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Calcium Ion Detection Using Miniaturized InN-based Ion Sensitive Field Effect Transistors

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Abstract: An Ultrathin (~10 nm) InN ion sensitive field effect transistor (ISFET) with gate regions functionalized with phosphotyrosine (p-Tyr) is proposed to detect calcium ions (Ca^{2+}) in aqueous solution. The ISFET was miniaturized to a chip size of 1.1 mm by 1.5 mm and integrated at the tip of a hypodermic injection needle (18 G) for real-time and continuous monitoring. The sensor shows a current variation ratio of 1.11% with per decade change of Ca^{2+} and a detection limit of 10^{-6} M. The response time of 5 sec. reveals its great potential for accomplishing fast detection in chemical and physiological sensing applications. The sensor would be applied in medical diagnosis and used to monitor continuous and real-time variations of Ca^{2+} levels in human blood in the near future.

Keywords: calcium; ion-sensitive field-effect transistor (ISFET); indium nitride (InN)

1. Introduction

Calcium is an important element in the human body, and it plays a significant role in maintaining regular physiological functions in the human digestion, endocrine, blood, urinary and immunity systems, and well as when the body exercises. In particular, traces of calcium ions in cells are responsible for message transfer, controlling human metabolism, skeleton growth, muscle tone, the level of pH in blood, electrolyte equilibrium, hormone secretion, body temperature, cell proliferation, cell adhesion, etc. If the regulation of calcium ions becomes unbalanced in the human body, many problems will occur [1, 2]. A shortage of calcium ion concentration in blood below 0.035 g/ml will cause severe nerve and muscle tightening. Some parts of cells will be affected by a shrinking phenomenon. Furthermore, a lack of calcium ions will affect the regulation of proteins, fats, and carbohydrates leading to malnutrition, anorexia, constipation, retardation, etc. Some medical research shows that a lack of calcium ions will cause crisp bones, a loss of immune functions, cell division hyperthyroidism, as well as cancer and other related diseases. Indium nitride (InN) is a new development in III-nitride semiconductor materials. InN has the unique properties of high electron concentration near the surface, high chemical stability, and high sensitivity to the environment, all of which show great potential in detecting chemical species and biological molecules [3-6]. By using these distinct properties, we expect to develop an InN calcium chemical sensor for medical diagnosis, with the capability of detecting changes of calcium ion concentration in the human body in real time.

Technology in the semiconductor industry has been growing since the invention of the transistor. In the beginning, silicon and germanium substrates were mainly used in the semiconductor industry. However, researchers found that silicon and germanium have limitations in many applications. Because of these limitations, more and more new materials have been studied. InN is one of these promising new materials, due to its unique characteristics, such as surface charge accumulation, high electron concentration, high chemical stability, and high sensitivity. In order to develop new applications for InN there is a need for greater research into the properties and effectiveness of InN ion sensitive field effect transistors (ISFET).

ISFETs have many advantages compared to the traditional glass electrode. These include miniaturization, high S/N ratio, fast response time and the fact that they are easily integrated with CMOS technology into mass production. Wurtzite InN has recently been confirmed as a narrow band gap material, which is about 0.7 eV [7-9]. The InN surface has a strong two-dimensional electron gas accumulation (~10^{13} cm^{-2}) which is suitable for sensors and is affected by the external environment. The general explanation of the surface electron accumulation is from InN band structure. The band structure shows that the Γ point of the Fermi stabilization energy (E_{FS}) is higher than the conduction band, so the InN surface energy state becomes a donor type. These surface donor type energy states will release electrons near the surface and make InN (about 5 nm) have a higher electron density. When an InN surface adsorbs charged ions, the gate potential will be changed, thereby affecting the surface electron concentration and making the source - drain current change. The InN surface energy state is a positively charged donor type state, thus the anion will be adsorbed in the surface and form a Helmholtz Double Layer [10, 11]. It will deplete more electrons near the surface, resulting in the increasing resistance of InN thin films, and finally the decrease of source - drain current.

