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Design and performance analysis of an NSFET-based biosensor for the early detection of dengue

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ABSTRACT

Healthcare industry is changing due to technological breakthroughs that spur creative methods for diagnosing and treating illnesses. This study examines the development of nanowire-based stacked field-effect transistor (NSFET) biosensors for the early detection of dengue virus. Dengue fever is severe threat to public health and a flavivirus spread by mosquitoes. About half of the global population is at risk due to an endemic illness in tropical and subtropical regions, which affects approximately 100 million individuals annually in 130 countries. The virus has four antigenically distinct serotypes, and there may be a fifth. These serotypes induce variety of clinical symptoms. This can include benign infections that go away on their own or extremely serious, potentially fatal consequences like organ failure, plasma leakage, and bleeding. While many techniques are now used to diagnose dengue fever in the laboratory, no single technique satisfies the optimum standards for speed, economy, sensitivity, specificity. To close this gap in dengue diagnosis, newer detection technologies are desperately needed. This ultrasensitive label-free electrical device can detect the dengue virus (DENV) early on and prevent severe additional harm to humans. To detect various DENV concentrations in human blood and demonstrate potential for eventual point-of-care (POC) detection, NSFET constructed and simulated in this work.

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1. INTRODUCTION

The healthcare sector has undergone a dramatic change in recent years due to technological breakthroughs. Since the beginning of human life on Earth, environmental and climate change caused by humans have affected human health by causing infectious diseases and various cancers. Humans are currently affected by more than 100 different types of cancer and more than 217 infectious diseases. But as science and technology advanced, we were able to gain a greater grasp of the physiological states, the scientific principles underlying diseases, and the molecular components involved. Numerous avenues for new medical technologies for early diagnosis and cure have been made possible by this thorough understanding of the molecular mechanisms underlying diseases. Improving early diagnosis and treatment is thus made easier by measuring the presence or change of particular molecular biomarkers in urine, blood, or serum.

Mass spectrophotometry, flow cytometry, polymerase chain reaction (PCR), automated blood cell analyzers, enzyme-linked immunosorbent assay (ELISA), two-dimensional (2D) gel electrophoresis, and other sophisticated instruments are used in modern medical diagnostic procedures to identify particular biomarkers [1]. Even though these techniques are reliable, further steps like purification and chromatographic processing of sample concentration are required prior to detection. In addition, these methods are costly, labor-intensive, and time-consuming. Their application in real-world situations is limited by all of these drawbacks, and the primary focus is on using point of care (POC) devices, like drinking hemoglobin meters and blood glucometers. POC refers to medical diagnosis at or near the patient care site [2]. These POC tests allow for rapid results, the replacement of laboratory tests, and the timely start of necessary care.

Given this, DNA-based analytic methods have drawn a lot of interest due to their potential to completely transform cancer diagnosis. DNA-based methods provide a promising path for sensitive and targeted detection by utilizing the distinct genetic fingerprints linked to cancer cells. A promising instrument for molecular detection among the many technologies used in DNA analysis is the nanosheet field-effect transistor (NSFET)-based biosensor. NSFET-based biosensors are solid-state instruments that can identify pH variations brought on by interactions between DNA molecules. These sensors' small size, high sensitivity, quick reaction time, and label-free detection capabilities are some of their advantages over conventional detection techniques. NSFET-based biosensors are especially well-suited for point-of-care testing, real-time monitoring, and customized medicine purposes because of their characteristics.

Investigating the development of NSFET-based biosensors and its implications for technologically improved healthcare is the aim of this project. By combining DNA analysis techniques with NSFET-based biosensors, specific genetic biomarkers associated with blood cancers can be found. Better treatment strategies and better patient outcomes may result from the subsequent advancements in early cancer identification, which may allow clinical professionals to intervene at the earliest stages of the disease.

