Design and Performance Analysis of ISFET using various Oxide Materials for Biosensing Applications

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Abstract The healthcare industry is always changing because of technological breakthroughs that spur new methods of diagnosing and treating illnesses. This study investigates the development of Ion Sensitive Field Effect Transistor (ISFET) sensors for DNA-based blood cancer diagnosis. This work presents the design of a two-dimensional ion-sensitive field-effect transistor. Concentration fluctuations and transfer characteristics with different oxides are studied using blood from two electrolyte solutions. It is possible to evaluate how the modeled device can be utilized as a pH sensor or a biosensor in healthcare applications by looking at how the pH changes for different oxides. Additionally, several oxides were examined in the simulated ISFET devices' output characteristics. Blood is used as the electrolyte to study the device's sensitivity for different oxides. When pH 7.4 is considered, SiO_2 oxide is significantly more sensitive than other oxides. The resulting 2D-ISFET exhibits remarkable blood electrolyte sensitivity and holds potential as a quick detection tool for blood cancer. The results show that the ISFET possesses drain-induced barrier lowering (DIBL), greater ON-current (I_{ON}) and switching ratio (I_{ON}/I_{OFF}), and decreased subthreshold swing (SS). The pH sensor's sensitivity and the suggested equipment can detect up to 30 fg/mL of blood cancer biomarkers. An important development in technology-driven healthcare is the emergence of DNA-based blood cancer detection utilizing ISFET sensors. This opens up new avenues for improving cancer diagnosis and patient outcomes.

***Index Terms*—10nm Technology; ISFET; ISFET sensors; Blood cancer; Cancer diagnostics; LOD;2D-ISFET.**

I. INTRODUCTION

THANKS to technological breakthroughs, the healthcare sector has undergone a significant transition in recent years. These developments have opened the door for fresh methods of diagnosing, treating, and detecting illnesses, which has eventually improved patient outcomes. The identification of cancer, a vital component in reducing the worldwide cancer burden, is one area where technology has demonstrated great promise. Leukaemia, lymphoma, and multiple myeloma are blood malignancies that are among the most common and deadly cancers. Patient survival rates can be greatly impacted by timely intervention and individualised treatment plans, which depend on the early and correct identification of blood cancer. Traditional diagnostic approaches, like biopsies and imaging technologies, have been essential in the identification of cancer. But there's a growing demand for novel and more considerate methods that can support early diagnosis, allow for real-time monitoring, and offer individualised treatment choices.

Given this, DNA-based analysis methods have drawn a lot of interest due to their potential to completely transform the way cancer is diagnosed. DNA-based methods present a promising avenue for sensitive and specific diagnosis by utilizing the distinct genetic markers linked to cancer cells. Ion-Sensitive Field-Effect Transistor (ISFET) sensors have become a potential instrument for molecular detection among the different technologies used in DNA analysis. Solid-state ISFET sensors can identify pH shifts brought on

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by interactions between DNA strands. These sensors have several benefits over conventional detection techniques, such as their small size, high sensitivity, quick reaction times, and label-free detecting capability. Because of their characteristics, ISFET sensors are especially well suited for point-of-care diagnostics, personalized medication, and real-time monitoring.

Blood cancers represent a major global health concern and include a wide range of diseases, including leukemia, lymphoma, and multiple myeloma, as shown in Figure 1. The uncontrolled growth and multiplication of blood cells in these disorders cause disruptions to the body's immune system and other essential systems. Prompt and precise identification of blood malignancies is essential for efficient treatment strategizing and enhanced patient results.

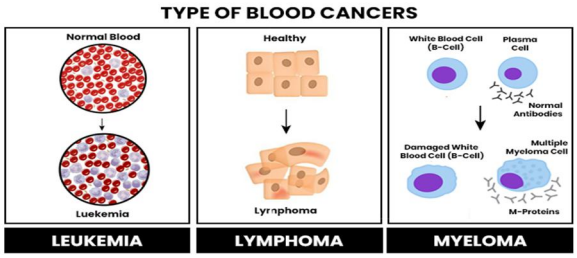

Fig. 1 Types of blood cancers [1]

Historically, the diagnosis of cancer has been dependent on intrusive methods like biopsies and imaging methods to collect tissue samples for examination. Although these techniques have been extremely helpful in the identification of cancer, they frequently have drawbacks, including requiring specialized facilities, invasiveness, and a lengthy procedure. Innovative, non-invasive methods that can improve early detection, allow for real-time monitoring, and support individualized treatment plans are becoming increasingly necessary. The blood cancer stages are depicted in Figure 2.

