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Design and Simulation of Graphene-Based Biosensor for SARS-CoV-2 Variants Detection

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Abstract:
In December 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in Wuhan City, China, and disseminated globally. The fatality rate increased until vaccines were used to control the infectious and morbidity rate worldwide. Key lessons learned from this 3-year pandemic emphasize the imperative to continually enhance diagnostic technologies for the specific detection of emerging viral infections. The COVID-19 pandemic demonstrated the emergence of multiple variants resulting from mutations in SARS-CoV-2, notably the recent and highly transmissible, Omicron variant, posing challenges in detecting asymptomatic cases. National pandemic prevention and control would be significantly hampered without early precautions. Therefore, this study proposed to design and simulate the graphene field effect transistor for the SARS-CoV-2 variants detection biosensor. Using COMSOL Multiphysics 5.6 software, the model incorporates two sets of Graphene Field Effect Transistors, each coated with different antibodies, anti-Delta and anti-Omicron antibodies. Upon the exposure of Omicron variant to the sensing area, the Graphene Field Effect Transistor containing anti-Omicron antibodies (Ab2E8a) will undergo color contour changes that indicates interaction on the graphene layer which is the binding of Omicron antigen with anti-Omicron antibodies. This simulation demonstrated the capability of the Graphene Field Effect Transistor biosensor to detect multiple SARS-CoV-2 variants. Hence, this biosensor offers a promising tool for COVID-19 control through rapid and precise early-stage diagnosis of COVID-19.
Keywords: COVID-19; Biosensor; Graphene; COMSOL; Antibodies

1. INTRODUCTION

The Coronavirus disease 2019 (COVID-19) pandemic, as of June 2023, has recorded over 767 million confirmed cases and more than 6.9 million deaths. The causative virus, SARS-CoV-2, is found to be mutating continuously and resulting in new variants which includes the most recent ones, Delta and Omicron. The new variants exhibit increased infectiousness with less symptoms or are asymptomatic. The use of newly developed vaccines has effectively controlled the infection rate and reduce global mortality. However, the on-going mutations of SARS-CoV-2 underscore the need for advanced technology in rapidly diagnosing viral infectious strains. Therefore, this study proposes to design and simulate a graphene-based biosensor for SARS-CoV-2 variants detection.

Graphene field effect transistor biosensor is found to be successfully employed for the rapid detection of SARS-CoV-2 (1). With favorable physical and chemical properties, graphene-based materials are suitable to be used in the development of super-sensitive biosensors. There are numerous studies that have explored graphene-based materials usage in developing highly sensitive biosensors including the detection of bacteria such as *Escherichia coli* and *Salmonella typhimurium* (2). The versatility extends to the detection of Zika virus, cardiovascular disease, and hormone proteins using the graphene immunosensor.

In this study, the graphene-based biosensor that uses graphene field-effect transistor, for COVID-19 detection is optimized using Ab2E8a and Ab2E8b antibodies as the antibodies can detect Omicron and Delta variants respectively. This study provides information on how graphene field effect transistor can contribute to the early diagnosis of Delta and

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Omicron variants through detecting the presence of different SARS-CoV-2 variants. This suggests the potential use as a screening device, especially for asymptomatic individuals that eventually reduce SARS-CoV-2 transmission.

2. METHODOLODY

2.1 Designing Graphene Field Effect Transistor Biosensor

Figure 1a shows the overview of the Graphene Field Effect Transistor (GFET) setting. The most important part is the sensing platform that is made up of graphene coated filter paper. The graphene coating is highly contributing to electrical conductivity to the biosensor. On top of this filter paper and graphene-based thin film, gold electrodes, which are known to possess high electrical conductivity and good chemical stability (3), were placed to further improve the electrical read out (Figure 1b). The presence of the receptor binding domain (RBD) in the spike protein of SARS-CoV-2 is detectable when electrons accelerated by the gold are broadcast over the thin-film sensing platform, resulting in an increased output signal from the platform.