NSFET-based biosensors help monitor pH levels and ion concentrations in biological investigations and healthcare facilities, enabling researchers and medical personnel to make well-informed decisions. NSFET-based sensors help industrial process control by guaranteeing ideal conditions for food processing and fermentation, which preserves the quality and safety of the final product. Furthermore, NSFET-based sensors incorporated into management systems enable the hydroponics and agriculture sectors to track nutritional requirements and maximize the development of plants. These examples illustrate the significance of management applications as centralized platforms, enabling the collection, visualization, and analysis of NSFET-based sensors data. Through the integration of NSFET-based sensors, management applications enhance monitoring capabilities, set thresholds, generate alerts, and support data-driven decisions for effective management in diverse fields.

Here is the structure of the paper: An introduction stresses the importance of early detection in preventing serious complications, dengue fever's broad prevalence, and the complexity of its serotypes, all of which contribute to dengue fever's status as a worldwide health problem. Current diagnostic technologies are reviewed in the background and literature section, with an emphasis on their limitations and the increasing interest in field-effect transistor-based (FET) biosensors. The suggested technique details the material selection, functionalization process, and simulation using visual technology computer-aided design (TCAD) tools to create a new ultrasensitive dengue virus (DENV) biosensor called a gate-all-around nanosheet field-effect transistor (GAA NSFET). The next part, "device simulation and design parameters," goes into further detail about the electrical and structural properties taken into account during the simulation process. In the results and discussion section, we show how the sensor reacts to different concentrations of DENV and compare its sensitivity and specificity to that of more traditional biosensing methods. The paper continues by discussing the NSFET biosensor and how it could be used in portable, easy-to-use, and future-integrated point-of-care diagnostic systems. The conclusion wraps up the study by summarizing its main points and outlining its future directions, which may involve applying the findings in the real world or expanding the study to other infectious diseases.

2. LITERATURE REVIEW

Advances in medical diagnostics have been made possible by the exploitation of a distinct class of nanomaterials with special features by advances in nanoscience and nanotechnology [3]. Nanostructured materials can be tailored to various sizes and forms and have excellent physical and chemical properties. Increased chemical activity, a high surface-to-volume ratio, and electrical behavior that may be adjusted make these materials attractive for molecule level detection in the nano domain. Following the formation of the bio interface, the nanomaterials are essential for electron conduction and biomolecule immobilization. Furthermore, the development of smaller devices is made possible by the materials' modest dimensions. The sensitivity, selectivity, and accuracy of the POC device can be significantly improved by using nanomaterials like graphene, carbon nanotubes (CNTs), nanoparticles, quantum dots, nanorods, and nanowires into the biosensor manufacturing process. The use of nanomaterials in the production of POC devices has led to the development of several transduction methods, including optical, electrical, electrochemical, mass-sensitive, magnetic, and thermometric.

One-dimensional (1D) metal oxides, among other nanomaterials, have shown promise in the production of point-of-care diagnostic devices because of their strong adsorption capabilities, high surface reactivity, improved electron-transfer kinetics, and appropriate immobilization matrices for biomolecule conjugation. Common 1D metal oxides that provide a biocompatible surface with increased biological activity include aluminum oxide (Al2O3), titanium oxide (TiO2), zirconium oxide (ZrO2), cerium oxide (CeO2), magnesium oxide (MgO), iron oxide (Fe3O4), manganese oxide (MnO), barium oxide (BaO), copper oxide (CuO), vanadium oxide (V2O5), and zinc oxide (ZnO) [4]. Because of its special qualities, including its broad band gap (3.37eV), free-exciton binding energy (60 meV), strong electrochemical characteristics, and high isoelectric point (IEP=9.5), ZnO has garnered increasing interest in biosensing [5], [6]. ZnO is a viable template for creating POC devices because of its increased electron mobility and diffusion coefficient when compared to other metal oxides. Moreover, the addition of nanoparticles to ZnO matrices enhances their electrical, optical, and surface contact properties, improving their biosensing capabilities [7]. Additionally, the electrospinning approach makes it simple to dope or incorporate the right nanomaterial to create composite or doped ZnO nanowires [8], [9].

Flexible materials like papers and polymers are currently being employed more and more as substrates for POC device fabrication since they are disposable, affordable, can be produced in large quantities, and have the potential to be integrated with wearable technology for smart POC diagnostics [10]. Because polymer-based substrates, including polyethylene terephthalate (PET), have benefits over paper-based substrates, they can withstand temperatures up to 180 degrees Celsius and enable temperature-controlled processes [11]. Additionally, liquid samples are not absorbed by polymer-based substrates, which speeds up the precise conveyance of target samples for detection [12], [13].