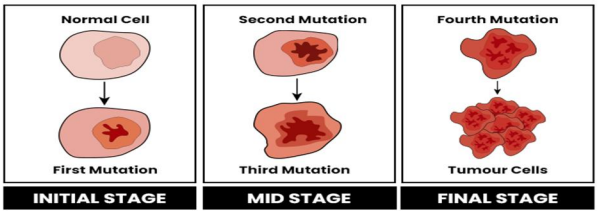

Fig 2: Stages of blood cancer [2].

Developing Ion-Sensitive Field-Effect Transistor (ISFET) sensors has drawn interest as a technique that could improve DNA-based cancer detection. Solid-state ISFET sensors measure pH variations brought on by interactions with DNA molecules. These sensors' miniaturized size, high sensitivity, quick response time, and label-free detection capabilities have shown them many advantages over traditional detection techniques. ISFET sensors are appealing for healthcare applications because they can also be used for point-of-care diagnostics and real-time monitoring [3].

ISFET sensors have been investigated in a number of studies for use in blood cancer detection and other cancer diagnostics. For example, the study showed how to use ISFET sensors to successfully detect genetic abnormalities specific to leukemia, highlighting the technology's potential for early diagnosis and disease progression tracking [4].

Li et al. conducted a study that utilized ISFET sensors to identify circulating tumor DNA (ctDNA) in the blood of patients suffering from lymphoma. The researchers attained high sensitivity and specificity in ctDNA detection, underscoring the potential of ISFET-based technologies for real-time, non-invasive monitoring of genetic alterations linked to cancer [5], [6]. Furthermore, investigated how to combine ISFET sensors with microfluidic platforms to identify numerous DNA alterations linked to myeloma. The study proved that the combined strategy was feasible for the sensitive and precise detection of genetic biomarkers, opening a possible path for early diagnosis and individualized treatment plans [7].

Furthermore, Wang et al.'s study highlighted the development of DNA-based analysis methods for cancer diagnosis. It highlighted the function of ISFET sensors in enhancing sensitivity and enabling real-time monitoring [8]. Various researchers highlighted how ISFET devices helped in biosensing platforms [9]-[14], [23], [24].

It is imperative to recognize the existing constraints and difficulties within this domain. These include the requirement for additional validation research, sensor performance optimization, detection protocol standardization, and interaction with current clinical workflows [15]- [21]. It will be imperative to address these issues to fully utilize the potential of ISFET-based technologies in clinical settings. The literature on ISFET sensors-based DNA-based blood cancer diagnosis emphasizes how important this new technology is to improving healthcare.

The experiments presented showcase the promise of ISFET sensors for the specific, sensitive, and real-time detection of genetic biomarkers linked to blood cancers. By leveraging the benefits of ISFET sensors and DNA-based analysis tools, researchers and clinicians can establish technology-driven healthcare, resulting in early identification, personalized treatment methods, and improved outcomes for patients with blood cancers. The use of ISFET sensors in DNA-based blood cancer detection is a significant advancement in technology-driven healthcare, as it provides new opportunities for enhancing cancer diagnosis and patient outcomes.

II. Gate Oxide Materials

The sensitivity and performance of the sensor are directly impacted by the gate oxide material selection in ISFETs (Ion-Sensitive Field-Effect Transistors). The targeted pH measurement range, stability, desired sensitivity, and manufacturing compatibility all play a role in the gate oxide material selection process. As table 1 illustrates, each material has benefits and drawbacks, and scientists are still

looking into new gate oxide materials to enhance ISFET performance.

Material	Advantages	Limitations	Description
Silicon Dioxide (SiO_2)	- Good electrical insulation properties. - High stability. - Compatible with standard silicon fabrication processes.	- Limited sensitivity compared to high-k dielectrics. - Lower dielectric constant.	The most commonly used gate oxide material in ISFETs. It is grown through thermal oxidation of the silicon substrate.
Titanium Dioxide (TiO_2)	- High dielectric constant for increased sensitivity. - pH-sensitive properties. -Potential for biofunctionalization.	- Lower stability compared to SiO2 and high-k materials. - More complex fabrication process	Titanium dioxide gate oxides can be prepared using techniques like sol-gel deposition or ALD. They exhibit unique properties suitable for ISFET applications.
Silicon Nitride (Si_3N_4)	- Higher dielectric constant compared to SiO_2. - Improved sensitivity. - Good electrical insulation properties	- Slightly lower stability compared to SiO2. - More challenging fabrication process	Silicon nitride gate oxides are typically deposited using techniques like CVD or PECVD.
Hafnium Dioxide (HfO_2)	- High dielectric constant for enhanced sensitivity. - Improved signal-to-noise ratio. - Suitable for advanced CMOS fabrication processes	- Requires specialized deposition techniques (ALD) - Potential reliability issues.	Hafnium dioxide gate oxides are deposited using techniques like ALD. They offer high-k properties and have gained attention in recent years.
Magnesium Oxide (MgO)	- High dielectric constant for improved sensitivity. - Enhanced electrical properties. - Compatible with standard silicon fabrication processes	- Limited stability at extreme pH ranges. -Potential issues with moisture absorption	Aluminum oxide gate oxides can be deposited through techniques like ALD or PVD. They offer high-k properties and are widely used in ISFETs.