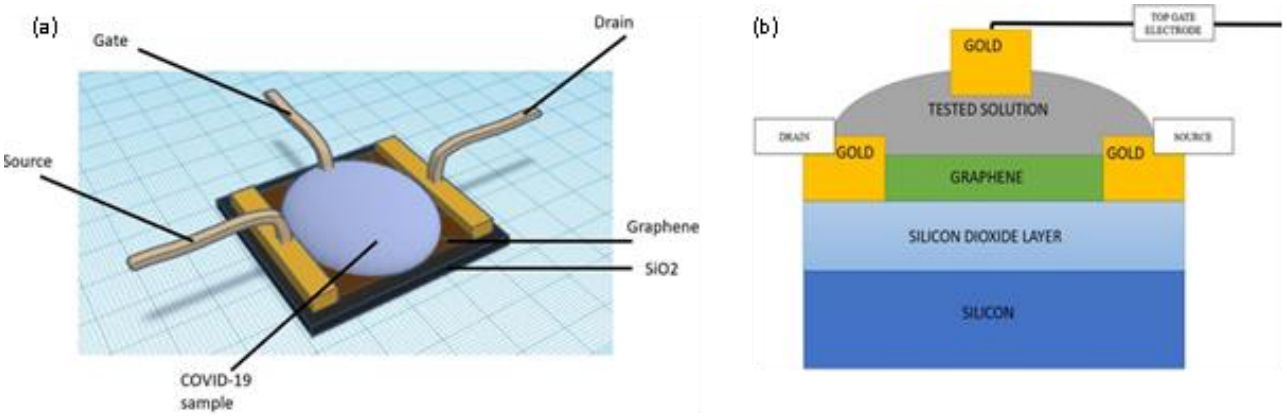


Figure 1. Schematic overview of (a) GFET transistor on the left and (b) Design structure of GFET on the right.

The GFET was designed and simulated using the semiconductor module from COMSOL Multiphysics. The semiconductor module in the software was used to allow analysis of the transfer and drain characteristics. The GFET parameters used in this study were adapted from GFET structure by Krishna et al. (4) and as indicated in Table 1. The final design is as depicted in Figure 1b. There were two GFET sensing platforms, and both were included in the design to fulfill multiple antibodies immobilization on each graphene surface. The antibodies were named Ab2E8b (anti-Delta) and Ab2E8a (anti-Omicron).

Table 1. GFET parameter (4).

Device parameter	Value
Thickness of graphene	0.35 nm
Thickness of silicon dioxide layer	6 nm
Dielectric constant/ Relative permittivity	4.2
Thickness of gold contact	50 nm
Thickness of Silicon	300 nm
Gold contact length	500 nm
Drain voltage (Vd)	10 mV
Gate voltage (Vtg)	0 V
Source voltage (Vs)	0 V
Width (W)	4 μm
Donor Concentration	1×10^{18} cm^{-3}

Other than the sensing platforms, the casing and electrode strips of the biosensor were designed using SolidWorks software. The design was inspired by the available glucometer which also uses electricity to supply voltage power for conducting the glucose test.

2.2 Simulation of GFET Biosensor to Detect Multiple Variants by using COMSOL Multiphysics

In this study, COMSOL 5.6 was used to prepare the Model Builder user interface that consists of all the steps in the modelling workflow. COMSOL Multiphysics is particularly well-suited for biosensor simulation due to its multiphysics

approach, specialized modules, and user-friendly interface designed to cater to the complexities of biological and biochemical systems.

Multiple variants detection GFET biosensor were simulated using two different antibodies which were Ab2E8b (specifically for capturing the RBD on SARS-CoV-2 Omicron) and Ab2E8a (specifically for binding RBD on SARS-CoV-2 Delta). The equations of formation of the antigen-antibody complexes are as following:

$$Ab2E8b(ads) + AgO = Ab2E8aAgO \quad (1)$$

$$AAb2E8b(ads) + AgD = Ab2E8bAgD \quad (2)$$

For this experiment, a 3-dimensional (3D) model design of the GFET biosensor was used to simulate the flow of the analyte whereas 2-dimensional (2D) model design of the sensing area was used to simulate the electron transfer. All the parameters were set accordingly before beginning the simulation. The 2D model provides functional characteristics of the GFET biosensor as the analyte flowing uniformly. Investigation of the particle transport and reactions within the sensing platform areas were allowed. Several simulation fields including semiconductor module, chemistry interface, transport of diluted species, laminar flow and surface reaction were also performed in this study.

2.2.1 Semiconductor Module

The Semiconductor Module (Figure 2a) was used to simulate semiconductor devices using the standard drift-diffusion method, the density-gradient formulation, the Schrodinger equation, or the Schrodinger-Poisson equation. As a result, it gave specific tools for fundamental physics investigation of semiconductor device functioning. It could simulate bipolar transistors, metal-semiconductor field-effect transistors (MESFETs), metal-oxide-semiconductor field-effect transistors (MOSFETs), insulated-gate bipolar transistors (IGBTs), Schottky diodes, and P-N junctions. MOSFETs include graphene field-effect transistors.

