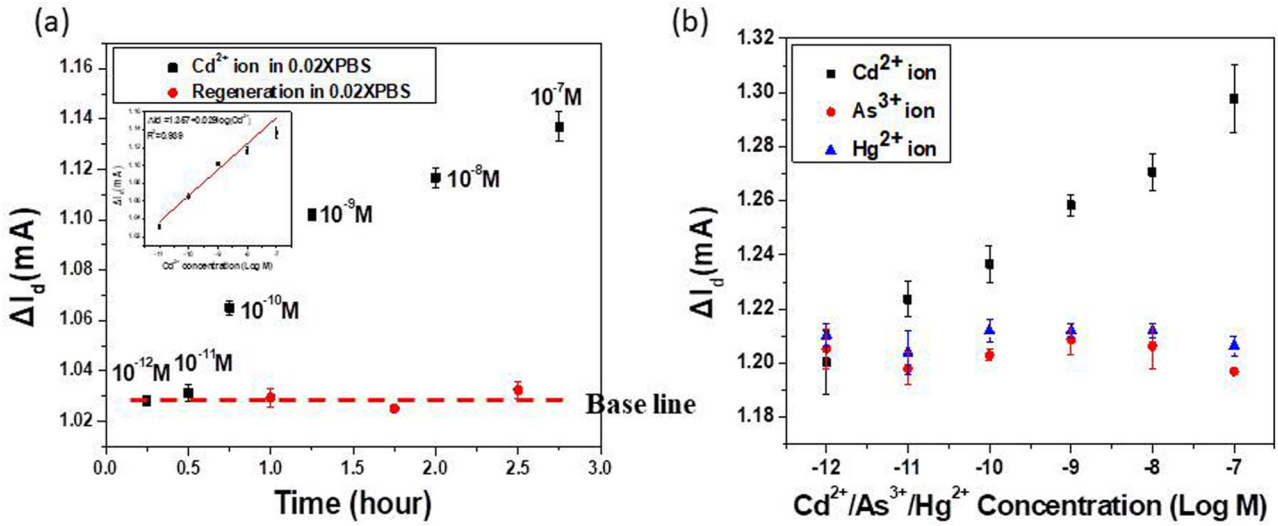

FIG. 4. (a) Electrical response ΔI_d of cadmium ion-selective sensor and the regeneration. (b) Confirmation of the selectivity characteristics of Cd-ISMFET with the separated solution method.

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was measured for different Cd^{2+} concentrations ranging from 10^{-11} to 10^{-7}M, as shown in Fig. 3(b). Figure 3(c) shows the ΔI_d measured at different V_{g2} with only PBS and without Cd^{2+} ions in solution. By combining Figs. 3(b) and 3(c), it can lead to a correlation between V_{g2} and Cd^{2+} concentration, as shown in Fig. 3(d). The fitting slope in Fig. 3(d) indicates the sensitivity, 71 mV/decade, which is beyond the ideal Nernst sensitivity (29.58 mV/decade).

