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(Research Article)

Analysis of output characteristics of ion sensitive field effect transistor based biosensor for measurement of pH in biochemical solutions

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Abstract

The need for improved system's response time, sensitivity, selectivity and miniaturization has continued to form the premise for focusing research attention on innovative design and development of biochemical sensors. Ion sensitive field effect transistor (ISFET) can be used to innovatively drive biochemical sensors for the measurement of concentration of ions and molecules in solutions. This simulation study focuses on the determination of output characteristics of ISFET pH sensor as applied in the measurement of concentration of hydrogen potential (pH) which is a function of the proton concentration in an analyte solution. The pH of a target analyte interacts with the ion sensitive membrane of ISFET to produce charges which in turn changes the potential of the working electrode of the sensor. The output characteristic of interest is the gate voltage of ISFET which is a function of pH concentration of analyte under study. The relationship between the sensor's input pH concentration and its output gate voltage describes the sensitivity of the device. From the results obtained from the study, as the input pH concentration was increased from 5 to 11, the output gate voltage ISFET pH sensor increased from 2.65 V to 2.9 V.

Keywords: ISFET; Ph; Sensor; Concentration; Analyte; Transistor

1. Introduction

An efficient way of developing reliable biosensor device for detecting a wide range of ions and biomolecules in analyte solutions is through the introduction of ion and biomolecule sensitive element into electronic transducers. This type of electronic biosensor can help in translating biological activities into measurable electrical variables. Put differently, the goal of such biosensor is to respectively detect and measure the presence and concentration of certain analytes in solution and in turn produce a quantifiable electrical signal that is proportional to the measured quantity. [1][2]. The possibility of developing an enzymatic selective biosensor that can be adopted for specific applications depends largely on the specificity property of target ions or biomolecules such as enzymes, antigens, antibodies, etc. Specific applications include medical applications such as the detection of pH and blood glucose concentrations among others.

Ion-sensitive field-effect transistor (ISFET) is a modification of metal-oxide-silicon field-effect transistor (MOSFET). It presents a technological advancement in which gate contact of normal MOSFET is replaced by an ions selective membrane giving it the capability to sense ionic and molecular concentrations in solution. This ISFET-based biosensor possesses the advantage of fast response time and miniaturization, low output impedance, and high signal-to-noise ratio [3].

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1.1. Overview of Fabrication Process of ISFET

Conventionally, the structure of Si-SiO_2-Si ISFET has an upper deposition of the ion-sensitive membrane and a backside gate-type ISFET structure [4] [5]. By standard technology, ISFET functional areas are formed within silicon islands that were carved from a silicon wafer. The isolation of the silicon island from a solution is realized by possible combinations of layers of Silicon Oxide – Silicon Nitrate (SiO_2 - Si_3N_4), Silicon Oxide - Tantalum (V) Oxide (SiO_2 -Ta_2O_5), etc. The sequence of the major fabrication process of ISFET is as follows:

- Oxidation of silicon wafer (SiO_2);
- Bonding of two silicon wafer by SiO_2 layer;
- Thinning of silicon wafer of Si- SiO_2-Si structure;
- Drain and source diffusion, channel stopper diffusion;
- Etching of thin silicon wafer to form Si islands;
- Gate oxidation and chemical vapor deposition (CVD), Si_3N_4, CVD or Ta_2O_5 deposition;
- Deposition and chloridation of the silver electrodes;
- Contact hole etching, metallization;
- Scribing and wire bonding;
- Molding the pad part and the bonding wires.

