Dual Key-Parameter Sensing System Development for Urolithiasis Recurrence Prevention

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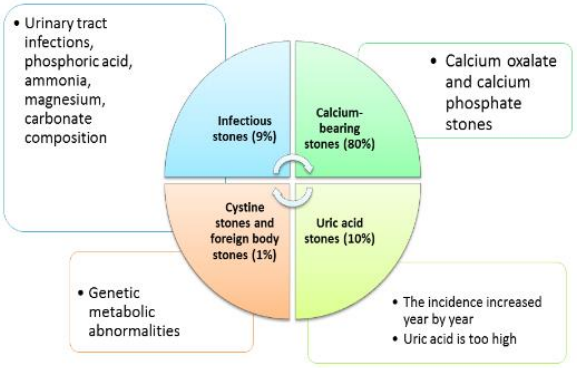
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ABSTRACT
In this paper, we propose a dual key-parameter readout system for the application of urolithiasis recurrence prevention. Two major urine quality indicators pH and Ca^{2+} are sensed to assist a patient in assessing the condition of his urinary system. Ion Sensitive Field Effect Transistors (ISFET) and Constant Voltage Constant Current (CVCS) readout circuit are used for pH and Ca^{2+} monitoring. The prototype with these sensors and readout circuit was integrated and tested in the laboratory. In addition, it was designed and intended to be fabricated in UMC 0.18um CMOS process. The experimental results of the prototype and SPICE simulation readout circuit present a promising performance referred to commercial meters for individual parameter sensing.

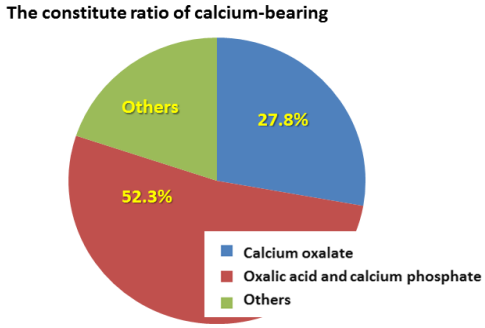
CCS Concepts
• Hardware→Communication hardware, interfaces and storage→Sensor applications and deployments

Keywords
Urolithiasis; Potentiometric sensor; Ion-sensitive field-effect transistor; Constant Voltage Constant Current (CVCS); Readout circuit; pH value; CMOS process

1. INTRODUCTION
Urolithiasis is one of the most common diseases in the urinary system. Patients with urolithiasis usually suffer from back pain, hematuria, or renal edema. More than 10% of people in Taiwan have suffered or are suffering from it [1]. The rate of recurrence has been increasing over recent several years. If the prevention and treatment of stones can be successfully traced, patients can stop the problems caused by disease. Based on research data surveyed and shown in Figure 1 (a) and (b), the main component of urinary tract or kidney stones is that more than 80% are calcium-containing stones [2].



(a)



(b)

Figure 1. (a). Urinary tract stones classification (b). Calcium-containing stone composition data analysis [1, 2].

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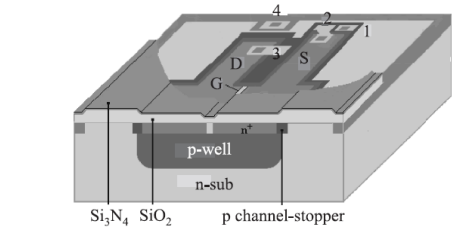
In addition, the references showed that in the urine of patients a persistence of low pH (pH = 5.5), is a significant feature of idiopathic uric acid stones [3]; and if the pH of patient's urine is too low, hypocitraturia may be caused by the incomplete ability to excrete acid, which may also be an important factor in the formation of calcium-containing stones [4]. So, this research focused on urine pH and Ca^{2+} concentration sensing to serve as a risk factor for evaluating urinary stone recurrence. In addition, ion sensitive field effect transistors are used for potentiometric and biological sensing applications for a long time [5]. However, accommodating dual sensors in one readout circuit and one reference electrode with low supply voltage is still worth

developing. The method and system design for this two-parameter sensing readout circuit was developed in section 2, where the preparation of a calcium ion sensing membrane was explored too. The experimental results of the prototype and simulation performance of the on-chip readout circuit are discussed in section 3. The conclusion and future work are described in the section 4.