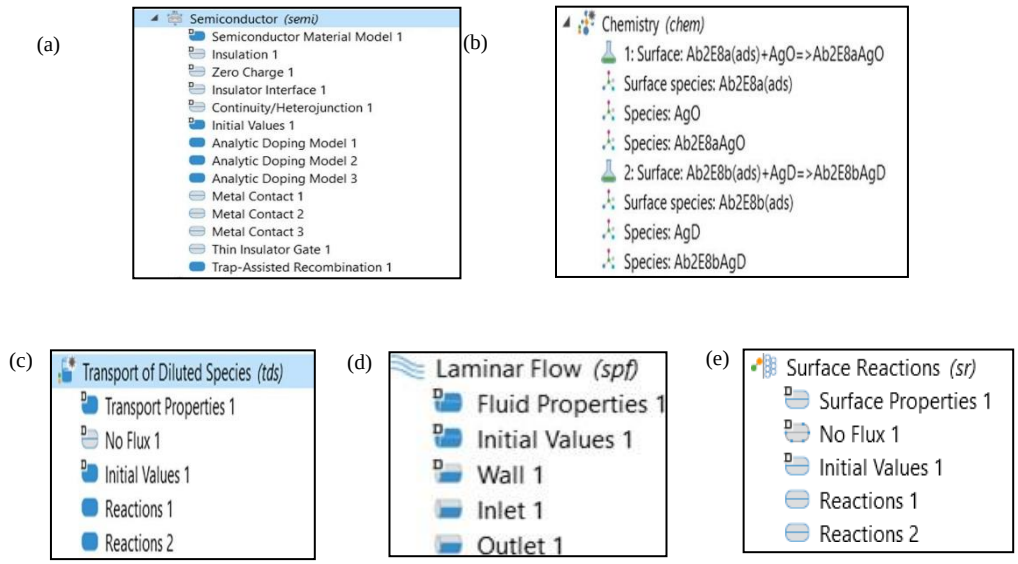


Figure 2. Simulation fields conducted using COMSOL 5.6 including (a) semiconductor module, (b) chemistry interface, (c) transport of diluted species, (d) laminar flow, and (e) surface reaction.

2.2.2 Chemistry Interface

The chemical interface (Figure 2b) can be used to generate reaction kinetics as well as compute transport and thermodynamic parameters for usage in 1D, 2D, and 3D models. It may be found in the Chemical Species Transport section and when creating a physics interface. Simulations may be used to simulate, investigate, and optimise a specific chemical species or reaction system. It also collects all mixture variables and attributes to be used in a space-dependent model. As a result, it assists engineers to understand the chemistry, ideal size, and design of the system, as well as how it interacts with other physics that may be present virtually.

The variables are derived from the parameters of the species and the reaction. User-defined expressions can overwrite all preset constants and expressions. As a result, two equations have been given as the chemical reaction that will occur on the surface of graphene in this study. The first equation (equation 1) happened on the first GFET sensing region, which involves the reaction of Ab2E8a interacting with RBD-Omicron antigen to form the antigen-antibody complex. The second equation (equation 2) represents the reaction of Ab2E8b interacting with RBD-Omicron antigen to form an antigen-antibody complex, which took place on the second GFET sensing region.

2.2.3 Transport of Diluted Species

The Interface for the Transport of Diluted Species provides a predefined modelling environment for exploring the development of chemical species carried by diffusion and convection. The physical interface presupposes that all species present are diluted, which means that their concentration is low when compared to a solvent fluid or solid. When the concentration of the solvent exceeds 90 mol percent, the combination is called dilute. Because of the dilution, mixture parameters like density and viscosity can be the same as those of the solvent. Fick's law regulates the diffusion of solutes, dilute mixes, or solutions in this study. Ionic migration, also known as electrokinetic flow, is used to compute the concentration field of a dilute solute in a solution.

The Transport of Diluted Species interface (Figure 2c) supports the simulations of chemical species transport by convection, migration, and diffusion in 1D, 2D, and 3D models. In addition, all types of chemical reactions influence the species transport in porous media. The reactions represent change in species concentration per unit volume porous medium per time. Reaction terms are used on the right-hand side of the governing equation to represent these processes. Throughout transportation, there were two reactions involved that respected to the two chemical reactions.

