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Developing an Ultrasensitive Silicon Nanowire based ISFET Biosensor to Identify Dengue Fever Early

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ABSTRACT

Dengue fever is a swiftly proliferating mosquito-transmitted viral illness that presents a considerable global health issue, especially in tropical and subtropical areas. Present diagnostic methods, such as ELISA and RT-PCR, exhibit constraints regarding speed, cost, and sensitivity, highlighting the need for innovative biosensing technologies aimed at facilitating early detection. This investigation delves into the creation of an ultrasensitive, label-free Silicon Nanowire based ion sensitive Field-Effect Transistor (SiNW based ISFET) biosensor aimed at the early detection of the Dengue virus (DENV). The proposed biosensor aims to identify DENV at very low concentrations in human blood samples, enabling swift diagnosis and prompt medical action. The performance of the sensor is assessed via simulation with the COMSOL semiconductor module, focusing on critical parameters including sensitivity, specificity, and limit of detection (LOD). The findings indicate that the SiNW based ISFET biosensor shows significant potential for high-precision DENV detection, presenting a promising alternative to traditional diagnostic methods. This study advances biosensing technology and demonstrates the practicality of SiNW-based ISFET for point-of-care applications, potentially enhancing dengue fever management and minimizing severe complications linked to delayed diagnosis.

Keywords: *Silicon nanowire, ISFET, Dengue, RT-PCR, Comsoul Multiphysics.*

1. INTRODUCTION

Dengue fever stands as a highly common mosquito-borne viral infection, representing a significant risk to public health worldwide. The Dengue virus (DENV), classified within the Flavivirus genus, is responsible for this condition. It comprises four antigenically distinct serotypes: DENV-1, DENV-2, DENV-3, and DENV-4, with ongoing research into a potential fifth serotype. The disease is prevalent in more than 130 countries, mainly in tropical and subtropical areas, impacting around 100 million people each year [1]. Although certain infections may present with mild symptoms and resolve on their own, more severe instances can result in serious complications, including plasma leakage, hemorrhagic fever, and organ failure, potentially leading to fatal outcomes if not properly diagnosed or treated.

Timely and precise identification of DENV is essential for effectively managing outbreaks and minimizing morbidity and mortality rates. Nonetheless, existing diagnostic methods, such as enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR), and rapid antigen tests, frequently face challenges related to cost, sensitivity, specificity, and turnaround time [2]. The swift advancement of severe dengue symptoms highlights the critical necessity for a detection method that is not only highly sensitive but also cost-effective and rapid, facilitating prompt medical intervention. Current diagnostic methods, although effective, do not achieve an ideal equilibrium among speed, cost-effectiveness, sensitivity, and specificity [3]. Methods such as ELISA and PCR necessitate specialized laboratory environments and skilled personnel, rendering them impractical for quick, point-of-care applications in areas with limited resources. Moreover, existing antigen-based lateral flow assays, despite their speed, frequently exhibit low sensitivity during the initial phases of infection [4]. Consequently, creating a novel biosensing method capable of detecting DENV at low concentrations in real-time is essential for enhancing early-stage diagnostics.

Field-effect transistors serve as the fundamental component for semiconductor nanowires in the construction of biosensors [5]. Silicon stands out as an excellent FET material primarily due to its cost-effectiveness and widespread availability. SiNWs can be produced as single crystal structures with adjustable diameters, exhibiting excellent performance in FET device applications [6]. Typically, FET biosensors that utilize SiNWs demonstrate several advantages [7]. At first, the sensitivity to various chemical and biological entities can be fine-tuned by accurately controlling the kind and concentration of dopants in SiNWs. Second, surface dangling bonds can be effectively passivated by the naturally occurring silicon oxide. [8].