Kun-Wei Kao is currently studying at National Tsing Hua University in Taiwan, Institute of NanoEngineering and Microsystems Ph.D's program. His interests focus on InN-based ambient sensors and wafer-level nanostructures for bio/opto applications. He worked as a LCD Equipment Engineer of HannStar Display andSemiconductor Process Engineer of Powerchip Semiconductor from 2004 to 2006. He received his Master degree in Opto-Electronic Engineering from National Yunlin University of Science & Technology in 2009.

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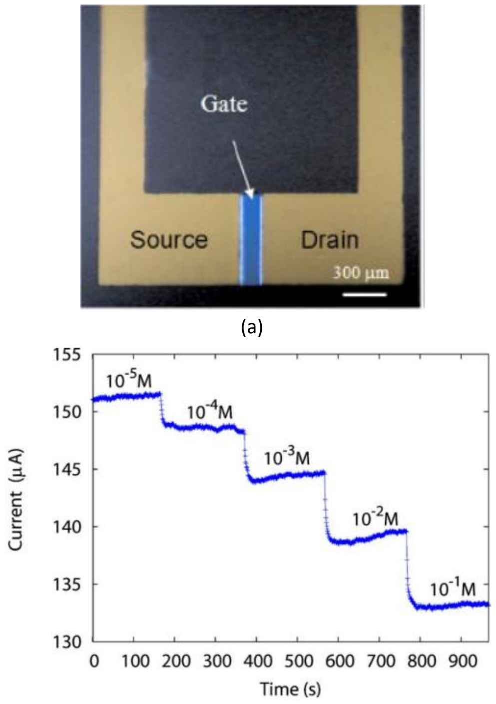
Ultra-thin film (10 nm) InN ISFET was used to detect the anion, with a sensitivity of 5 μA / decade, and a response time of less than 10 seconds [12, 13]. Figure 1 (a) shows the InN ISFET structure. The blue part is a gate as sensing area, and the golden part is metal. The entire structure used Si as the substrate, epitaxial AlN as an intermediate buffer layer, and finally InN was deposited on the top. Figure 1 (b) shows the dynamic current response of InN ISFET in potassium chloride aqueous solution. When the potassium chloride concentration increases, the more chloride ions are adsorbed on the InN surface, and the more electrons will be depleted near the surface, which causes an increase in resistance and a decrease in current periodically.



(a)

(b)

Figure 1. (a) InN ISFET structure, the blue part is gate as sensing area. (b) dynamic current response of InN ISFET in potassium chloride aqueous solution.

This article presents the idea of depositing ultrathin and uniform film with atomic level thickness using a molecular vapor deposition (MVD) technique. This ultrathin film is applied through a surface modification method to create InN based chemical sensors with high sensitivity and high selectivity towards calcium ions. This sensor has the advantage of being a small device which provides simple measurements and a fast response, no reagent contamination, and easy to achieve real-time, multi-parameter and simultaneous measurements. In the future, it is expected that this chemical sensor will find useful applications in medical measurement.

2. Materials and methods

2.1 Performance Parameters of ISFET

In this section we will introduce and define the parameters used to measure ISFET performance, including sensitivity, response time, and limit of detection. All of the parameters are defined in reference [14]. The most important parameter for ion sensors is sensitivity. For years, many research studies focused on ion sensors which have a specific sensitivity for ions. Sensitivity is defined as when the aqueous solution concentration changes 10 times (decade), and the corresponding ISFET surface gate potential or current changes in volume. Sensitivity represents the performance of a sensor: the higher the sensitivity the greater the ability to resolve smaller signal strengths.

Response time can be defined as the total time that elapses between the initial concentration (R_{initia}) and the final concentration (R_{final}) : $R_{initial}$ + (R_{final}-$R_{initial}$) *p (where p is the percentage). This percentage can range from 63% to 90%. In our experiment we use 90%. Limit of detection is defined as the minimum value of analyte concentration that can produce a sufficiently different signal from the signals of a blank sample. In this paper, the maximum standard deviation of noise signal is 0.01 μA.