In the fabrication of pH-sensitive ISFET, Si_3N_4 or Ta_2O_5 can be used as the top layer for the gate insulator. This ISFET type is an n-channel depletion-mode device, fabricated from a p-type silicon wafer. The gate composite insulator consists of an approximately thermally grown SiO_2 layer, overlaid by a CVD, Si_3N_4, or Ta_2O_5 film. Tantalum (V) Oxide (Ta_2O_5) films are prepared by thermal oxidation of tantalum, Ta in an oxygen atmosphere at 510^{o}C. The pH-sensitive gate was separated from the bonding pads as far as possible for easy encapsulation of the device. ISFETs and Silver/Silver Chloride (Ag/AgCl) reference electrode were integrated on the chip. Encapsulation molding was necessary only for the pads and the bonding wires using epoxy resin, since the side walls and backside of the diced chip were insulated by the SiO_2, Si_3N_4, Ta_2O_5 films. The leakage current between the FET and Ag/AgCl reference electrode was about 10^{-10} A. Possible design parameters of Si_3N_4 and Ta_2O_5 gate pH ISFETs are given in Table 1.

Table 1 Basic design parameters of Si_3N_4 and Ta_2O_5 gate pH ISFET [4]

Parameter	**Ta_2O_5 gate**	**Si_3N_4 gate**
Linear range measurements (pH)	1-12	1-12
pH sensitivity (mV/pH)	55-57	48-54
Selectivity, K_{HNa}(K_{HK})	10^{-9}	10^{-6}-10^{-8}
Long-term instability	0.5	2-3
Hysteresis (pH)	0.02	0.05
90% response time (s)	1	1

2. Literature Review

By virtue of the advancement in microelectronic technologies, research studies have been focused on the innovative design and development of ISFET-based biosensors with possible application in areas such as medical diagnosis, agriculture, ecosystem monitoring, or biochemical sciences. The studies that have been carried out so far in these areas of application indicated that the possibilities are endless.

Hai et al, [1] presented a hybrid bioelectronic sensor to detect reagents that can inhibit the enzymatic activities of acetylchlorine esterase analyte. This was achieved by restraining the enzyme to ion sensitive surface of field effect transistor (ISFET). The sensitivity of the hybrid ISFET biosensor to the said analyte was about 10^{-5}M.

In the ISFET device proposed by Park et al, [3], it was designed to directly detect the surface charge of maltose binding protein (MBP) for the monitoring of changes in protein structure. Based on the study of the FET biosensor, a significant drop in the measured current from the MOS capacitance of the device revealed that the substrate-specific properties of the target protein could be successfully monitored by the biosensor.

Andrianova et al [7] employed Tantalum (V) Oxide (Ta_2O_5) as ion sensitive surface for their reported ISFET electronic biosensor. The structural layout of the proposed device was optimized for high sensitivity and reduced capacitance influence on subthreshold modes. Carnitine acetyltransferase was restrained on the ion sensitive surface of the device in order to detect the presence and concentration of L-carnitine.

Lau et al [8] developed cell-based biosensor for the detection of trehalose (saliva sugar) concentration in the saliva of patients. Recent study has shown that the presence of excess salivary sugar is biomarker for Alzheimer's disease. The working principle of the proposed bioelectronic sensor relies on the excessive expression of sugar sensitive gustatory receptors in Drosophila cells to detect the salivary trehalose using extended gate ion-sensitive field-effect transistor to improve device sensitivity and reliability [9].

Park et al [10] presented the design and fabrication of a dual-gate ISFET based biosensor for the detection and monitoring of biomarker charged protein in serum. Protein blocking layer with associated interfacial charges was used to minimize non-specific protein bindings on the proposed ISFET device since direct quantification was difficult. This regulated the interfacial charge and preserved their intrinsic electrical property. The output response of the biosensor as influenced by the interfacial charge was demonstrated through prostate cancer biomarker sensing. This made the proposed device suitable for medical diagnostic device [11].

Hara et al [12] proposed an electrochemical biosensing device which employed genetically engineered P450 monooxygenase for its enzymatic reaction process. ISFET configuration was employed for the implementation of the design. P450 monooxygenases was restrained the ion sensitive layer of the device for the sensing of chlorophenol compounds.