The modification of these oxide surfaces with receptors can be accomplished through established silanol chemistry, allowing for targeted surface functionalization and enhanced selectivity for specific analytes [9]. Ultimately, SiNWs within the nanoscale range could demonstrate quantum confinement phenomena when their diameters fall below 5 nm. The relationship between quantized conductance and molecular adsorption may serve as a basis for highly sensitive molecular detection [10]. The conductivity of SiNW-FET will vary when there is a change in the surface electrical field or potential of SiNWs. The top layer of the FET utilizes SiNW as a channel. A layer of Si dioxide situated beneath the SiNW functions as the back gate. Figure 1 presents a typical structure in cross-sectional view. The mechanism of conductance for accumulation and depletion modes is influenced by the presence of holes and electrons.

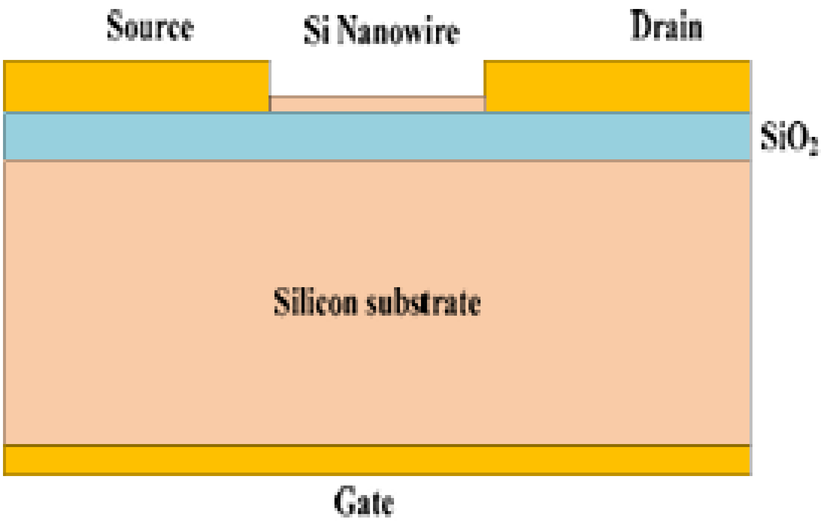

Figure 1: Structure of SiNW based ISFET

This work discusses the design and development of an ultrasensitive, label-free Silicon Nanowire Field-Effect Transistor (SiNW FET) biosensor aimed at the early detection of DENV [11]. Developing a highly sensitive SiNW FET-based biosensor capable of detecting low concentrations of DENV in blood samples [12]. Conducting a simulation of the sensor's performance through the COMSOL semiconductor module to assess its sensitivity, specificity, and electrical response. Investigating the practicality of incorporating this biosensor into point-of-care (POC) diagnostic systems for practical use in real-world scenarios.

2. BACKGROUND

An ISFET functions as an ion-sensitive field-effect transistor, designed specifically for measuring ion concentrations within a solution [13]. As the ion concentration, including pH levels, in the solution varies, there is a corresponding change in the current flowing through the transistor. Figure 2 illustrates the fundamental architecture of an ISFET [14]. The configuration resembles that of a traditional MOSFET, where the gate connection is distinct from the chip, utilizing a reference electrode placed in an aqueous solution that interfaces with the gate oxide [15]. The ion selective gate membrane serves as the dielectric that delineates the channel from the bulk, with the interface potential generated in accordance with the concentration of hydrogen ions (protons) [16]. There is an increasing focus on utilizing ISFETs as front-end transducers that bridge the ionic and electronic realms. The transformation of a chemical signal into an electrical one has been evidenced since the introduction of ISFET as a tool for electrophysiology [17]. The primary applications of ISFETs are found within the biomedical field, particularly as biosensors. Every biosensor incorporates a signal transducer that connects the molecular recognition elements, such as cells, antibodies, enzymes, and microorganisms, to the electrical signal [18]. The detection principles of these transducers can involve electroactive substances, as seen in electrodes, heat, as in thermistors, light photons, as in counters, changes in mass, as in piezoelectric devices, or changes in pH, as in semiconductor pH electrodes based on ISFETs.