III. Design of 2D ISFET

Under particular conditions, the design of a two-dimensional Ion Sensitive Field Effect Transistor (2D-ISFET) can be realized. The reference electrode is where the gate voltage is placed. The electrolyte is applied to the oxide surface during the device design process. A 10 mV drain voltage is supplied while the source is grounded. First, we assess the sensitivity after adding water to the electrolyte tank. With the bulk electrolyte's pH (pHb) adjusted and the drain voltage stable, we can see the structure's surface electric potential. Since there is a correlation between variations in pHb and doping concentrations, the doping concentrations at the source and drain areas are proportionate to the variations in pHb. Figure 3 illustrates the design of a two-dimensional ISFET [20] using the COMSOL Multiphysics programme. Table 2 lists all the simulated device parameters and dimension of the simulated device.

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Table 2 Simulated ISFET device parameters and dimensions.

Device Parameter	Dimension
Width	500 μm
Length	20 μm
Gate dielectric thickness	150 Å
Sheet resistance (source/drain region)	1.7 Ω⁄square
Doping of the substrate	1.3E+15 cm^{-3}
Depth of the junction	1.2 μm
GAMMA	0.3
Lateral diffusion	0.96 μm

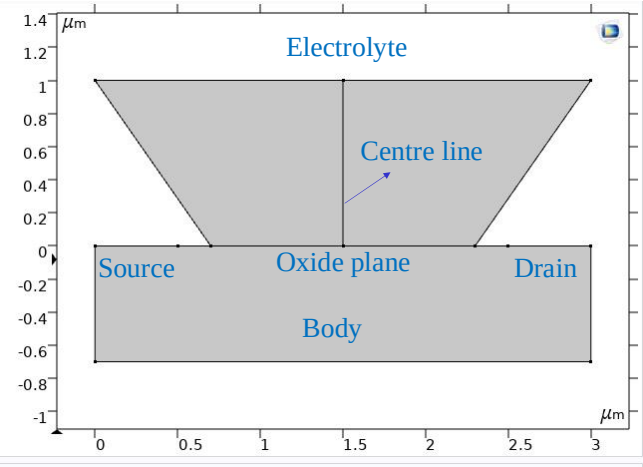

Fig. 3 Simulation model of 2D-ISFET sensor for detection of Blood Cancer.

Furthermore, the ISFET DC performance was investigated using the Cogenda Visual TCAD simulator. The dimensions and features of the devices used in the simulations are listed in Table 3. The Lombardi mobility model, Shockley-Read-Hall (SRH), and Auger recombination models are all used in the simulation to represent minority carrier recombination. The simulation uses the QDDM model from Visual TCAD, which will consider the quantum effects at lower nodes.

As the performance demonstration for ISFET is carried out using 3D Cogenda Genius TCAD, the models are considered as given in [22]. The following physical models are included with different conditions as mentioned below:

The low-field mobility model, called the Philips Unified Mobility model, considers how different types of impurities, carrier-carrier scattering, and carrier screening affect mobility.

Table 3 Device Parameters and Dimensions.