Jimenez-Jorquera et al [13] reported the development of a microsensor for the detection of environmental variables. This adopted the principles of ISFET based on semiconductor technology which offered additional advantage of integration of circuitry and multiple sensors in the same substrate. This system design sign has found application in the probing and monitoring electrochemical constituents such as toxins in the environment.

In the work of Muangsuwan et al [15], an immune-FET biosensor was presented for the detection of biotinylated products of polymerase chain reaction (PCR). Biotinylated PCR is employed in genetic and DNA testing to amplify genes associated DNA disorders in patients. It involves the process of covalently attaching biotin to a protein [16]. The FET-based biosensor was implemented with the adsorption of protein-A on the insulated gate surface of ISFET. for 90min. Next, the immobilized 1/500 diluted anti-biotin antibody was immobilized and adsorbed onto the Protein-A layer. The analysis of the device showed highly specific binding to the biotinylated PCR products. The immune-FET biosensor is a promising device for the sensing of biotinylated PCR product.

Sheliakina et al [17] reported a novel ISFET biosensor for the detection of arginine. It utilized immobilized urease in glutaraldehyde as a biosensing element by choosing optimal concentration of urea for the determination of arginine [18]. The selectivity of the proposed bio-detector was studied for different amino acids and satisfactory results of quantitative determination of L-arginine in samples were obtained.

Parizi et al [19] reported the application of ISFET for pH sensing and the conditions for improved selectivity were studied. The study showed that employing pH buffer solutions containing counter-ions, higher sensitivity which can exceed the Nernst limit can be achieved. Different sensing conditions studied verified the accuracy and validity of investigative experiments [20]

Saengdee et al [21] reported the use of aminopropyltriethoxysilane (APTES) to immobilize biomolecule on silicon derivative. The parameters such as concentration and reaction time that influence the efficiency of APTES immobilization process of biomolecule were studied [22]. The goal was to achieve the optimal APTES modification condition which produced a thin and stable APTES layer on silicon nitride (Si_3N_4) surface. The results showed that there is a direct nexus between the thicknesses of APTES modified ion selective layer and APTES concentration and reaction time. The thicker the APTES modified sensing layer of ISFET, the lower the sensitivity of proposed biosensor due to what is known as ion shielding effect.

Saengdee et al [23] proposed ISFET biosensor where the biomolecule selective layer was modified with APTES and glutaradehyde to achieve aldehyde coated surface. The resulting immune-detector was aimed at detecting the presence and concentration of antigen 85 complex B which is a major secretion product of Mycobacterium tuberculosis. Hence, the biosensor is suitable for real-time diagnosis of Mycobacterium tuberculosis.

ISFET biosensor with a sensitive nanoprobes at the gate using dextran-capped silver nanoparticles was the focus of the work done by Zhao et al [24] for the detection of Concanavalin A and glucose. The mechanism of the device allows for reusability and it overcomes the Debye screening of the FET device in saline solutions [25].

Douthwaite et al [26] reported a self-powered wearable ISFET electrochemical sensor. The thermoelectrically powered system was developed with application-specific integrated circuit, power management chips and thermoelectric generators. The device was aimed at sensing analytes in biofluids such as perspiration [27]. The master-piece laid the foundation for fabrication of self-powered sensors for perspiration analysis in healthcare and sports science applications.

Huang et al [28] reported an ISFET targeted at the accurate detection of potential of Hydrogen (pH) in DNA sequencing. In the proposed work dual-mode sensing is possible, namely, optical and chemical modes. The proposed ISFET based pH sensor was fabricated in standard CMOS image sensor (CIS) process for reliable determination of microbead physical locations with CIS pixel. The performance analysis of the proposed CMOS dual-mode sensor results a well correlated pH map and optical image for microbeads with a pH sensitivity of 26.2mV/pH [29].