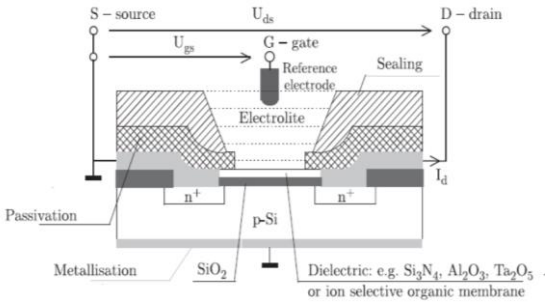
2. METHOD AND SYSTEM DESIGN

2.1 ISFET Sensor and Characterization

Ion Sensitive Field Effect Transistors (ISFET) used as one platform for urine pH and Ca^{2+} sensing was fabricated by the Institute of Electronic Technology (IET) Poland. Figure 2 (a) and (b) show the cross-section views of a p-well ISFET which the device size of channel area is 600 um in width and 16 um in length [6]. Based on the standard CMOS process partially, the major H+ sensing layer of dielectric material was formed by Si_3N_4 thin film with 65 nm in thickness over the regular SiO_2 insulating layer with 65 nm in thickness.



(a)



(b)

Figure 2. (a). The cross-section view of a p-well ISFET (b). Description of bias conditions of an ISFET [6].

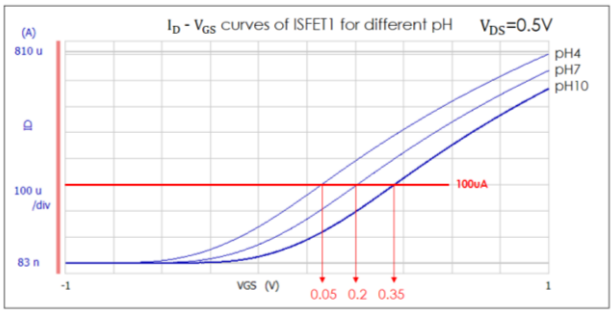


Figure 3. I_D-V_{GS} curves based on various pH solutions.

Based on the biasing configuration and assisted by Agilent B1500 semiconductor analyzer, the I_D-V_{GS} curves of ISFET for various pH solutions are shown in Figure 3. The measurement shows that ISFET operates as a depletion-mode device due to its negative turn on voltage. As the setting of V_{DS}=0.5V and I_D current selected as 100 uA, we can see the corresponding V_{GS} values varies from 0.05 V to 0.35 V for pH4 up to pH10 solutions. The variation means that the sensitivity of ISFET is around 50mV/pH.

2.2 ISFET Sensing Principles [7]

Compare to the conventional Metal-Oxide-Semiconductor Field-Effect-Transistor (MOSFET), the ISFET shown in Figure 2(b) exposes its gate area as a sensing region to the electrolyte with an extra reference electrode.

Referred to the ISFET sensing principles depicted in [7] and a typical single ISFET constant voltage constant current (CVCC) floating gate readout circuit shown in Figure 4 [8], the major equations (1) to (4) for the FET-based ion sensors follow the drain current equation of a MOSFET except that the threshold voltage (V_{TH}) is a function of the ion concentration as shown in Eqn. (1). Where the I_{DS} is drain current, μ_n is mobility of electron carriers in semiconductor layer, C_{ox} is oxide capacitance density, W/L is device aspect ratio, V_{GS} is gate-source voltage, V_{DS} is drain-source voltage, and $V_{TH(ISFET)}$ is the threshold voltage of ISFET.

$$I_{DS} = \mu_n C_{ox} \frac{W}{L}\left[\left(V_{GS} - V_{TH(ISFET)}\right)V_{DS} - \frac{1}{2}V_{DS}^2\right] \quad (1)$$