2.2.4 Laminar Flow

The Laminar Flow interface (Figure 2d) was used to compute the velocity and pressure fields for the flow of a single-phase fluid in the laminar flow regime. A flow remains laminar as long as the Reynolds number is below a certain critical value. At higher Reynolds numbers, disturbances tend to grow and cause transition to turbulence. The equations solved by the Laminar Flow interface are the Navier-Stokes equations for conservation of momentum and the continuity equation for conservation of mass. The Laminar Flow interface can be used for stationary and time-dependent analyses. The inlet and outlet are assigned as the fluid enter and exit the GFET sensing area.

2.2.5 Surface Reaction

The Surface Reactions Interface (Figure 2e) solves for an arbitrary number of surface concentrations and bulk concentrations. It refers to the species in the solid material that constitutes the bulk of the reactive surface. It serves to model surface and bulk species chemical reactions on the boundary. The surface reaction 1 is on the first GFET whereas the surface reaction 2 is on the second GFET.

2.2.6 Overall Model

There were 2 design models which are 2D and 3D models. Each of the models consisted of a different module since both will undergo different simulation fields to get their respective results output (Figure 3). After completing design, the physics parameter needs to be set up and run the simulation to get the output results.

3. RESULTS AND DISCUSSION

3.1 GFET Biosensor Design

The suggested outer design of the GFET Biosensor is shown in Figure 4. The casing that has similar size and function as glucometer is suitable to be used with the GFET as the casing can supply voltage to the electrode strip specifically at the sensing area to undergo the test. There are six electrodes connected to the casing since there are two GFET models in the sensing area. Each of the GFET consists of three electrodes which are the drain, source and top-gate electrode.

The GFET sensing area consisted of several layers which are graphene, silicon dioxide and silicon. The electrode was made up of gold nanoparticles that function as a probe for the electron movement from drain to source. There are 2 sets of GFET sensing area where one of the sets indicated the presence of Delta variants while another set was used to indicate Omicron variant. The 2D GFET model and 3D GFET model were designed using the same parameter.

3.2 Simulation of GFET Biosensor with Multiple Variants Detection by Using COMSOL Multiphysics

Based on Figure 5, the dark blue colour contour indicates that there is no velocity on that area. Hence, we can infer the absence of liquid movement in the separated channel at the middle of the GFET. So, the concept of designing two GFET with separated channels for the detection of two variants was a success since it helped prevent the liquid flow between the first GFET and the second GFET. Hence, the electricity or electron that flows in each set of GFET electrode would not be interrupted. Additionally, the liquid was aimed to flow in the same velocity for the entire area, but we were unable to achieve it.