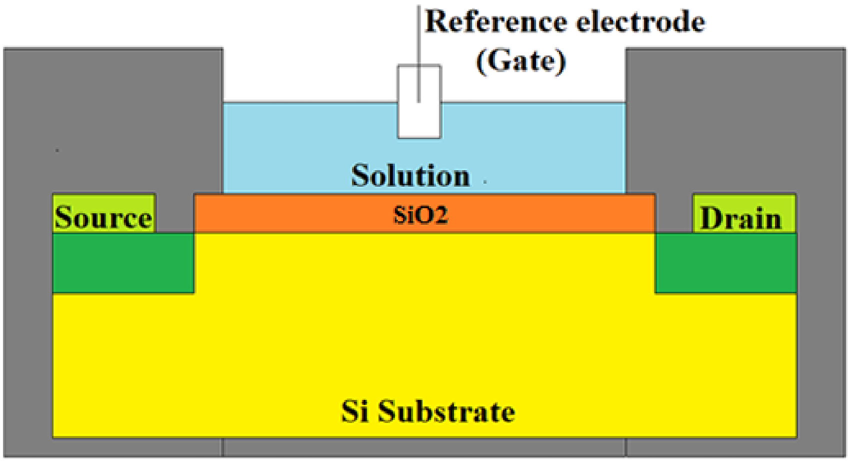

Figure 2: Basic Design of ISFET

The primary catalyst propelling investigations in this advancing domain is the process compatibility that the ISFET exhibits with standard CMOS processes [19]. Among the various silicon-based biosensors, ISFET-based biosensors stand out due to their favorable attributes, including seamless integration, high reliability, cost-effectiveness, and precise process control, along with enhanced sensitivity, speed, and miniaturization. The ISFET functions effectively as a standalone pH sensor or can be utilized as a biosensor, operating on the principle of detecting pH changes. The selection of ISFET as a pH sensor has garnered significant interest due to its numerous advantages compared to the traditional bulky glass electrode. It is durable, cost-effective, and compact, allowing for seamless integration [20]. The fabrication process flow is compatible with CMOS technology, demonstrating rapid response and excellent sensitivity across a broad pH range. For an ISFET to be effective as a biosensor, it is essential that it exhibits high pH sensitivity, as the pH ISFET chip is typically utilized in biosensor applications [21].

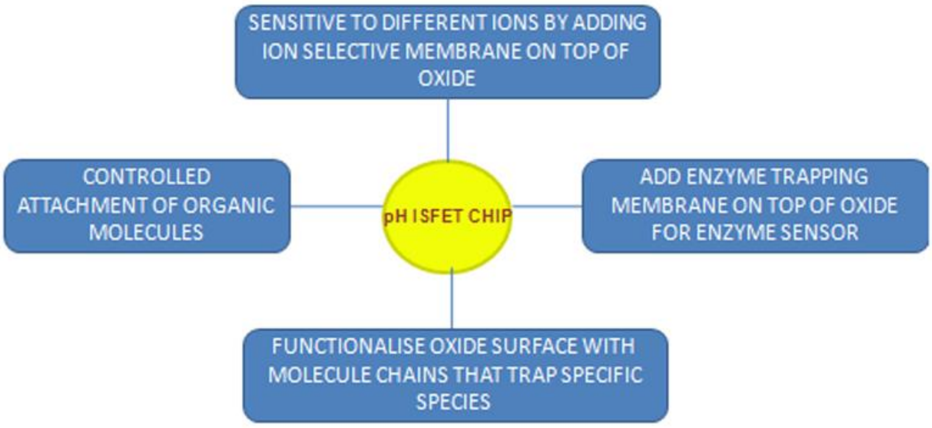

Figure 3: Functionality of ISFET chip

Biosensors utilizing ISFETs possess a structural benefit, as the biological layer is protected from the driven current due to the insulator present in the channel region. Consequently, the primary element influencing the characteristics of the biosensor is the gate insulator of the ISFETs [22].