Device Parameter	ISFET
Gate Length (L_G)	32 nm
Channel height	54 nm
EOT	0.78 nm
Spacer dielectric	Nitride, Air, SiO2, and hybrid spacer
Source/drain Length (L)	24 nm
Source/drain doping	2×10^{18} cm^{-3}
Channel doping	1×10^{15} cm^{-3}
Height of the gate	120 nm
Gate work function	4.685

IV. Result And Discussions

A. DC Performance Study of ISFET

The I_D-V_{GS} characteristics of ISFET in log and linear scale at $|V_{DS}|$ = 0.7 V and $|V_{DS}|$ = 0.04 V. In Figs. 4 and 5, drain current shows the transfer characteristics in linear and logarithmic scales, respectively. A range of spacer materials are considered at a fixed temperature of 300 K. V_{th}, I_{ON}/I_{OFF}, DIBL, and other important factors are needed to estimate the device's performance. The transfer properties for SiO2, HfO_2+SiO_2, air, and HfO_2+nitride are measured. The ratio of I_{ON} to I_{OFF} is a critical statistic for assessing the electrical performance of FET devices. The on-state current, or I_{ON}, gauges the device's capacity to manage power when the FET is activated.

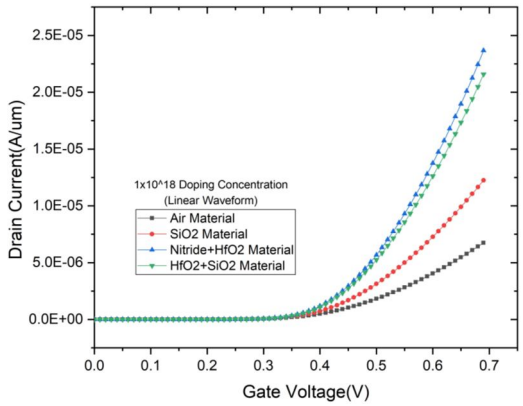

Fig.4 The Linear waveform for the ISFET in single-*K* and dual-*K* spacer.

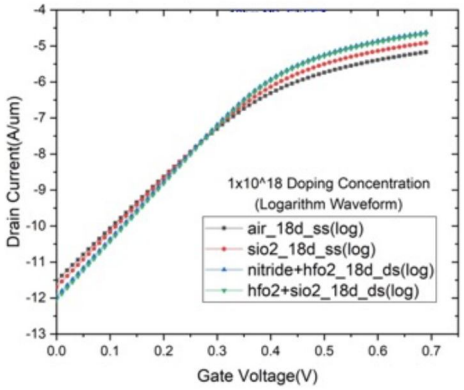

Fig.5 The logarithmic waveform for the ISFET in single-*K* and dual-*K* spacer.

SS and DIBL are the fundamental DC metrics used to evaluate subthreshold performance at lower technology nodes. The expressions for DIBL and SS are shown in equation 1 and 2 respectively.

$$DIBL\ (mV/V) = \left|\frac{V_{th1}-V_{th2}}{V_{DS1}-V_{DS2}}\right| \quad (1)$$

$$SS = \left[\frac{\partial log_{10} I_D}{\partial V_{GS}}\right]^{-1} \quad (2)$$

Using eq. 1, where N is the number of channels and V_{th1} and V_{th2} are the threshold voltages extracted at VDS of 0.7 V and 0.04 V, respectively, at $N\times(W_{eff}/L_G) \times 10^{-7}$ A, the constant current technique is utilized to find the DIBL. The main performance attributes of the suggested ISFET device are shown in Table 4.

Table 4 DC Performance metrics of the proposed ISFET.

Parameter	Simulated results
Threshold Voltage	0.36 V
On Current	2.26×10^{-6} A
Off Current	$1.04\text{x}10^{-11}$ A
On / Off Current Ratio	$2.17\ \text{x}10^{5}$
SS	57 mV/dec
DIBL	68 mV/V

B. Surface Electric Potential Study

The surface electric potential is one of the main prerequisites for a certain pH value. Blood electrolyte was utilized to replicate the 2D-ISFET. Since blood has a pH of 7.4, the electrolyte pH was set to 7.4 throughout the simulation. The surface electric potential of 2D-ISFET was studied with a drain voltage of 1 volt. Figure 6 shows that the doping concentration at the drain is derived as blood electrolytes on the 2D-ISFET device's surface. Furthermore, electric potential concentration was studied for various dielectric materials at the oxide plane. The blood sensor using 2D-ISFET was simulated for various oxide dielectric oxide materials.

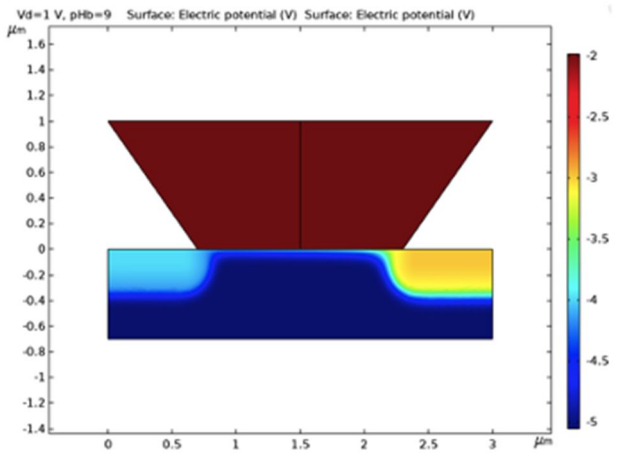

Fig. 6 Surface electric potential of blood electrolyte at drain voltage 1 volt.