Lee et al [30] presented a sensitive immunosensor based on ISFET with dual gate operation for the sensing of hepatitis B surface antigen. The sensitivity of the proposed immunosensor was enhanced by careful design of the nanostructure of the field effect transistor. The study of the performance of the sensor showed that it is suitable for clinical diagnosis of various diseases.

2.1. Theoretical Formulation

In compliance with the Boltzmann distribution model, the pH value, the potential of H^+ ions at the sensor surface is given by [19]:

$$pH_s = pH_B + \frac{q\psi_0}{2.3kT} \quad (1)$$

Where:

Subscript S = pH at the sensor surface

Subscript B = pH in the bulk solution

$\psi_0 =$ The potential drop across the diffusion layer.

The capability to collect charges at the sensor surface due to the change in surface pH, also known as the intrinsic buffer capacity (β_i) is given by [31]:

$$\beta_i = \frac{d\sigma_0}{-qdpH_s} \quad (2)$$

Where:

$\sigma_0 =$ Sensor surface charge density

$pH_s =$ pH at the sensor surface

The diffusion capacity (C_d) refers to the capacity to store opposing charge in solution near the sensor surface as a result of the change in surface potential [19]:

$$C_d = \frac{d\sigma_0}{d\psi_0} \quad (3)$$

Equation (3) can be rewritten as:

$$\frac{d\psi_0}{dpH_s} = -q\frac{\beta_i}{C_d} \quad (4)$$

Following the differentiation of Equation (1) with respect to pH_B, and substituting Equation (4), the sensitivity of surface potential to the bulk pH is obtained as:

$$\frac{d\psi_0}{dpH_B} = -2.3\frac{kT}{q}\left(\frac{1}{1+\alpha}\right) \quad (5)$$

And

$$\alpha = \frac{2.3kTC_d}{q^2\beta_i} \quad (6)$$

Where:

α = dimensionless sensitivity parameter with a positive value.

It is to be noted that the sensitivity of potential at the sensor surface and the corresponding change of the sensor threshold voltage to the bulk pH are limited to 2.3 kT/q = 59 mV/pH which is referred to as the Nernst limit.

Many research and development efforts have been made to improve the sensitivity of the ISFET sensors. These include reengineering the sensing surface [32] [33]; reduction of the counter-ion charge screening [34] [40]; the application of electromechanical coupling methods [35][41]; modification of structural dimension of sensor surface [36], as well as the use of dual-gated structures to amplify response signal [37][38][39].

3. Methodology

The methodologies adopted for the study of ion-sensitive field-effect transistor (ISFET) for pH measurement is as shown in the process block diagram depicted in Figure 1

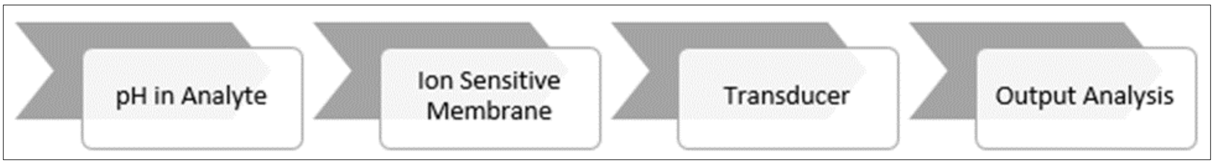

Figure 1 Methodological process block diagram

Recall that the ISFET sensor incorporate sample solution with pH concentration in place of the gate and oxide components of a MOSFET with a reference electrode immersed in the solution and an insulating layer appropriate for detecting a specific analyte as shown in Figure 2. The insulating layer typically defines the functionality and sensitivity of the ISFET sensor. The pH sensor is simulated and a performance study is carried.