Numerous biosensors have been developed based on theoretical developments with ISFET technology since Bergveld's invention of the ISFET biosensor in 1970 and Caras and Janata's report on the use of an enzymatically modified ISFET for the direct detection of penicillin in 1972. These two events happened in the same year. For instance, ISFET biosensors have made tremendous strides in recent years, opening up new avenues of investigation in the field of biosensing. Examples of such developments include the DNA (deoxyribonucleic acid)-modified field effect transistor (FET), which measures extracellular potential by sensing DNA hybridization; the cell-based FET, which measures extracellular potential by sensing cell metabolism; and the enzyme-immobilized FET, which measures H+ ion concentration. Applications of ISFET technology are currently widespread across several industries, with the biomedical and environmental monitoring sectors being the most prominent.

Since sensors are often more durable and flexible, they have been used to monitor a wide variety of chemical properties, such as potassium, conductivity, pH, salinity, nitrate, and phosphate. However, extensive laboratory testing against internationally accepted protocols that are already calibrated for fertilizing the crops is required before these sensors may be employed in soil testing. In electrochemical sensing, a voltage or current output is generated by an ion-selective electrode or an ion-selective field-effect transistor (ISFET) in response to the presence and activity of specific ions in a solution, while in biological sensing, a layer of immobilized enzymes sensitive to a specific nutrient is deposited on an electrode or electrochemical cell to monitor the reaction between the nutrient and the electrode. If you want to know how many hydrogen ions, for example, are in a solution, you can use a special kind of field-effect transistor called an ion selective field effect transistor (ISFET; for more on the pH scale, see ion selectivity). In the 1970s, someone had this idea. Ion-sensitive field-effect transistors (ISFETs) are a type of field-effect transistor that use a chemically sensitive structure by substituting an ion-sensitive membrane or layer for a metal gate electrode. The analyte species' chemical activity is translated into a potentiometric response, which is subsequently translated by the FET component into a change in the drain current, making the device a transducer. The solution itself serves as the gate electrode in this case. Ion sheaths cause a voltage to develop between the substrate and oxide surfaces.

3. DESIGN AND SIMULATION OF SINW BASED ISFET

The creation of the Silicon Nanowire Field-Effect Transistor (SiNW FET) biosensor entails a careful design and fabrication process, starting with the choice of materials for nanowire construction [24]. Silicon nanowires are selected for their outstanding electrical characteristics, elevated surface-to-volume ratio, and compatibility with biological systems. The fabrication of these nanowires can be achieved through a top-down method, utilizing lithographic techniques like electron beam lithography (EBL) and nanoimprint lithography (NIL), or through a bottom-up method, which involves vapor-liquid-solid (VLS) growth via chemical vapor deposition (CVD). The optimization of nanowire doping, whether n-type through phosphorus or arsenic or p-type via boron, is crucial for improving their electrical properties [25]. The nanowires are subsequently incorporated into a field-effect transistor configuration, with source, drain, and gate electrodes applied through metal evaporation techniques such as sputtering or electron beam evaporation.

To achieve precise detection of the Dengue virus (DENV), the SiNW surface is modified with biomolecules like antibodies, aptamers, or DNA probes that specifically attach to viral antigens. The process of functionalization initiates with the cleaning of the surface through the application of piranha solution or oxygen plasma, aimed at eliminating contaminants and activating hydroxyl (-OH) groups. A silanization process is conducted, utilizing molecules like 3-aminopropyltriethoxysilane (APTES) or (3-glycidyloxypropyl)trimethoxysilane (GPTMS) to establish reactive functional groups that facilitate biomolecule attachment. Following this, antibodies or aptamers specific to the dengue virus are covalently attached to the surface of the nanowire through the use of crosslinking agents such as glutaraldehyde or EDC/NHS. To reduce non-specific adsorption, unreacted sites are effectively blocked using bovine serum albumin (BSA). This functionalization guarantees elevated specificity in identifying DENV, resulting in alterations to the electrical properties of the biosensor when the virus binds.