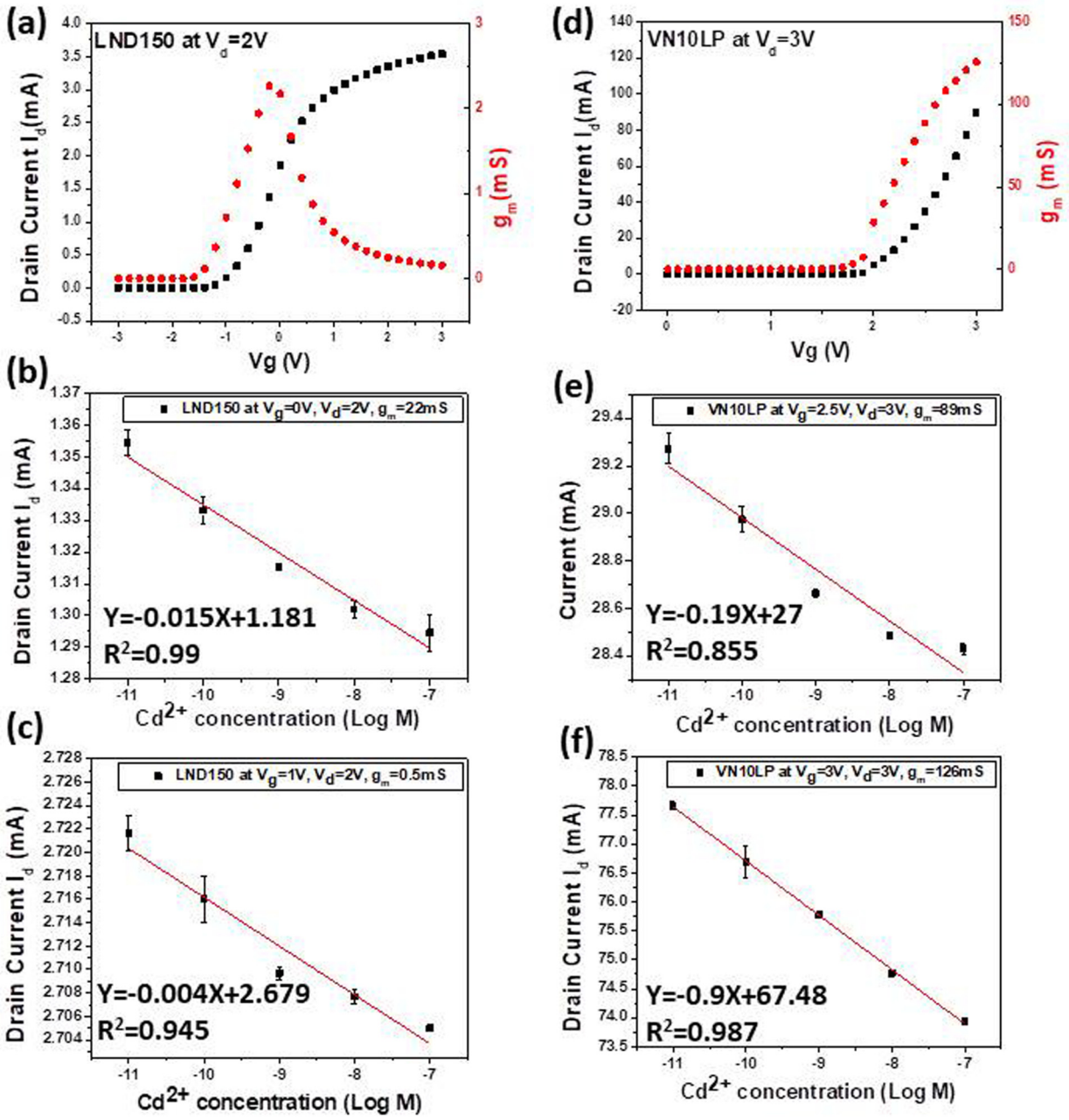

FIG. 5. (a) Drain current (I_d) and transconductance (g_m) vs gate voltage of the FET LND150 at V_d = 2 V. (b) The sensor measured with the FET LND150 at V_d = 2 V and V_g = 0 V (c) The sensor measured with the FET LND150 at V_d = 2 V and V_g = 1 V. (d) Drain current (I_d) and transconductance (g_m) vs gate voltage of the FET VN10LP at V_d = 3 V. (e) The sensor measured with FET VN10LP at V_d = 3 V and V_g = 2.5 V. (f) The sensor measured with FET VN10LP at V_d = 3 V and V_g = 3 V.

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In potentiometry, the potential drop can be calculated by the Nernst equation as shown in Eq. (1),

$$E_{ISM} = c + \frac{RT}{nF}\log[A], \tag{1}$$

where $[A]$ is the concentration of the target ion. F, R, T, and n are Faraday's constant, gas constant, temperature, and valence of the target ion, respectively. The valence of the cadmium ion is 2 and thus the ideal Nernst sensitivity is 29.58 mV/log[Cd^{2+}].

Figure 4(a) shows that after a cadmium ion solution was tested, the sensor was washed and soaked in 0.02× PBS until the sensor signal (ΔI_d) moved back to the baseline. After the signal returns to the baseline, the next concentration of the cadmium solution was dropped on the sensor and the electrical signal was measured. This test/regeneration process was repeated through the whole dynamic range, confirming that the electrical signals have indeed resulted from the cadmium ions captured by ionophore, but not from the baseline drifting.