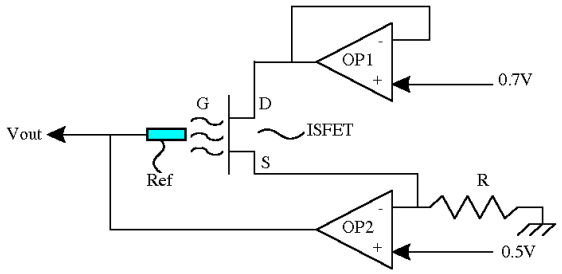


Figure 4. Constant Voltage Constant Current (CVCC) floating gate readout circuit [8].

With gate area exposed to the chemical solution, the threshold voltage of ISFET changes accordingly with the activity of ions in the chemical solution or electrolyte. This electrochemical phenomenon is defined by Nernst for single-ion, e.g., hydrogen in Eqn. (2) and (3).

$$V_{TH(ISFET)} = V_{TH(MOSFET)} - V_{CHEMICAL} \quad (2)$$

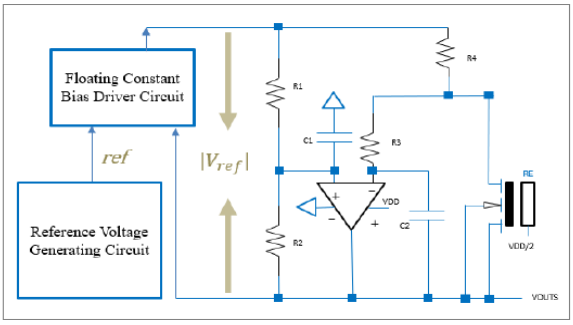
$$V_{CHEMICAL} = E_i + \frac{RT}{n_i F}\ln(a_i) \quad (3)$$

The $V_{TH(ISFET)}$ is a combined outcome of $V_{TH(MOSFET)}$ and $V_{CHEMICAL}$. The $V_{TH(MOSFET)}$ is threshold voltage of original MOSFET structure in ISFET, $V_{CHEMICAL}$ is electrochemically induced voltage in the threshold voltage of ISFET, E_i is the chemical constant, R is the gas constant, T is the absolute temperature in Kelvin, F the Faraday constant, n_i is charge of ion i, and a_i is ion activity of ion i. When ISFET is connected to a readout circuit, the output voltage *Vout* is usually the gate source voltage V_{GS} of ISFET. From (4), the V_{GS} of ISFET is proportional to the logarithmic function of ion activity a_i. Hence, the *Vout* of readout circuit reflects the ion activity [7].

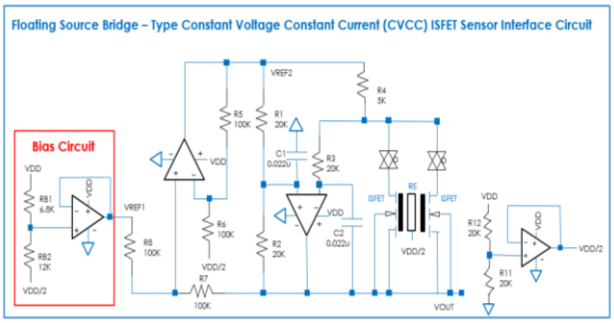
$$V_{GS(out)} = \frac{I_{DS}}{\mu_n C_{ox} \frac{W}{L} V_{DS}} + V_{TH(MOSFET)} - E_i - \frac{RT}{n_i F} \ln(a_i) + \frac{1}{2} V_{DS} \quad (4)$$

2.3 Readout Circuit Design

Constant Voltage and Constant Current (CVCC) readout circuit for ISFET sensor has been used widely due to its stable operation for choosing right V_{DS} and I_{DS} biasing. With the example shown in Figure 4 and the equation mentioned in (4), V_{DS} of ISFET with 0.2V or 0.5V setting and I_{DS} with 100 uA, ISFET may operate in the linear or non-saturation region. The output of floating gate terminal can be responded to the different concentration of H^+ or pH measured in Figure 3. However, the readout circuit shown in Figure 4 only can be applied to single parameter sensing due to the reference electrode as the floating output node.