2.2 Design of InN ISFET

The first part of this paragraph examines three important parameters which must be considered carefully in the design of InN ISFET. These are channel width to length ratio, Ohmic contact, and device encapsulation. The second part of this paragraph provides a description of the functionalization method and processes used to detect calcium ions using InN ISFET.

The heteroepitaxial growth of InN film on a Si (111) substrate was performed via nitrogen plasma-assisted molecular beam epitaxy. The InN/AlN film is composed of an ultrathin (10nm) InN epilayer and a thick (190 nm) AlN buffer layer. The electron mobility of InN is 33 cm^2/Vs, and the electron concentration is $2.3\times10^{20}\ cm^{-3}$ and the thickness is 10 nm.

The design of an InN ISFET must consider two parameters. First, is the channel width to length ratio of InN ISFET for determining the current of a device. The current of n-type FET can be expressed as in Equation (1).

$$I=e\mu_n n\frac{tW}{L}V_{DS} \tag{1}$$

Where I is the source-drain current, e is the elementary charge of an electron ($1.6*10^{-19}$C), μ_n is electron mobility, n is electron concentration, W is channel width, t is thickness of the semiconductor, L is channel length, VDS is the source-drain voltage. The electron mobility of InN is 33 cm^2/Vs, the electron concentration is $2.3\times10^{20}\ cm^{-3}$ and the thickness is 10 nm.

After considering all the parameters above, different designs of channel width to length ratio (W/L) 10 and 20 were used. When applied VDS is 2 V, the current estimated by Equation (1) is approximately on the order of one milliamp. When the current of an InN ISFET is so small that the equipment can’t measure it then the performance is very poor. When the current of an InN ISFET is too big it may destroy the device and affect the stability of the InN ISFET.

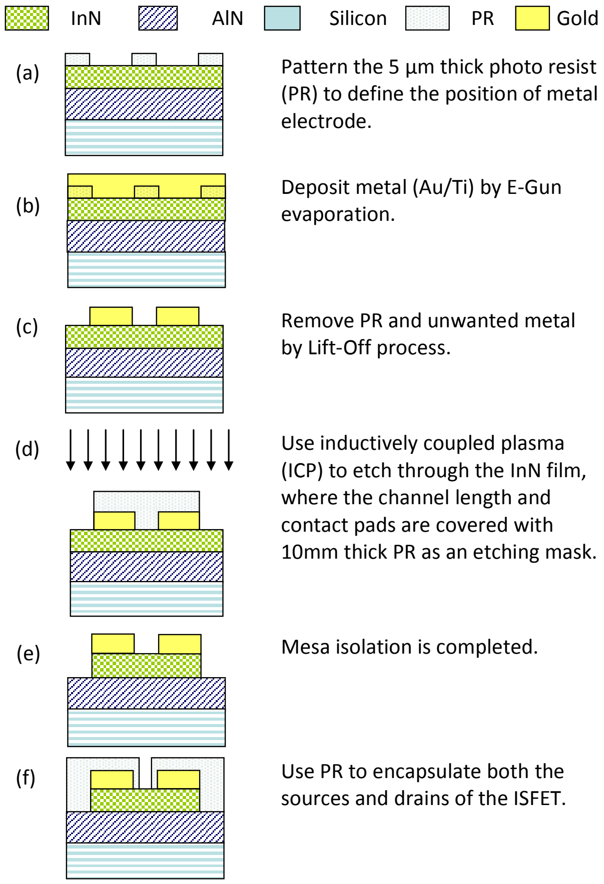
For electrical detection, it is important to obtain the ohmic contact on the electrode. Therefore, Au/Ti (150/80 nm) is adopted. The ohmic contact can be formed as $10^{-6}\ \Omega cm^{-2}$ in accordance with previous studies [15].

2.3 Process Flow

The process of InN ISFET uses three masks. One uses a lift-off technique to define the electrode. Another one uses an ICP to complete mesa isolation. Finally, a mask is used to define the gate region of the InN ISFET. The detailed growth process can be found elsewhere and the fabrication process of an ultrathin InN ISFET is presented in Figure 2.