C. Transfer Characteristic

The gate voltage is applied to the front gate of the ISFET design model. The drain current is the functional parameter for the appropriate gate voltage. The gate voltage is applied over the oxide surface of the conductor, which functions as the electrolyte in the proposed arrangement. The transfer characteristic for various oxides when blood is employed as an electrolyte solution is shown in the accompanying graph. SiO_2, a traditional dielectric oxide, has a larger drain current than other oxides, as can be seen from Figure 7's transfer characteristic. While Tantalum oxide (Ta_2O_3) has a notable increase, its drain current is only half that of SiO_2 oxide. As seen in Fig. 7, other oxides such as zinc oxide (ZnO) and magnesium oxide (MgO) have extremely small drain currents with varying gate voltages.

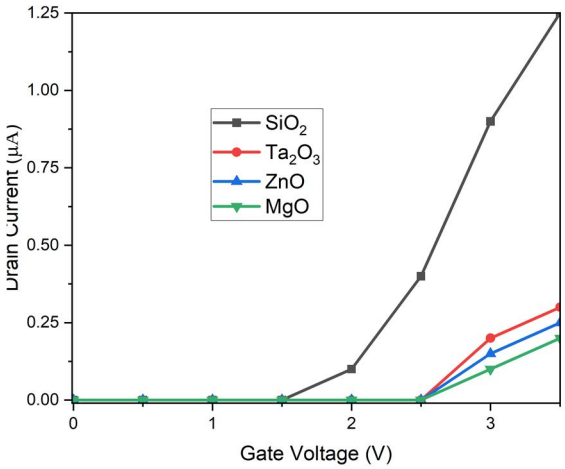

Fig. 7 Transfer Characteristics of 2D-ISFET for blood as electrolyte.

D. Output Characteristics with Varying Oxide for blood Electrolyte

Blood was used as the electrolyte in studying the developed 2D ISFET's output characteristics. An ISFET with varied SiO_2, Ta_2O_3, ZnO, and MgO oxides was simulated for drain

voltage variations ranging from 0 to 1.4 volts. Tantalum oxide has a higher current than other oxides, as the Id v/s Vd curve makes abundantly obvious, as illustrated in Figure 8. When blood is used as the electrolyte, SiO_2 likewise exhibits a noticeably higher drain current for the variable drain voltage Vd. Thus, it may be concluded that SiO_2 is a superior electrolyte for ISFET devices.

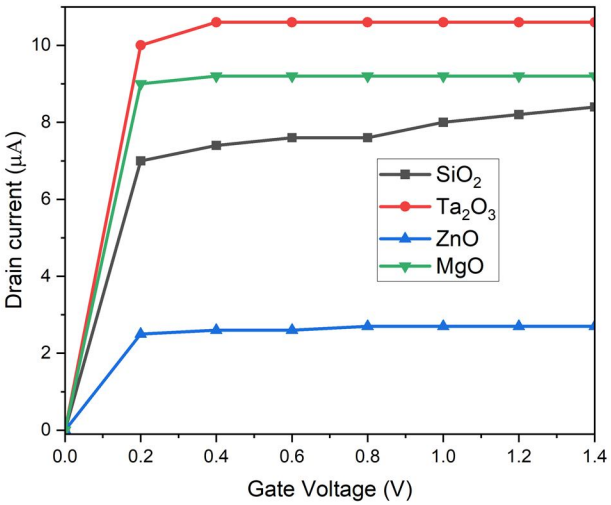

Fig. 8 Output Characteristics of 2D-ISFET for blood as electrolyte.

E. Sensitivity Study for Varying pH

The simulated 2D-ISFET's sensitivity changes when the oxide surface changes. We have included four distinct oxide layers in our experiment: Ta_2O_3, SiO_2, ZnO and MgO. It is the most crucial factor to be considered for the ISFET's functioning when used as a biosensor in medicine. We calculated the intended model while accounting for blood as electrolyte solutions. Figure 8 shows the output voltage for different pH values, which is the sensitivity of the ISFET sensor. Furthermore, the sensitivity study clearly says SiO_2 oxide has better sensitivity than other oxides for different pH values. SiO_2 oxide has an output voltage of 3.5 mV, which is comparably very high than other oxides simulated for the designed ISFET. Hence, the designed pH sensor can be used for blood cancer.