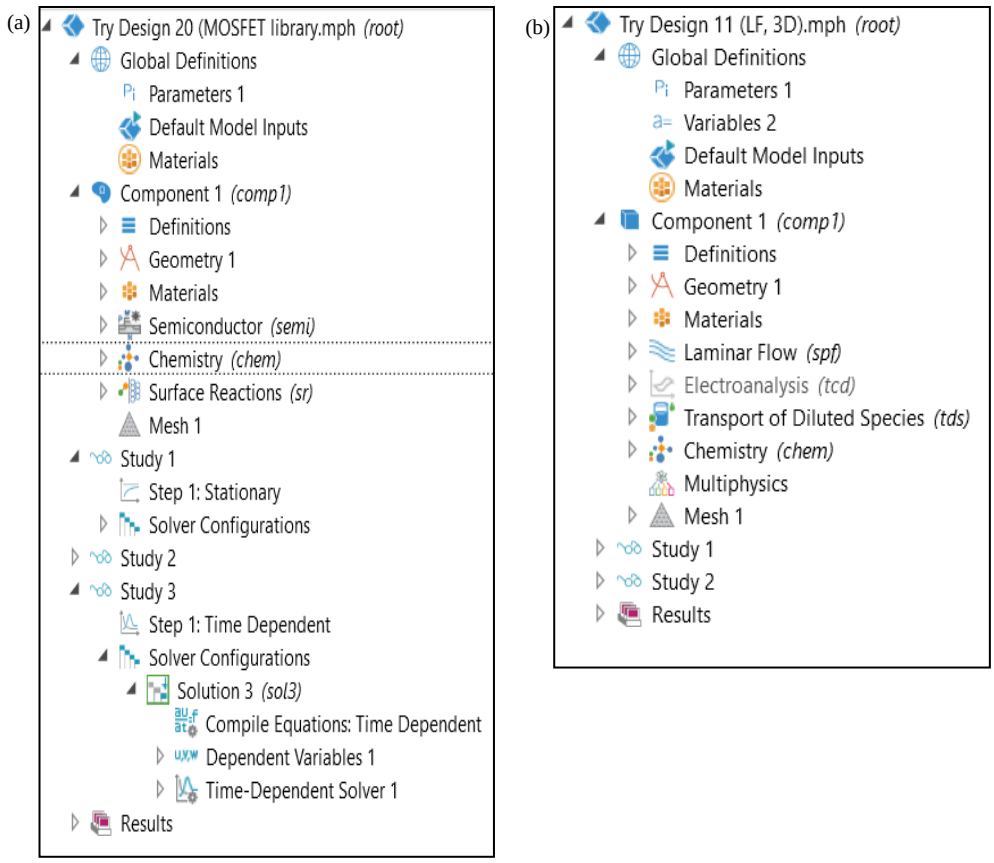


Figure 3. Overall module involved for (a) 2D model and (b) 3D model.

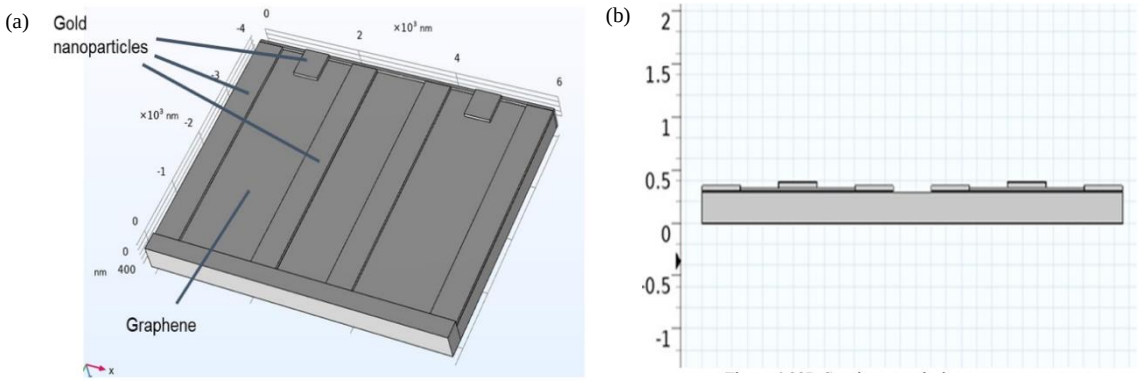


Figure 4. Sensing areas designed for (a) 3D and (b) 2D models.

The results of the simulation using the semiconductor module as the primary simulation field are shown in Figure 6. Based on both sets of results, there were differences in area of surface electron diffusion upon introducing different variants. Surface diffusion refers to a process of absorption of molecules within the pores and emigrated from one side to the other side of the membrane. The quantity of transported electrons depends on the amount of adsorption and mobility of the diffusive components. The red colour contour refers to high electron flow from drain to source, which was indicating the antigen-antibody complex. Thus, this complex enhanced the conductivity of the graphene thus facilitated electron transfer from drain to source.

Based on Figure 6b, the electron diffusion was more concentrated in the first GFET where the graphene layer was coated with Anti-Delta antibodies (Ab2E8b). In the presence of the Delta antigen in the solvent, an antigen-antibody complex form with the Ab2E8b antibodies. This results in electron movement from the source to drain for the first GFET that leads to an increase in electron diffusion.

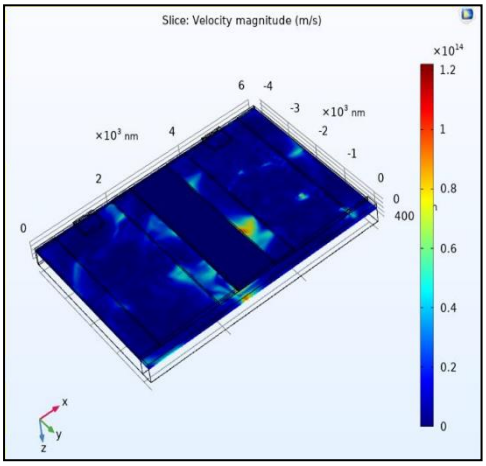


Figure 5. Velocity of the GFET design.