However, flexible substrate-based POC devices are still in the early stages of development, especially when it comes to flexible biosensors with nanomaterial integration [14]. As a result, we anticipate that new generations of flexible substrate-based POC devices, in conjunction with wireless and mobile technologies, will create a multitude of opportunities for the development of wearable, reliable, and early diagnostics devices. In this regard, the development of flexible substrate integrated biosensors based on ZnO nanowires for POC application is the main goal of this thesis.

The Latin word “sentire,” which means to identify, is where the term “sensor” comes from [15]. A sensor is a device that generates matching output signals in a measurable form in response to specific external stimuli, such as exposure to analytes, changes in ambient conditions, or modifications to some of its physical properties. Sensors are primarily divided into two categories based on their modes of operation: chemical and physical sensors. Physical sensors are sensing devices that respond to any physical qualities, including electromagnetic waves, pressure, and sound [16]. Likewise, a chemical sensor is a detecting device that responds to any chemical stimuli (such as smell and analyte exposure) and generates information that can be measured analytically [17]. The analyte interaction or stimulus at the sensor's particular reaction site causes a change in its chemical and physical characteristics, which results in a corresponding electrical signal [18]. After that, this signal is sent to a processing unit for response analysis.

The three primary components of a biosensor are as follows: i) a biorecognition layer that interacts with the target compounds in a bioalayte, such as an enzyme, antibody, cells, or tissue; ii) a transducing component that transforms the physicochemical changes brought about by biochemical interaction into an electrical, optical, thermal, magnetic, or acoustic signal; and iii) the signal processing unit, which processes the signal and transmits the information of a particular target interaction [19]. Numerous variables, including the medium's pH, temperature, pollutants, and the type and stability of the materials employed in the biosensor's construction, affect how well the biosensor performs. The primary parts of the biosensor are shown in Figure 1 [20].

The primary component of a biosensor is a bioreceptor or molecular recognition. The stability, specificity, and affinity for the target analyte are determined by the proper identification and functionalization of the biorecognition element [21]. The baroreceptor's sensitivity and selectivity stop the other substance in the biosample from interfering. The most often utilized bioreceptors include nucleic acids, enzymes, antibodies, and cells. Figure 2 depicts Schematic representation of the interaction between the target analyte and the biorecognition elements in the context of DENV virus detection.

Because enzyme-based biorecognition elements can convert catalyzed production products like light, heat, and electrons into quantifiable signals, they are more appealing for biosensing applications. The enzyme's immobilization technique, pH, temperature, and layer thickness all affect how well enzyme-based biosensors work [22]. A living cell's interaction with the extracellular and intracellular surroundings, as well as with any physiological parameters, and the transformation of the bioreporter's response into a quantifiable signal form the basis of cell-based recognition. Microorganisms, including bacteria, fungus, and cell proteins, can function as bioreceptors to identify a particular molecule or analyte. Due to signal amplification, these bioreceptors have a reduced detection limit. One of the main obstacles is immobilizing cells on the sensor surface and linking them with transducers.