(a)



(b)

Figure 5. (a) Basic building block of floating source CVCC circuit (b) Dual-ISFET floating source bridge-type CVCC circuit.

Therefore, we propose a modified readout circuit for multiple ISFETs used in dual key-parameters (pH and Ca^{2+}) sensing. This new readout circuit solves the problem of the circuit shown in Figure 4 to use one single supply voltage with 3.3V and can accommodate two ISFETs sharing one common reference electrode for Hydrogen and Calcium ions simultaneously by using floating source bridge-type CVCC circuit shown in Figure 5. The circuit block (a) describes the main concept used. The block includes the reference voltage circuit generator, floating constant bias driver circuit and core bridge-type floating source CVCC circuit and one sample ISFET. Where R1, R2, R4 and $R_{DS/ISFET}$ formed the bridge circuit, the fixed 0.5 V drop across R2 or V_{DS} of ISFET and constant current flow through R4 and ISFET will set up the non-saturated operating condition for ISFETs. Here, we choose R1=R2=20K to get $V_{R1}=V_{R2}=0.5V$ for the case of $V_{ref}=1V$ and maintain the $I_{DS,ISFET}$ with 100 uA by setting R4=5K. The readout circuit incorporated two low pass filters R1, R2, C1 and R3, R4, $R_{DS/ISFET}$ and C2 for removing noise signals from the power supply and the ISFET itself, from the external electromagnetic field interference or the fluid fluctuation during the set-up moment for testing [9].

2.4 Preparation of Calcium Ion Sensing Film

With the advantage of Si_3N_4 sensing membrane based ISFET, it is capable of forming a Ca^{2+} sensing membrane on its top of exposed Si_3N_4 region, i.e., the gate area of ISFET. The following materials and procedures are used to form the Ca^{2+} sensing membrane:

2.4.1 Materials

1) Using the commercial product [10]:
   Calcium Ionophore IV - Cocktail for membranes.
2) Composition:
   a) Calcium ionophore IV, 0.072 wt. %
   b) 2-Nitrophenyl octyl ether, 4.748 wt. %
   c) Poly(vinyl chloride), 2.379 wt. %
   d) Potassium tetrakis (4-chlorophenyl) borate, 0.022 wt. %
   e) Tetrahydrofuran, 92.780 wt. %

2.4.2 Procedures

1) Clean the sensing window of ISFET or EGFET with an **Acetone** solution, and then use an air blow gun to immediately dry the acetone solution.
2) Use a micropipette to draw enough THF to clean the sensing window, and immediately cover THF to avoid evaporation.
   Note: THF is hazardous liquid.
3) After dropping THF on the sensing window, immediately use the pipette to get 6ul of **Calcium Ionophore IV - Cocktail for membranes** with a new micropipette, and drop solution on the sensor window.
4) Within 5 seconds, replace the tip of the micropipette and get another 6ul of **Calcium Ionophore IV - Cocktail for membranes** to drop on the sensing window.
5) After completion, confirm whether there are bubbles or not. If there are no bubbles or very tiny bubbles, put them in a vacuum box and vacuum for one minute.
6) Place ISFET or EGFET with the calcium ion membrane in the desiccator until bubbles are not present. If bubbles are seen or some of the sensing window is not fully covered with calcium ion membrane, remove the calcium ion membrane then repeat step A to E.

2.5 On-Chip Integrated Read Circuit Design

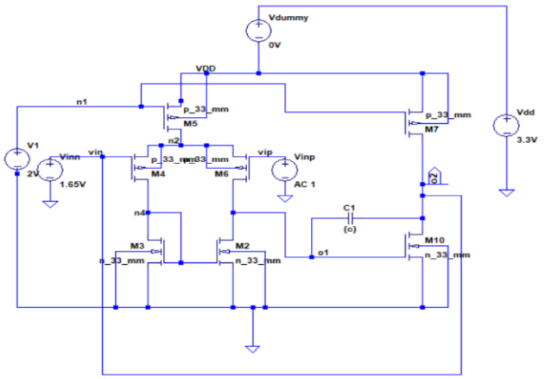


Figure 6. Schematic of 2-stage operational trans-conductance amplifier used for potentiometric readout circuit.