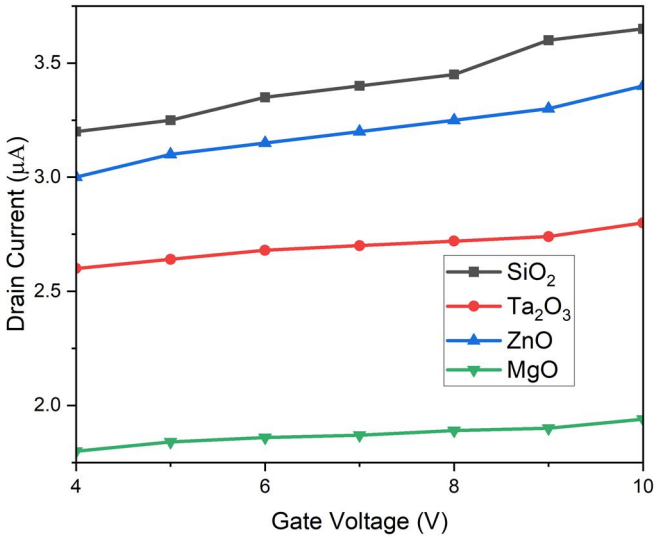

Fig. 9 Sensitivity of pH sensor.

Figure 9 depicts the sensitivity of the device for various pH for various materials.

F. Blood Cancer Detection using a designed 2D ISFET pH Sensor

Antigen and antibody reaction with Leukemia, lymphoma and myeloma was established in the 2D-ISFET device. The suggested methodology comprises several stages, including patient sample collection, preservation in cold storage, and application of the samples on the ISFET-designed biosensors. The primary goal of this investigation is to identify blood cancer cells in human blood. The following is the general idea behind myoglobin detection using an ISFET-based biosensor: a sensor that uses the electrolyte plane of the device can detect Molecules that are adhered to or separated from a surface. The biosensor's surface resistance changes due to the attachment and dissociation of one electron from the oxide plane. Blood cancer can be found on resistance from the output characteristic for varying biomarkers from 0 to 30 fg/mL. The limit of detection is the limit to which the lowest biomarker solution can detect the cancer cells. For that, device response was studied for antibody modification. Figure 10 depicts the limit of the detection study by collecting device responses. This device's response drain current (ID) is plotted by varying drain voltage from -0.1 volt to +0.1 volt. From the plot, the level of detection of blood cancer cells for the biomarker is 30 fg/mL.

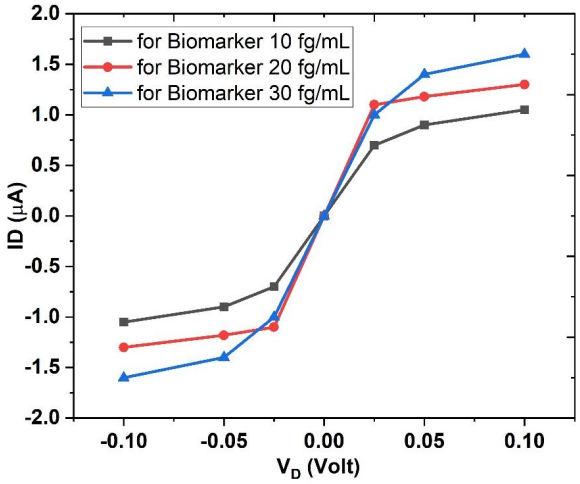

Fig. 9 Limit of Detection of blood cancer biomarker.

III. Conclusions

This work presents the design of a two-dimensional ion-sensitive field-effect transistor. Blood from two electrolyte solutions investigates concentration variations and transfer properties with different oxides. Examining how the pH changes for various oxides makes it feasible to assess how the modeled device can be used as a pH sensor or a biosensor in healthcare applications. The output characteristics of simulated ISFET devices were also examined for various oxides. The device's sensitivity is investigated for different oxides using blood as the electrolyte. Considering pH 7.4, SiO_2 oxide has noticeably higher sensitivity than other oxides. The resulting 2D-ISFET exhibits extremely high blood electrolyte sensitivity and has the potential to be a strong candidate for the quick diagnosis of blood cancer.

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