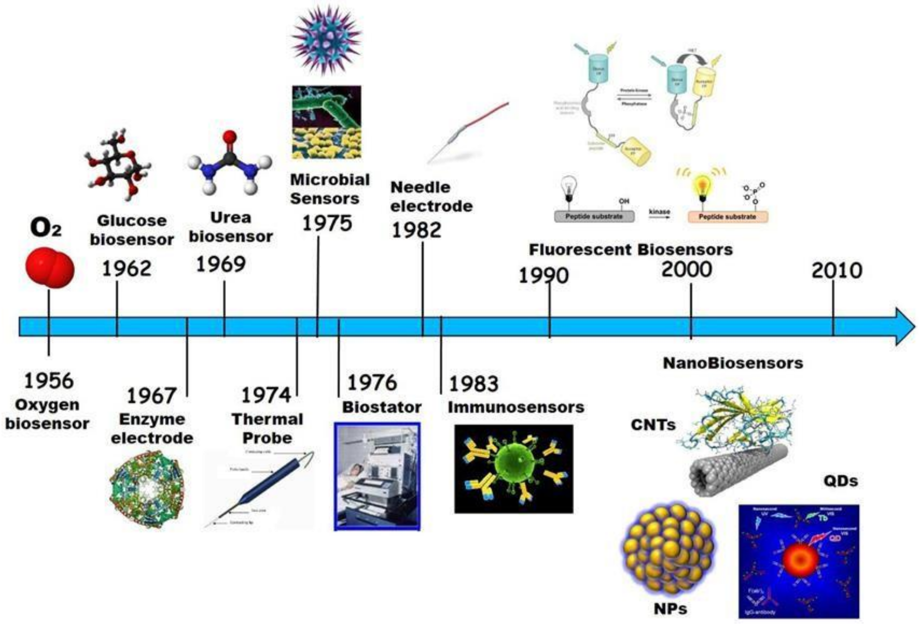

Figure 1. Biosensors with time line

The identification of nucleic acids (DNA, RNA, and peptides) depends on the structural alteration brought about by target binding. Mutagenicity, intercalations, strand breakage, or covalent or noncovalent chemical binding to the nucleic acid can all cause this structural alteration [23]. The identification of complementary strands by single-strand DNA to create double-strand DNA through hydrogen bonds and the measurement of the signal generated by this biochemical reaction form the basis of the DNA biosensor's operation. In a complex mixture, these components have a high level of selectivity towards the target species. When creating biosensors based on nucleic acid recognition elements, the immobilization step onto the sensing surface is crucial. The several biorecognition components affixed to the sensor surface and their interactions with the target analyte are depicted in Figure 2.

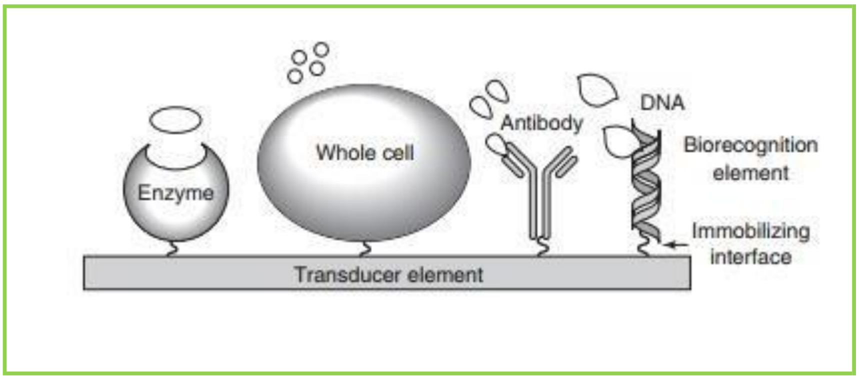

Figure 2. Interaction between the target analyte and the biorecognition elements

Invasive treatments like biopsies and imaging methods have historically been used to obtain tissue samples for analysis in cancer diagnosis [24]. Even while these techniques have been quite helpful in the identification of cancer, they frequently have drawbacks, including the requirement for specialist facilities, invasiveness, and a lengthy procedure. Consequently, there is an increasing demand for novel, non-invasive techniques that can improve early identification, allow for real-time monitoring, and support individualized treatment plans. Techniques for DNA-based analysis have become a viable way to transform cancer diagnosis. These methods offer the possibility of sensitive and specific detection by looking at the distinct genetic fingerprints found in cancer cells. It is possible to detect the presence of the disease, classify it, and track how well a treatment is working by using genetic biomarkers linked to blood malignancies. A technique that has drawn interest is the NSFET-based biosensor, which has the potential to improve DNA-based cancer diagnosis. Solid-state devices called NSFET-based biosensors may identify pH variations brought on by interactions with DNA molecules [25]. These sensors' small size, high sensitivity, quick reaction time, and label-free detection capabilities are just a few of the many benefits they have shown over traditional detection techniques. Furthermore, NSFET-based biosensors are appealing for use in healthcare applications due to their potential for point-of-care testing and real-time monitoring. Hence, this work presents a noble blood detection technique with the help of NSFET device for blood cancer detection with the target analyte.