The selectivity of Cd-ISFET is elucidated as shown in Fig. 4(b). The separation solution method is used to confirm the selectivity of Cd-ISMFET. The cadmium ion-selective membrane is immobilized on the sensing chip and utilized to test cadmium, arsenic, and mercury ion solution. These ions are prepared in 0.02× PBS and the concentration ranges from 10^{-12} to 10^{-7}M. As shown in Fig. 4(b), ΔI_d increases when the cadmium ion concentration is increased. After the cadmium ion was tested, the regeneration procedure was performed to wash out the cadmium ions from the membrane. Arsenic ion solutions were then dropped on the sensor and tested. The electrical signal (ΔI_d) does not show any significant change when the arsenic ion concentration is increased. A similar electrical response was obtained when the mercury ion solutions were tested with the Cd-ISMFET. The result shows that the Cd-ISMFET has good selectivity toward

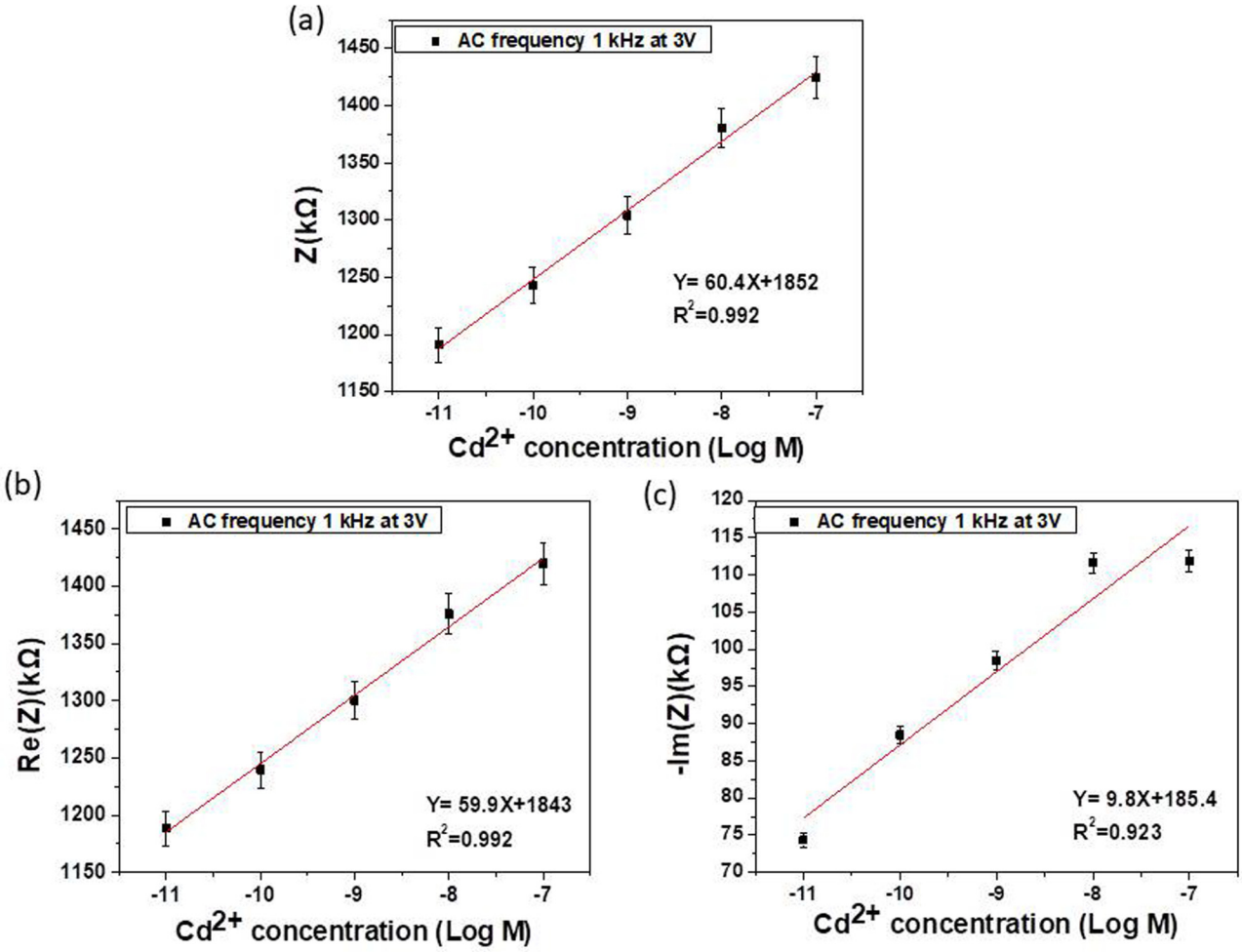

FIG. 6. (a) The total impedance (measured at 1 kHz and DC 3 V) vs cadmium ion concentration. (b) The real part and (c) the imaginary part of the total impedance varies with [Cd^{2+}] in a decade.