Table 1: Device parameters of SiNW based ISFET

Parameter	Value used
Length of the Gate	22 nm
NS thickness	5-9 nm
NS width	30 nm
Terminal Doping	10^{20} /cm^3
Effective oxide Thickness	0.73 nm
Height of the Gate	74 nm
Underlap material	Nitride
Terminal Pad length	15 nm
Doping of the channel	10^{18} /cm^3
Terminal underlap length	7 nm
work function (Gate)	4.6 eV

Simulations are conducted using COMSOL Multiphysics, specifically its Semiconductor Module, to assess the performance of the SiNW FET biosensor prior to experimental fabrication. The biosensor is conceptualized as a three-terminal device comprising source, drain, and gate electrodes, with meticulous attention given to material properties including nanowire dimensions, doping concentration, oxide thickness, and metal contacts. The analysis of charge transport employs Poisson's equation alongside the drift-diffusion model to examine carrier movement. Several parameters are fine-tuned, such as doping concentration (light doping for enhanced charge sensitivity), nanowire diameter (ranging from 10 to 50 nm), channel length (between 100 and 500 nm), and source-drain voltage (from 0.1V to 1V). The simulation offers essential insights into charge transfer dynamics, carrier mobility, and variations in conductance due to virus binding, contributing to the optimization of sensor design prior to fabrication.

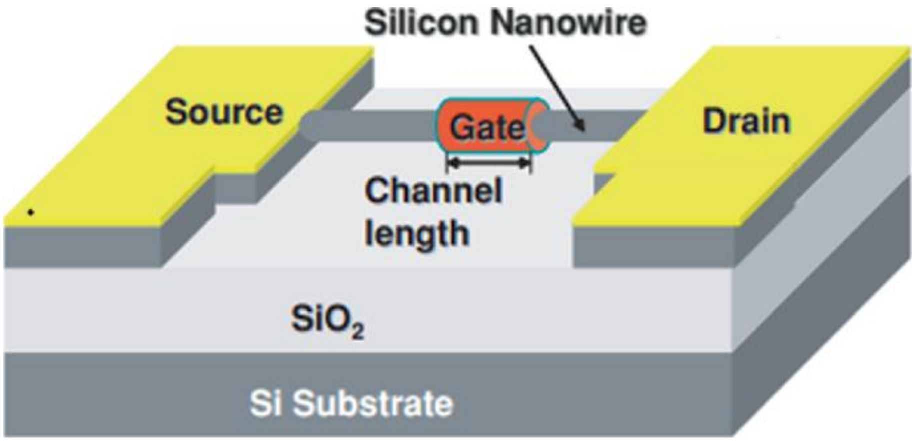

Figure 4: Schematic View of SiNW based ISFET

After fabrication, the biosensor is subjected to experimental validation by calibrating it with various concentrations of DENV in buffer solutions or human serum samples. A baseline electrical response is first established in a phosphate-buffered saline (PBS) solution. The sensor is subsequently subjected to escalating concentrations of DENV, generally spanning from femtomolar (fM) to nanomolar (nM), in order to ascertain its detection limit. Essential electrical parameters, including source-drain current (I_DS), threshold voltage (V_T), and transconductance (g_m), are assessed with the aid of a semiconductor parameter analyzer. The biosensor undergoes testing with non-target viruses like Zika and Chikungunya to evaluate specificity, thereby ensuring minimal cross-reactivity. The process of data analysis includes graphing current variations in relation to viral concentration, assessing the signal-to-noise ratio (SNR), and performing reproducibility tests to confirm the sensor's dependability.