From the key circuit proposed in Figure 5, there are four amplifiers used to provide major functions including analog

ground (Vdd/2 reference level) generator, floating reference voltage with 1V across the VREF2 to V out node, and the bridge circuit to generate one floating source Constant Voltage and Constant Current for non-saturated ISFET operation and pH sensing. The schematic of two-stage operational trans-conductance amplifier (OTA) is shown in Figure 6 and the simulation results of this amplifier using UMC 0.18um CMOS process are summarized as the AC response in Figure 7 and performance parameters listed in Table 1. All performance parameters of this building block meet the specifications for potentiometric readout circuit applications.

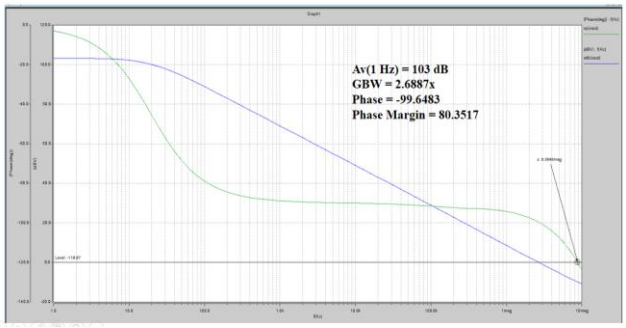


Figure 7. The frequency response of the proposed OTA.

Table 1. Simulation results of OTA designed

Parameter	Spec.	Parameter	Spec.
Power Supply (V)	3.3V	PSRR(+/-)	107.02dB / 103.55 dB
Avo(dB)	103dB	CMRR	106dB
Phase Margin	81^o	Total Power	250.64uW
Slew Rate(+/-)	0.85 V/uS / 4.115 V/uS	The whole readout circuit layout area	463x163um^2

2.6 On-Board System Implementation

Based on the readout circuit discussed in Figure 5 (b), the system shown in Figure 8 is using two potentiometric sensors that share the same readout circuit. An ISFET sensor is used for measurement of pH and the other Ca^{2+} selective membrane coated ISFET or EGFET (Extended Gate Field Effect Transistor) sensor is used for measurement of Ca^{2+}.

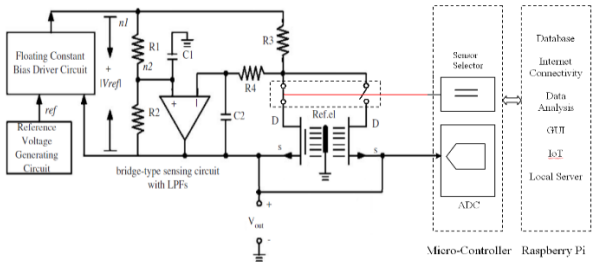


Figure 8. The block diagram of the proposed dual key-parameter sensing system.

A digital output of microcontroller acts as a selector between two sensors, while the ADC input channel measures the voltage from the readout circuit. The micro-controller also plays the role for 2-point calibration for providing a wider? measuring and accurate range of pH solutions. The system can be developed further with wireless transmission capability

3. RESULTS AND DISCUSSION

3.1 On-chip and On-board System

For the proposed system development, we verified the design concepts through on-chip and on-board prototype realization. Figure 9 shows the layout view of the test chip with a whole potentiometric read out circuit which has an active area of 463x163um^2 and each OTA building block consumes only static power about 250 uW.

In addition, the prototype of the whole readout system follows the signal and power management shown in Figure 10 (a) and the implementation of the system is demonstrated in Figure 10 (b).