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arsenic and mercury ions. The selectivity is simply due to the high selectivity of the cadmium-specific ionophore in the membrane.

In order to elucidate the working principle of Cd-ISFET, two different FETs, LND150 and VN10LP, were used and compared. Figures 5(a) and 5(d) show the drain current (I_d) and the transconductance (g_m) vs V_g at constant V_d for LND150 and VN10LP, respectively. Obviously, the maximum g_m of LND150 is much smaller than that of VN10LP. Figures 5(b) and 5(c) show I_d vs $[Cd^{2+}]$ of the sensor at $V_d = 2$ V for $V_g = 0$ V and $V_g = 1$ V, respectively. The slope (sensitivity) at $V_g = 0$ V, as shown in Fig. 5(b), is significantly larger than that at $V_g = 1$ V, as shown in Fig. 5(c). The difference in sensitivity at $V_g = 0$ and 1 V is due to the very different g_m at the two bias conditions. Figures 5(e) and 5(f) show the I_d vs $[Cd^{2+}]$ at $V_d = 3$ V using VN10LP for $V_g = 2.5$ and 3 V, respectively. The slope (sensitivity) at $V_g = 3$ V is much larger than that at $V_g = 2.5$ V, due to the larger g_m (~126 mS) at Vg = 3 V, compared to that (~89 mS) at $V_g = 2.5$ V.

The I_d–V_d characteristics of LND150 and VN10LP are provided in Figs. S1(a) and S1(b) in the supplementary material, respectively. LND150 is operating in both saturation and linear regions. The chosen operation bias for this MOSFET is not only to consider the linear or saturation region but also the power consumption, which is relevant to the heat generated in the FET channel. Elevated temperature in the channel may affect the fluctuation and stability of the device. VN10LP is operating in the saturation region. In this FET, because of the much larger transconductance than that of LND150, more power consumption is acceptable due to the improved S/N ratio.

From the results shown in Fig. 5, it is obvious that the g_m plays a key role in the sensitivity of the sensor. Thus, the mechanism of the sensor can be explained as the gate voltage drop in the membrane caused by the heavy metal ions, which are captured by the ionophore, leads to the amplification of the signals through the transconductance (g_m) of the FET.

To further confirm the sensor mechanism, the AC impedance analysis is used to investigate how cadmium ions change the membrane impedance. Agilent B1500A/B1530A semiconductor analyzer is employed to conduct this measurement. For the impedance measurement, we directly probe on the sensing electrode and the extended electrode without connecting to the FET. Figure 6(a) depicts the total impedance vs the cadmium concentration from 10^{-11} to 10^{-7}M. The impedance was measured at 1 kHz and DC 3 V. As the cadmium concentration increases, the total impedance also raises. Figures 6(b) and 6(c) show the real part and the imaginary part of the total impedance vs $[Cd^{2+}]$, respectively. It is clear that the total impedance change has mostly resulted from the change of the real part caused by cadmium ions. This may be attributed to the reduced mobility of mobile ions caused by the complex of cadmium ions and the ionophores, leading to an increased impedance. The increased imaginary part may have resulted from the electric-double-layer capacitance change. More investigation is needed in future works. The increased total impedance successfully explains the decreased drain current of the FET shown in Figs. 5(b), 5(c), 5(e), and 5(f). The increased impedance causes more gate voltage drop in the membrane, leading to a smaller voltage applied on the extended electrode, resulting in the decreased drain current of the n-channel FET. The impedance change indicates that the voltage drop caused by heavy metal ions simply follows Ohm's law. When the membrane is connected to the FET through the extended electrode, the tiny voltage change can be amplified with the FET, based on the g_m at the operation bias. Because the sensing mechanism is based on Ohm's law, the sensitivity is therefore not limited to the ideal Nernst sensitivity. The sensitivity of this sensor depends on the composition and the fabrication process of the membrane. Compared to a complex amplification circuit, a well selected FET is much simpler and more flexible to amplify the voltage change in the membrane. This ISM-impedance modulated FET sensor is a highly integrated and simplified device but has a high sensitivity, low detection limit, and low cost. It is also easy to realize a sensor array with such kind of design for multiple target ion detection.