3. DESIGN AND SIMULATION OF NSFET BIOSENSOR

Utilizing 10 nm technology, the NS-FET device boasts a three-dimensional (3D) structure. Figure 1 shows the 10 nm device from both the front and the side. With a Lg of 10 nm and a fin width of 10 nm, the NS-FET is manufactured. Twenty nanometers is the total height of the channel and the two fins, each of which is ten nanometers tall. The planned channel spacing for the NS-FET is 15 nm, and it has two channels. The three-dimensional perspective of the GAA NSFET is depicted in Figure 3(a). The code for the device is created using visual TCAD. A thickness of 5 to 9 nm is achieved by the device. The gadget has a width that varies between 10 and 50 nm. In the process of making devices using SOI technology, the Buried Oxide layer of SiO2 material is used because it provides lower parasitic capacitance, better switching, and low power dissipation. The virtual building's cross-section is displayed in Figure 3(b).

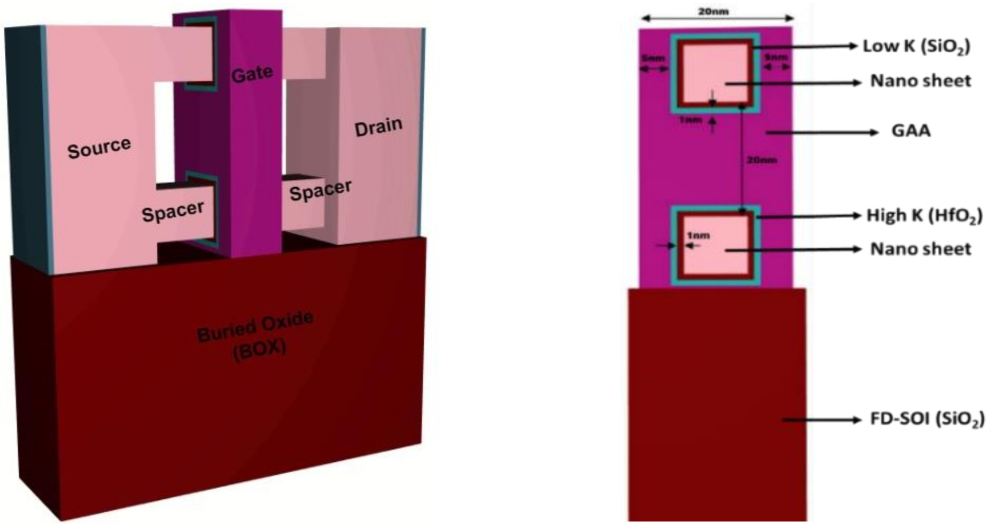

Figure 3. The three-dimensional perspective of (a) simulated device structure of NSFET device and (b) cross-sectional view of the device

Figure 3 shows the schematic of the biosensor that has been suggested, the gate-all-around nanosheet field-effect transistor (GAA NSFET). The source, drain, and gate are shown in the 3D model in Figure 3(a), along with the nanosheet channel, which is encased in the gate electrode for better electrostatic control and increased sensitivity. The gate is separated from the source and drain regions using spacers, and the device is constructed atop a buried oxide (BOX) layer that provides support to the fully depleted silicon-atop-insulator (FD-SOI) platform, further enhancing performance and minimizing leakage. Two nanosheet layers implanted between high-k (HfO_2) and low-k (SiO_2) dielectrics are shown in the cross-sectional view of the device in Figure 3(b). The sensitivity is improved by the high-k dielectric's enhancement of the gate capacitance, parasitic capacitance is reduced by the low-k dielectric, and the entire stack is wrapped by the gate in a GAA arrangement. For point-of-care biosensing applications like early dengue virus detection, this nanoscale structure shows promise for precise control and ultrasensitive detection.

To model the generation-recombination process, TCAD employs models such as the density gradient model for quantum potential correction, the Roulston model for narrow band gap modeling, and the coherent scattering and Lombardi surface mobility models for the Brillouin scattering mechanism. The simulation's device settings are displayed in Table 1.