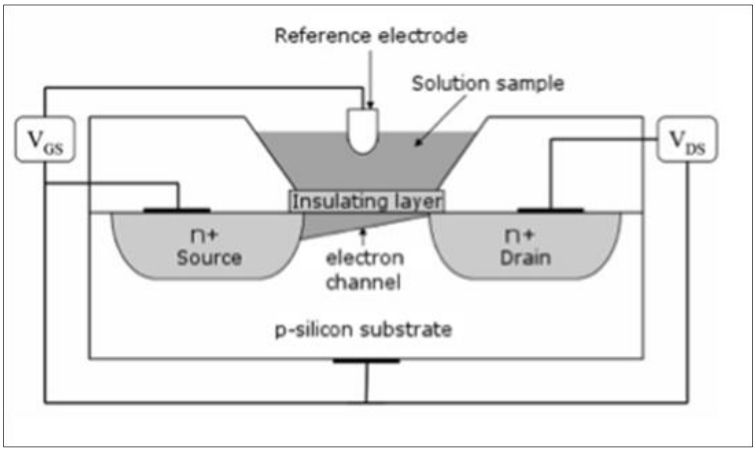

Figure 2 Schematics of pH ISFET

The study process is simulated in COMSOL Multiphysics. The hydrogen potential (pH) which is a function of the proton concentration in the analyte interacts with the ion sensitive membrane to produce charges which in turn changes the potential of the working electrode of the proposed pH sensor. The sensor is modeled in 2D space exploring the coupling between physics of semiconductor to model the MOSFET aspect of the ISFET and electrolyte to model the ionic diffusion in the electrolyte aspect. The physics for the electrolyte domain are based on the principles of Diffuse Double Layer. The dedicated Thin Insulator Gate boundary condition is used to define the thin oxide layer. The electric potential at the outer surface of the oxide is given by the electric potential of the electrolyte in direct contact with the Stern layer; the potential across the Stern layer in the presence of hydronium and hydroxide ions. The bulk electrolyte potential is given by the equation combining the gate voltage applied on the reference electrode, the work function of the electrode metal, and the equilibrium potential of the reference electrode. The charge density on the oxide surface is given by the equilibrium reaction between protons and the proton binding sites on the oxide surface. The chemical activity of the protons on the oxide surface is related to the hydronium ion concentration in the bulk electrolyte via the Boltzmann distribution function.

The simulation study of the fully coupled 2D model was carried out to analyze the drain current response of the modeled pH sensor in relation to drain voltage response for varying values of pH in the analyte. Additionally, the gate voltage of the device was also examined in relation to varying pH values and constant drain current.

4. Results and discussion

The output characteristics of the pH ISFET are as shown in Figure 3 and 4. In Figure 3 the drain current output obtained was plotted against the output drain voltage for a constant gate voltage of 2.6V and three different values of pH that is 3, 7 and 11. A steady state values of 4uA, 12uA and 18uA were obtained for the three different pH values employed for the analysis. The significance of this result is that, as the pH value increases the drain current output of the device increases.