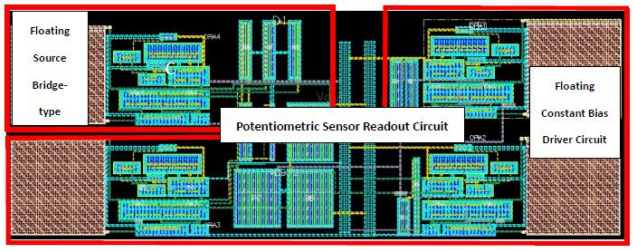
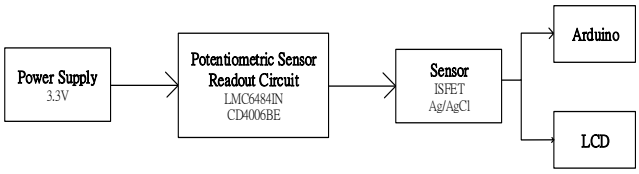
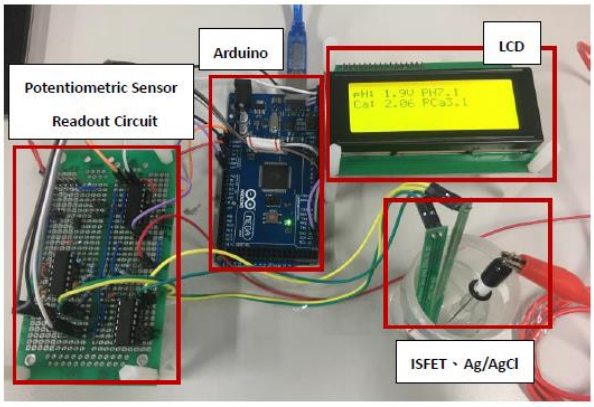


Figure 9. Layout view of core readout circuit (463x163um^2).



(a)



(b)

Figure 10. (a)The signal and power management of the system (b) The on-board prototype of the whole readout system.

3.2 Measurements of pH and Ca^{2+} Sensors

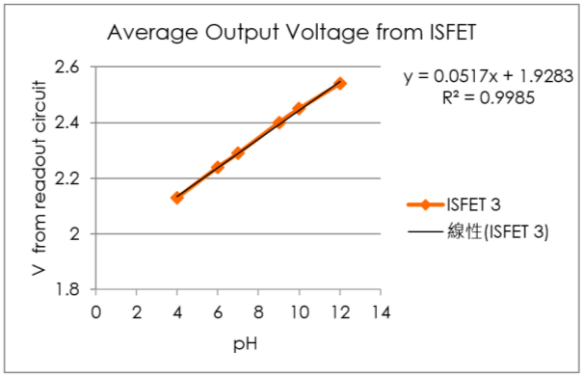
The ISFET sensor and the potentiometric readout circuit are connected to the Arduino Uno microcontroller with LCD display.

Since the normal hydrogen ion (pH) range of human urine is pH 4.5 ~ 8, the concentration is tested intensively. The solution measured in this study is pH 4, 6, 7, 8, 10, 12, used. The measurement results are used to make a graph, and the ideal trend line slope and the regression coefficient of determination (R^2) are compared to ensure the stability of the sensor.

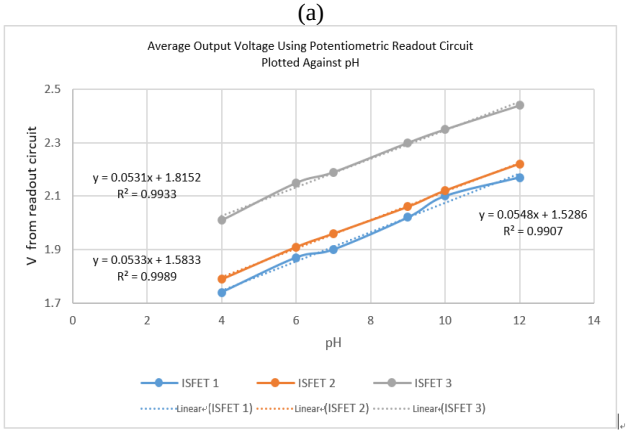
The Si_3N_4 based ISFET can be served as a direct pH sensor without any post processing, but served as a pCa sensor, it needs further Ca^{2+} ion sensing membrane prepared in 2.4