Table 1. TCAD simulation device parameters

Region	Dimension
Gate length	10 nm
Tox (High-K)	1 nm
Tox (Low-K)	1 nm
Spacing oxide (Low-K)	10 nm
Spacing oxide (High-K)	5 nm
S/D doping concentration	1E20
Fin pitch	20 nm
Fin height	10 nm
Fin width	10 nm
Work function	4.5 eV
Box	45 nm

The NS has a thickness of 5–10 nanometers and a breadth of 10–50 nanometers. The primary objective of the research is to find the optimal dimensions by considering the nanosheet's thickness and width. The built device's simulation results form the basis for an examination of the device's numerous parameters. As shown in Figure 4, the electric field is stronger in the spacer region of the device. Less noticeable is the impact on the channel. At VDS=0.75 volt and VGS=0.7 volt, Figure 5 shows the potential variation of the simulated NSFET and the distribution of the doping concentration (Nd) of the device.

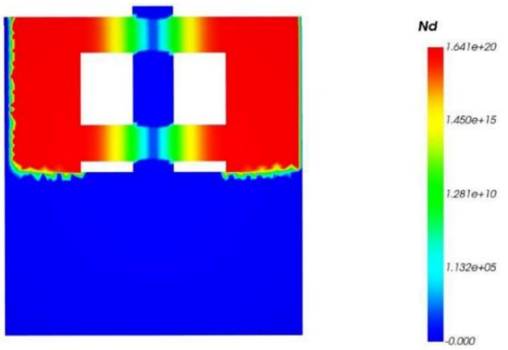

Figure 4. Doping concentration (Nd) of the simulated NSFET

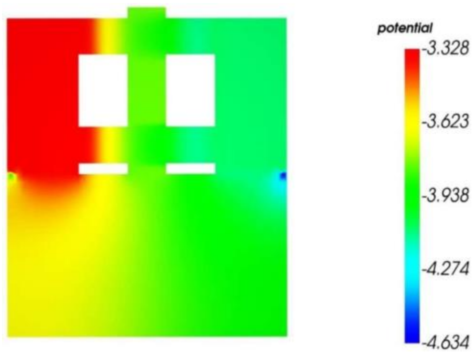

Figure 5. Potential distribution of the simulated GAA NSFET

4. RESULTS AND DISCUSSION

To diagnose the dengue virus here we designed the NSFET based biosensors. The different oxide materials are used to construct the NSFET and the best oxide is selected using the simulation results. Visual TCAD was used to simulate the transistor in order to obtain various properties, such as V-I, DIBL, and SS.

4.1. Space region materials and transistor characteristics

Figure 6 shows the results on a linear scale and Figure 7 shows the results on a logarithmic scale for better visualization of the subthreshold behavior. Both figures showcase the transfer properties of the proposed GAA NSFET device under varied dielectric conditions. When studying the sensitivity and switching capability of the transistor, these graphs are essential, especially for biosensing purposes. For the sake of consistency and thermal stability across performance parameters, the simulations assume that all spatial regions within the device keep a constant temperature of 300 K. Critical device metrics like threshold voltage, ON/OFF current ratio, subthreshold slope (SS), and drain-induced barrier lowering (DIBL) can be evaluated using the transfer characteristics, which plot the drain current versus gate voltage. The switching efficiency, leakage current, and sensitivity to small changes caused by interactions between target antigens are all determined by these factors taken together. This study aims to understand the influence of various dielectric material combinations on transfer characteristics by evaluating Air, SiO_2, HfO_2 + SiO_2, and HfO_2 + Nitride. One example is HfO_2, which has a high k value and is used to increase gate control and decrease leakage through increasing gate capacitance. On the other hand, pairings with low k dielectrics, such as air or SiO_2, have various effects on the electrostatic environment. By comparing these configurations, we hope to find the one that works best with the NSFET biosensor in terms of electrical performance and sensitivity for dengue virus detection.