2.4 Functionalization

O_2 plasma cleaning was used after 1 hour of vapor deposition. APTMS with − NH_2 functional groups reacted to the cross-linker, glutaraldehyde, which was used to immobilize O-phospho-l-tyrosine (p-Tyr) with phosphate end. Later an immersion in 1 mM p-Tyr solution took place for 12 hours. The functionalization process is shown in Figure 3.



(a) Pattern the 5 µm thick photo resist (PR) to define the position of metal electrode.

(b) Deposit metal (Au/Ti) by E-Gun evaporation.

(c) Remove PR and unwanted metal by Lift-Off process.

(d) Use inductively coupled plasma (ICP) to etch through the InN film, where the channel length and contact pads are covered with 10mm thick PR as an etching mask.

(e) Mesa isolation is completed.

(f) Use PR to encapsulate both the sources and drains of the ISFET.

Figure 2. InN ISFET Process Flow.

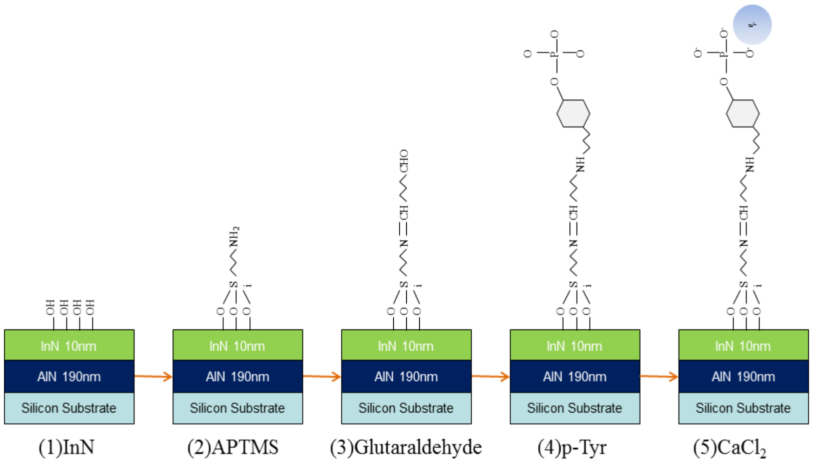


Figure 3. Functionalization flow chart.

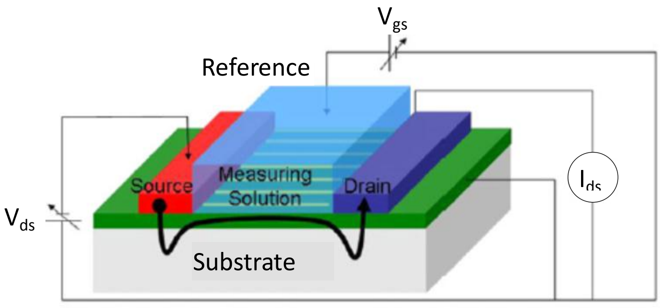


Figure 4. ISFET structure.

2.5 Electronic Detection Method

A general ISFET is a three-terminal device, with source, drain and gate between them, used to detect chemical or biological molecules. In order to respond to calcium ions, we have to do chemical modification on the gate. Figure 4 is a diagram of a typical ISFET structure.

When the charged ions bind to the sensing membrane, the ions will establish an electric field in the gate region, which changes the surface potential and affects the channel current. When the charged ions and the carriers in the channel have the same kind of charge then ions will deplete the channel, which will decrease the carrier in the channel and cause increases in resistance and current degradation. On the other hand, if the charged ions and the carriers in the channel have a different kind of charge the charged ions will accumulate more carriers near the surface, causing the current to increase. Calcium ions are positively charged in an aqueous solution, and the charged ions will increase the channel current in the InN ISFET. Figure 5 is the schematic diagram for the sensing mechanism [15].