In this research, we employ Cd-ISFET to detect cadmium ions in human serum without any pre-treatment and compared it to cadmium ion solution in PBS buffer, as shown in Fig. 7. The cadmium ion concentration in the human serum sample has been

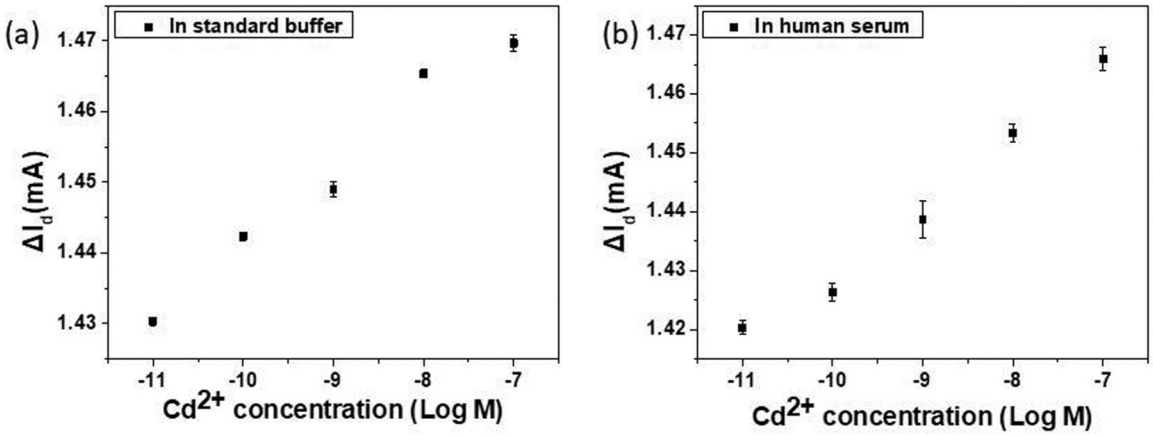

FIG. 7. Electrical characteristics for cadmium ion (a) in a 0.02× PBS buffer and (b) in human serum.

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confirmed to be lower than the detection limit of the laboratory-based instruments. We spike the cadmium ions into a human serum sample with cadmium ion concentrations ranging from 10^{-11} to 10^{-7}M. The sensor first established a calibration curve in the standard buffer as depicted in Fig. 7(a). ΔI_d increases as the cadmium ion concentration increases with the detection limit, as defined by the Clinical and Laboratory Standards Institute (CLSI),[37,38] near 10^{-11}M (8.91×10^{-12}M). After regeneration, the sensor detects cadmium ions in human serum as shown in Fig. 7(b). An increasing trend is observed in the calibration curve of cadmium ions with the dynamic range being 10^{-11}–10^{-7}M that includes the regulation limitations of the human body, which is 0.3–1.2 ppb (2.67×10^{-9}–1.07×10^{-8}M). Proteins or other molecules in the serum may have non-specific binding on the membrane surface, but they are not able to drive into the membrane. Only the target ion can pass through the selective membrane and drive into it. From the impedance analysis, it shows that the real part of the total impedance dominates the sensor signal. The real part represents the bulk region of the membrane, not the surface region. Thus, this can explain why serum does not affect the sensor signals. We believe that the behavior of the sensor in the human serum environment is a breakthrough in the field of heavy metal ion detection and is good enough for clinic trials for cadmium toxicity testing.

IV. CONCLUSION

In this study, a unique extended gate structure of FET has been developed for cadmium ion detection in human serum with a portable measurement system. The sensitivity of Cd-ISFET is 71 mV/decade, which is much higher than the ideal Nernst sensitivity of 29.58 mV/decade. The dynamic range for the sensor is from 10^{-11} to 10^{-7}M, which includes the toxicity regulation limits for human exposure. The detection limit is 0.83 ppt. The mechanism of Cd-ISFET has been investigated by using different FET measurements and AC impedance analysis. The transconductance of the FET is the primarily effective factor for enhancing the sensor signal. The FET, VN10LP, with higher g_m at a high gate bias was employed to enlarge the sensor signal. AC impedance analysis is consistent with the FET sensors' results and indicates that the sensor signals are primarily dominated by change of the real part of total impedance, which is attributed to the change of ion mobility. The sensor successfully detects cadmium ion in human serum and its performance is not influenced by the complex composition of the serum sample. This study does not only reveal the mechanism of the sensor in depth but also demonstrates the ability and potential of our sensor to detect heavy metals at permissible toxicity levels under the influence of native microenvironments.

SUPPLEMENTARY MATERIAL

See the supplementary material for the FET I–V characteristic.

ACKNOWLEDGMENTS

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DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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