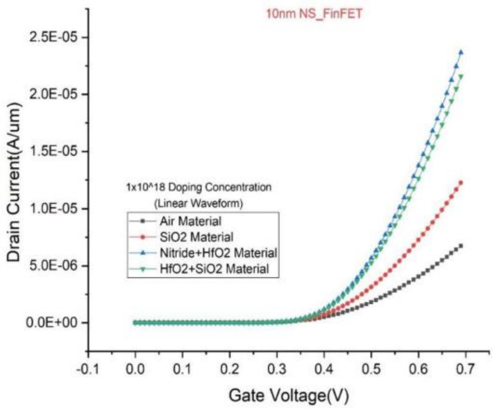

Figure 6. Properties of the proposed GAA NSFET (linear scale) for transfer (ID~VGS)

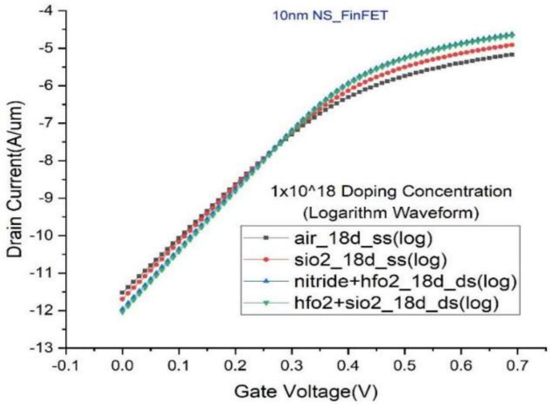

Figure 7. The proposed GAA NSFET's transfer characteristics (ID~VGS) on a logarithmic scale

The ratio of on current to off current is a useful indicator of field effect transistor (FET) electrical performance. The on-state current to the Vg, or ION, is a measure of the FET's power handling capability and an indication of how well it conducts current when turned on. Vth is an important parameter for how FET-based circuits work, how CMOS circuits are designed, and how transistors work. To optimize transistor performance in integrated circuits, one must be aware that the threshold voltage can be changed. Both virtual devices with variable space material have their threshold voltages shown in Table 2.

Table 2. Threshold voltage (Vth) for NS-FET and FINFET for variable space region

Spaces Material	NS-FET(Vth)
SiO2	0.25
Air	0.25
HfO2+SiO2	0.25
Nitride+HfO2	0.26

The ION/IOFF ratio, sometimes called the switching ratio, is a way to quantify the performance of a semiconductor device. Because it reveals how well the transistor can go from its ON (conducting) to its OFF (non-conducting) state, it plays an important role in digital circuit design and when thinking about power efficiency. The ION/IOFF ratio is the ratio of the ID (ION) when the transistor is ON to the ID (IOFF) when it is OFF.

4.2. Sensitivity study

Quantifying the sensor's ability to detect different amounts of the target (such as the NS1 antigen or the entire virus) is the goal of a sensitivity research for a Dengue virus detection NSFET device. This aids in figuring out the dynamic range, response consistency, and Limit of Detection (LOD). The sensitivity of the simulated NSFET biosensor varies with the spacer material. Air, SiO2, HfO2+SiO2, and HfO2+nitride are the four different spacers that we have used in our experiment. When it comes to the operation of the NSFET biosensor in the medical field, it is the most important consideration. Using blood as an electrolyte solution, we computed the desired model. Figure 8 displays the transfer characteristics of the NSFET biosensors with various dielectric spacers. Additionally, it is evident from sensitivity studies that HfO2+SiO2 dielectric spacer is more sensitive than other oxides for a range of 5 fg/Ml to 30 fg/Ml of NS1 antigen. The output drain current of HfO2+SiO2 spacer is 3.7 mA, which is significantly higher than that of other dielectric spacers that were simulated for the NSFET biosensor design. Air as a spacer dielectric has the lowest sensitive to NS-1 antigen.

4.3. Detection of dengue using a designed NSFET biosensor with various DENV concentrations

The NSFET biosensor demonstrated antigen and antibody response to Dengue virus DENV. The collection of patient samples, their preservation in cold storage, and their application to the NSFET biosensor are all steps in the proposed process. Finding the proper DENV antigen and antibody is the main objective of this study. Antibodies or aptamers that bind selectively to dengue virus particles or proteins (such as the NS1 antigen) functionalize the surface of the nanowire. This creates a biorecognition interface on the NSFET. The surface charge changes when the dengue virus or its protein attaches itself to the nanowire's receptor. As a result, the transistor's current flow is changed by changing the conductivity of the nanowire channel. It is possible to measure these electrical signal variations in real time and link them with the viral concentration.