4. RESULTS AND DISCUSSION

This study examines the surface electric potential of a 2D Ion-Sensitive Field-Effect Transistor (ISFET) characterized by a threshold voltage (V_t) of 1, while varying pH levels of 3, 7, 9, and 11, employing silicon dioxide (SiO2) as the oxide surface. The simulation results, derived from COMSOL Multiphysics, are illustrated in Figure 5, showcasing contour plots of the surface potential distribution across various pH values. Subfigures (a) through (d) represent pH levels of 3, 7, 9, and 11, respectively. Grasping the modulation of the surface potential is essential for evaluating the pH sensing capabilities of the ISFET. As the pH increases from 3 to 11, a notable change in the surface potential is observed. This trend illustrates the essential sensing mechanism of the ISFET, wherein variations in the hydrogen ion (H+) concentration in the solution directly affect the surface charge of the SiO2 layer. Under acidic conditions characterized by low pH, the high concentration of H+ ions results in the protonation of surface sites, which in turn influences the potential distribution. In alkaline conditions (high pH), the reduced H+ concentration leads to and a subsequent alteration in the surface potential. The observed trend is consistent with the theoretical behavior of ISFETs. The findings illustrated in Figure 6 indicate the successful adjustment of the 2D-ISFET's surface potential through changes in pH levels, validating its appropriateness for pH sensing applications within the range of 11. The results indicate a promising avenue for precise pH measurement.