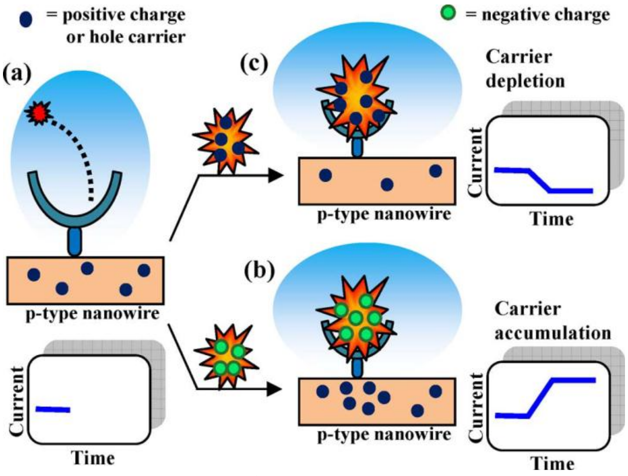


Figure 5. Schematic diagram for the sensing mechanism.

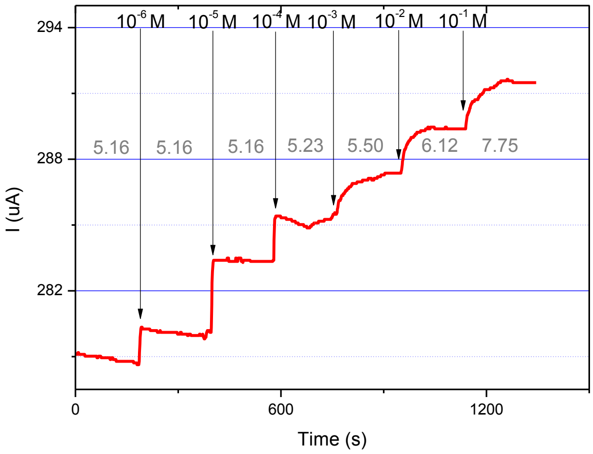


Figure 6. The calcium current response graph of InN ISFET after functionalization.

3. Results and discussion

After using p-Tyr to modify the calcium ion solution, the resulting changes in the dynamic current were measured, as shown in Figure 6. We can detect modifications in the role of calcium on the InN ISFET surface when the current variation signals show a stable upward trend ladder, and the concentration of calcium ions changes along a continuum from 10^{-6} M to 10^{-1} M.

Response times at different calcium concentrations are listed in Table 1. When the calcium ion concentration changes from 10^{-6} M to 10^{-4} M, the response time is less than 5 seconds, which implies a very fast response time, whereas the reaction time increases to 1 minute when calcium ion concentration changes from 10^{-3} M to 10^{-1} M. Because complexation reactions between calcium ions and O-phospho-l-tyrosine (p-Tyr) take place easily in contexts when the concentration of ions is low, the result is that current change stabilizes fast. The complexes of calcium account for better absorption sites, and c compete with other calcium ions when the concentration of ions increases. So, a high concentration of calcium ions are less prone to complexation reactions, which causes the response time to be elongated and shows a smoother curve on the dynamic current changes chart.

4. Conclusion

An ultrathin (~10 nm) InN ion sensitive field effect transistor (ISFET) with a gate region functionalized with phosphotyrosine (p-Tyr) is proposed to detect calcium ions (Ca^{2+}) in aqueous solution. The sensor shows a current variation ratio of 1.11% with a per decade change of Ca^{2+} and a detection limit of 10^{-6} M. The response time of 5 seconds reveals its great potential for accomplishing fast detection in chemical and physiological sensing applications. The ISFET was miniaturized (chip size: 1.1 mm * 1.5 mm) and integrated at the tip of a hypodermic injection needle (18 G). In the future, the InN ISFET sensors will be integrated and tested in real-time situations. These will include situations where existing pieces of medical equipment, such as arterial catheters (A-line), are used. The sensor would be applied in medical diagnosis for monitoring continuous and real-time variations in the concentration of Ca^{2+} in human blood.

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