Resistance from the output characteristic for different bio markers from 0 to 30 fg/mL can be used to identify dengue virus particles or proteins. The lowest biomarker solution that can identify the targeted protein is known as the limit of detection. The antibody modification was investigated for that device response. The limit of detection investigation by gathering device response is shown in Figure 9. Plotting the device's response drain current (ID) involves changing the drain voltage between -0.1 and +0.1 volts. The graphic makes it evident how much NS1 antigens were detected for the biomarker with 30 fg/mL. It is evident from the Figure 9 that the detection of antigen is high even for 30fg/mL of dengue virus particles or proteins.

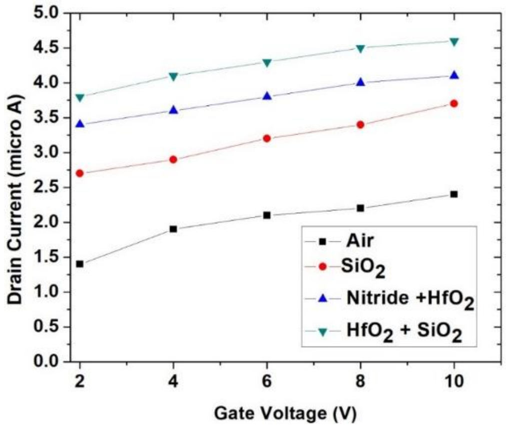

Figure 8. Sensitivity of the NSFET device to NS1 antigen with various spacer materials

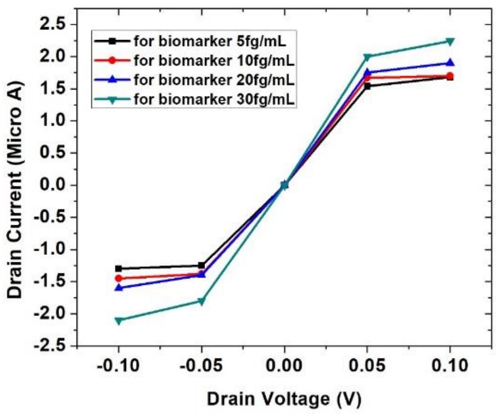

Figure 9. Limit of detection of DENV bio marker (NS1 antigen)

5. CONCLUSION

In order to detect the non-structural protein 1 (NS1) antigen, a biomarker released into the bloodstream during the early stages of dengue infection, this work presents the design and simulation of a gate-all-around nanosheet field-effect transistor (GAA NSFET) biosensor. This biosensor is seen as a highly promising solution for early dengue virus detection. Conventional diagnostic procedures have detection limits much higher than the sensor's remarkable sensitivity, which allows it to detect NS1 concentrations as low as 30 femtograms per milliliter (fg/mL). The presence of the virus changes the conductivity of the nanosheet channel, which is made possible by the label-free and ultrasensitive electrical response of the NSFET structure, which enables this performance. In order for the device to bind to the target antigens selectively, it is functionalized with dengue-specific antibodies on its surface. By modifying the current via the nanosheet, the surface charge distribution changes upon binding, allowing for real-time detection without extra processing or labeling procedures. By optimizing gate control, the gate-all-around arrangement improves the sensor's sensitivity to local electrostatic environment changes brought about by interactions between antigens and antibodies. In addition, the design is conducive to point-of-care (POC) diagnostics because it is easy to transport, deploy, and costs little, which could pave the way for extensive testing in areas with limited resources. This technology offers a quick, highly sensitive, specific, and scalable biosensing platform that addresses critical limitations in current dengue detection approaches. It will significantly impact global public health efforts against dengue disease.

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AUTHOR CONTRIBUTIONS STATEMENT

This journal uses the Contributor Roles Taxonomy (CRediT) to recognize individual author contributions, reduce authorship disputes, and facilitate collaboration.

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
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Madhavi Tatineni										✓		✓	✓	✓

C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest regarding the publication of this paper.

DATA AVAILABILITY

Data availability is not applicable to this paper as no new data were created or analyzed in this study.

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