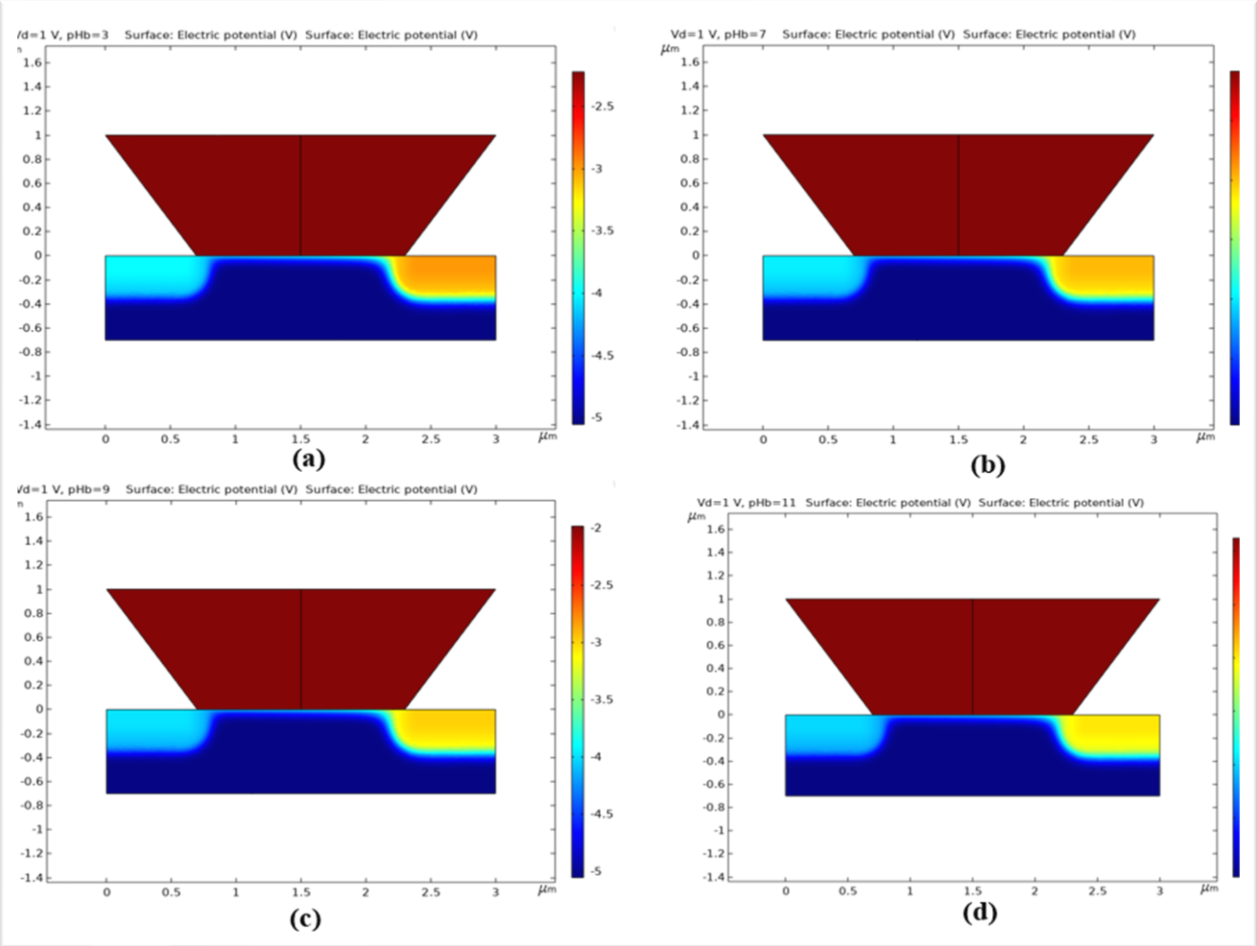

Figure 5: 2-Diode Insulated Field-Effect Transistor (FET) Surface Potential for Vd= 1 for pH=3,7,9, and 11 on an oxide surface of SiO2.

This study examines the electrical properties of a 2D Ion-Sensitive Field-Effect Transistor (ISFET) across different pH levels (3, 7, and 11), utilizing SiO2 as the gate oxide material. Figure 6 illustrates the output characteristics (Id-Vd curves) of the ISFET with a constant gate voltage (Vga) of 2.6V across various pH values. The figure illustrates a distinct relationship between the drain current (Id) and the pH of the electrolyte. A notable reduction in Id is evident as pH rises from 3 to 11. The alteration of the drain current is linked to the modifications in the surface charge of the SiO2 layer, which occur as a result of fluctuations in the hydrogen ion (H+) concentration within the electrolyte. Under acidic conditions (low pH), the increased concentration of H+ ions results in protonation of the SiO2 surface, thereby affecting the channel conductivity and leading to an elevated drain current. In contrast, when alkaline conditions prevail (high pH), the diminished H+ concentration leads to deprotonation or increased negative charge on the surface, which subsequently causes a decrease in the drain current. This observed trend underscores the ISFET's responsiveness to variations in pH levels.

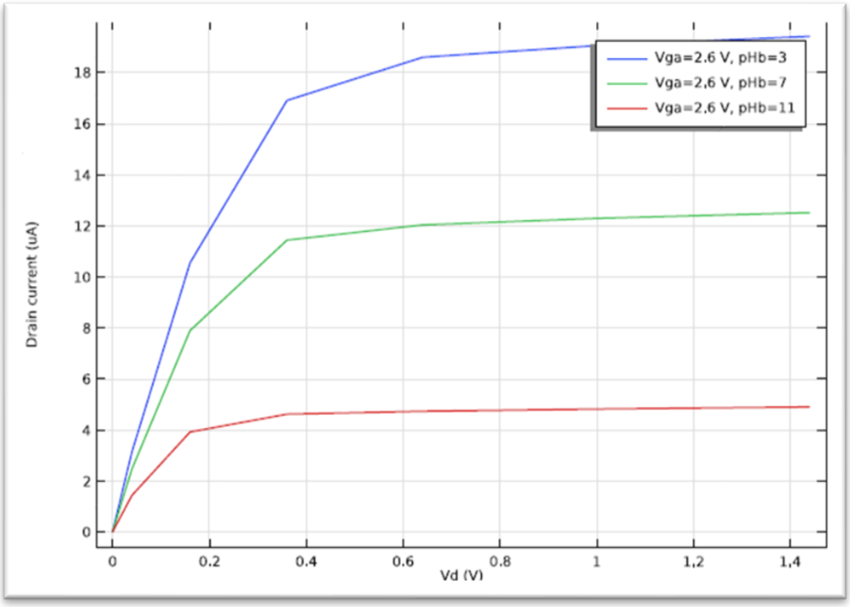

Figure 6: Id-Vd curve of the 2D- ISFET with different Ph Value of bulk electrolyte at constant Vga = 2.6 volt with SiO2 as oxide surface

Additionally, Figure 7 illustrates the transfer characteristics (Id-Vga curves) of the 2D-ISFET corresponding to the same pH values. The curves depict the correlation between the drain current and the gate voltage (Vga) while maintaining a constant drain voltage (Vd). The transfer characteristics demonstrate a clear alteration in the threshold voltage (Vth) as pH levels change. With an increase in pH, the threshold voltage shifts to more positive values, suggesting that a greater gate voltage is necessary to attain the same drain current. The direct relationship between Vth and pH underpins the mechanism of pH sensing with ISFETs. The threshold voltage shifted as the pH increased from 3 to 11. The findings illustrated in Figures 6 and 7 distinctly showcase the ISFET's capability to identify variations in pH by altering its electrical properties. The results indicate the promise of this 2D-ISFET featuring a SiO2 gate oxide for precise and dependable pH sensing applications.