In addition, the sensing range of pH and pCa to be considered for urine testing is as follows: the value of pH indicates the acidic or alkaline characteristics of the electroyte. Further, the Ca^{2+} will be evaluated by collecting urine of normal adults in 24 hours. The concentration of calcium ion should be between 2.5 to 6.25 mmol [11]. i.e., according to the formula pCa = – log [Ca^{2+}](M), it can be found that the normal urine of calcium ion range is between pCa 2.6 to 2.2.

The experimental results of output voltages through single ISFET and three ISFETs versus various pH solutions shown in Figure 11(a) and (b) exhibit acceptable and consistent sensitivity around 53+/-2mV/pH. Regarding the measurements of Figure 11(b), the initial DC voltage offsets (1.75 V, 1.8 V and 2.0 V @pH=4 solution) of each ISFET can be cancelled and calibrated through the post processing programmed in the micro-controller.



(a)



(b)

Figure 11. (a)The signal and power management of the system (b) The on-board prototype of the whole readout ssystem.

The test result of ISFET-based Ca^{2+} sensor by using the readout circuit system developed in this research is shown in Figure 12. The sensitivity is around 27 mV/pCa and is valid for pCa up to 4. The sensing capability meets the usage for urine pCa sensing in the range between pCa=2.2 to 2.6.

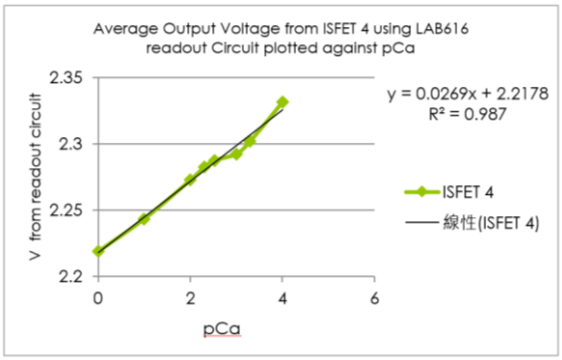


Figure 12. The performance of the ISFET-based pCa sensor.

The ISFET-based sensors for pH and pCa using the proposed potentiometric readout circuit are summarized in Table 2. The experimental results have shown that the developed sensor and readout circuit have acceptable sensing linearity of the pH-value from 4 to 12 and pCa up to 4.

Table 2. The performance of dual key-parameter system

Sensing Parameter	Sensing Range	Normal Human Urine	Capability to be used
pH	4 – 12	4.5-8	Yes
pCa	Up to 4	2.2-2.6 (collection for 24 hours)	Yes

4. CONCLUSIONS

In this research, we propose a dual key-parameter readout system for the application of urolithiasis recurrence prevention. Based on the demand of a point-of-care test device, the systematic studies from sensor preparation and characterization, sensor interface circuit design, on-chip and on-board system implementation were explored. The experimental results have shown that the developed sensor and readout circuit have acceptable sensing linearity of the pH-value from 4 to 12 and pCa up to 4. Because the mechanism of urinary stone formation is complicated and caused by a number of factors, even more key parameters such as uric acid, conductivity, etc. in urine are suggested to be monitored in order to provide enough evaluated information for urolithiasis recurrence prevention. Therefore, in the near future, we will continue to develop an advanced and complete readout system which will be capable of sensing four key parameters including pH, pCa, uric acid and conductivity from spot urine regularly. Through the long-term sensing data collection and analysis, the analyzed results can be evaluated by urologists and help patients with urolithiasis to have a better life style to reduce the rate of urinary stone recurrence.

5. ACKNOWLEDGMENTS

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research funding; and the National Center for High-Performance Computing, Taiwan as well as the Taiwan Semiconductor Research Institute (TSRI) for the technical and chip tape out support.

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