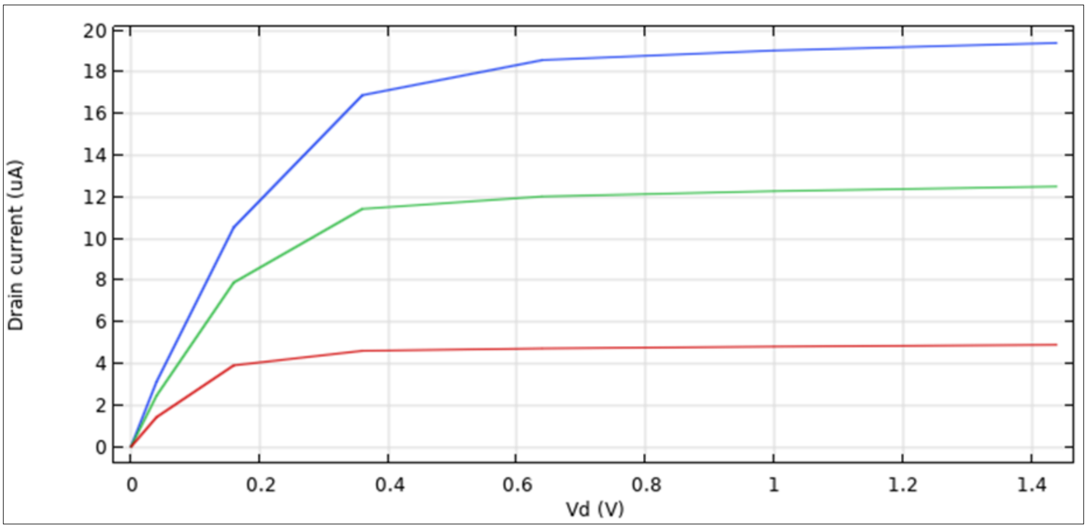

Figure 3 The drain current response plotted against drain voltage for different pH values

Figure 4 shows the relationship, at constant drain current, between the output gate voltages of the pH sensor in relation to the varying pH value of the analyte which constitute the input of the sensor. The plot of the input pH concentration against the output gate voltage describes the sensitivity of the ISFET pH sensor. As shown in the plot, the output gate voltage increased linearly from 2.65 V to 2.9 V as the pH input value increase from 5 to 11.

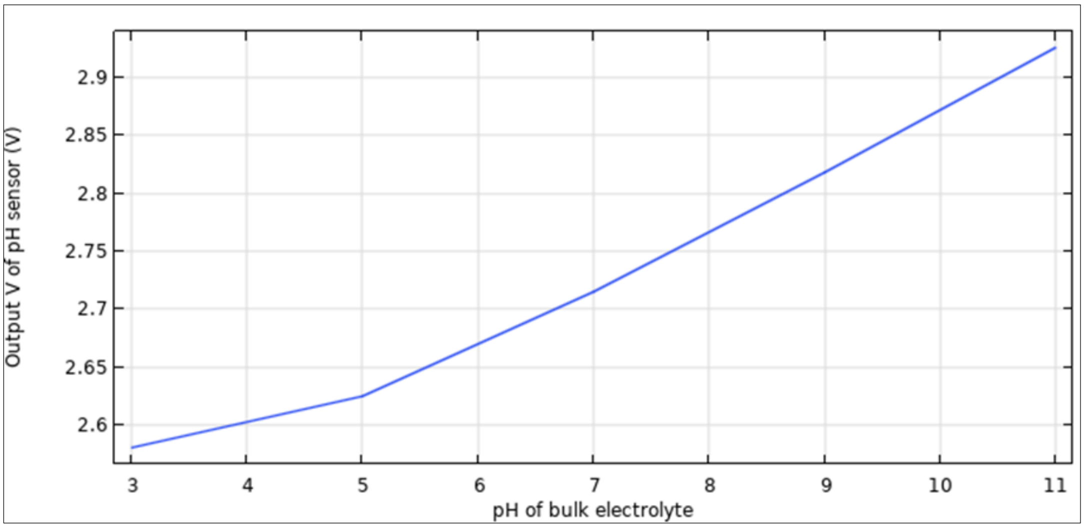

Figure 4 Drain current response in relation to drain voltage response for varying values of pH in the analyte

5. Conclusion

The simulation study focused on the determination of output characteristic of ISFET pH sensor as applied in the measurement of concentration of hydrogen potential (pH) which is a function of the proton concentration in the target analyte solution. pH of target analyte interacts with the ion sensitive membrane of ISFET to produce charges which in turn changes the potential of the working electrode of the sensor. The output characteristic of interest is the gate voltage of ISFET which is a function of pH concentration of analyte under study. The relationship between the sensors's input pH concentration and its output gate voltage describes the sensitivity of the device. From the results obtained from the study, as the sensor's input pH level was increased from 5 to 11, the output gate voltage increased from 2.65 V to 2.9 V.

Compliance with ethical standards

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Disclosure of conflict of interest

The author declares no conflict of interest.

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