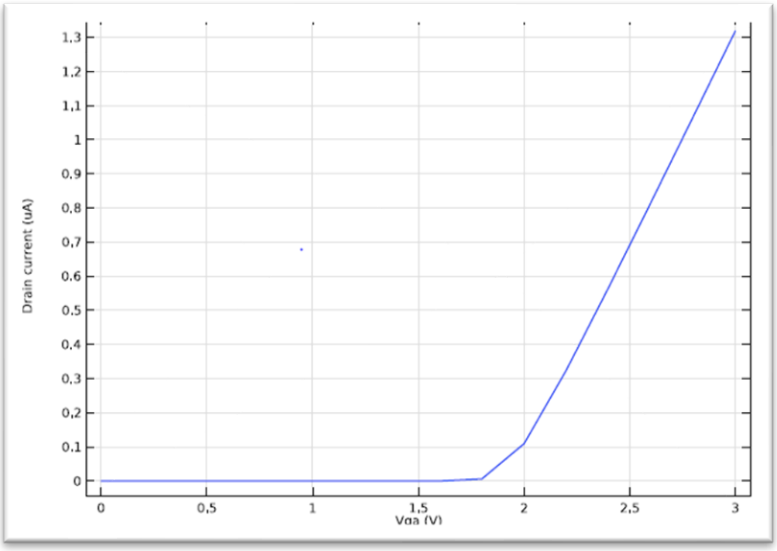

Figure 7: Transfer characteristics of 2D-ISFET with SiO2 as oxide surface.

The evaluation of the SiNW FET biosensor's performance is conducted through key metrics such as sensitivity, specificity, limit of detection (LOD), and response time. Sensitivity refers to the variation in electrical signal corresponding to each unit concentration of DENV, playing a vital role in identifying low viral loads during the early stages of infections. The evaluation of specificity involves testing the sensor with various flaviviruses to ensure that it accurately detects DENV selectively. The limit of detection (LOD), indicating the minimum concentration at which the sensor can effectively identify DENV, is anticipated to fall within the femtomolar to attomolar range, exceeding traditional diagnostic techniques such as ELISA and RT-PCR. The response time is a crucial element, as an optimal biosensor should deliver results in seconds to a few minutes, enabling swift diagnostics. The SiNW FET biosensor, with its impressive sensitivity, specificity, and rapid detection capabilities, holds the promise to transform dengue fever diagnostics, especially in resource-constrained environments where timely intervention is essential.

5. CONCLUSION

This study effectively showcases the capabilities of a Silicon Nanowire Field-Effect Transistor (SiNW FET) biosensor as an ultrasensitive and label-free detection platform for the Dengue virus (DENV). The simulation and analysis conducted with the COMSOL semiconductor module demonstrate that the proposed biosensor shows exceptional sensitivity and specificity, positioning it as a strong candidate for early detection of dengue. The capacity to identify minimal levels of DENV in blood samples highlights its promise for swift, real-time diagnostics, essential for averting serious dengue complications. While there are notable benefits, several obstacles persist, such as the necessity for experimental validation, the refinement of fabrication methods, and the incorporation of portable detection systems for point-of-care applications. Future investigations ought to concentrate on practical assessments using clinical samples, enhancing the stability and scalability of the sensor, and examining its versatility for identifying additional viral pathogens. This work lays the groundwork for advancing biosensors that have the potential to transform diagnostics for infectious diseases, especially in resource-constrained environments where dengue fever continues to pose a significant public health challenge.

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