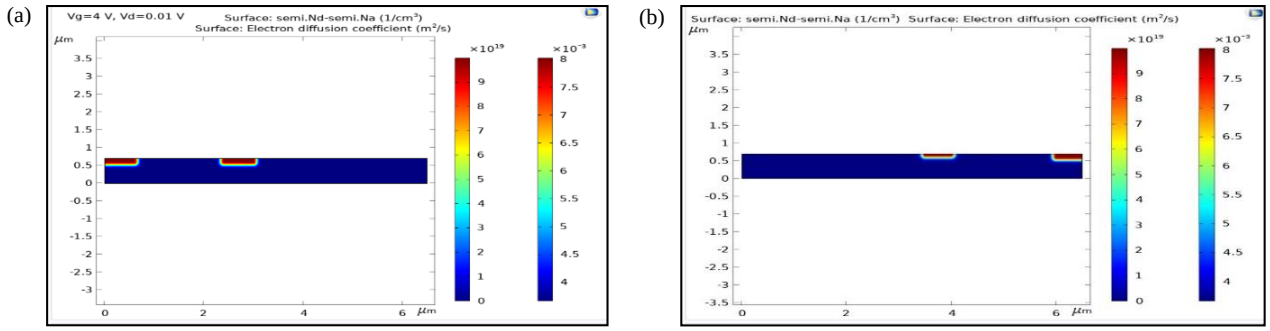


Figure 6. Electron diffusion when introduced with (a) RBD-Delta antigen and (b) RBD-Omicron antigen on the GFET sensing platforms.

3.3 Working Mechanism of the GFET Biosensor

The working principle of the GFET biosensor was based on the field effect concept which enables to control the conductivity of the semiconducting material in the channel region. The conductivity of the GFET changes according to the charged particles that are attached to it. For example, the depletion of charge carrier occurs in the complete cross-section of GFET when a negatively charged antigen molecule is attached to the surface, resulting in a decrease of electrical conductance and the drain current. Similarly, when a positively charged protein binds to a GFET biosensor, the conductance increases. These phenomena were demonstrated in COMSOL Multiphysics through the chemical reaction and transport of diluted spices modules, as well as the semiconductor module.

The antigen in a solution would be added to the immobilized antibodies to form complexes and the chemical reaction is as stated in equations (3) and (4),

$$[k]_{Ag} + [k]_{Ab} \Leftrightarrow [k] \qquad (3)$$

where $[k]_{Ag}$ is the concentration of SARS CoV-2 antigen (for each Variants); $[k]_{Ab}$ represents the concentration of 2E8mAb or CB6 antibodies; [k] signify the complex concentration.

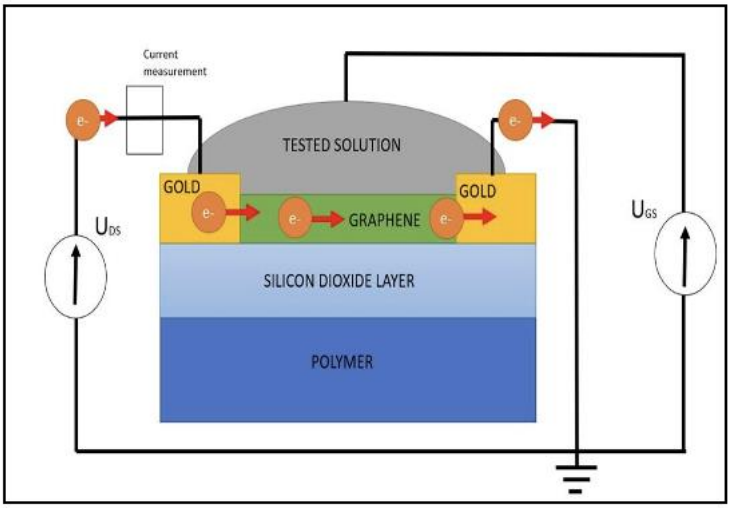
Next, for the functionalization of the GFET, it involved the receptors that are attached to the sensors for detecting specifically charged biomolecules, the RBD protein of COVID-19 Delta and Omicron variants. Interaction between the receptors and the target molecules would generate an electric field on the surface of the GFET biosensor that led to considerable change in the conductivity of the biosensor. Hence, functionalization of GFET was one of the most essential factors in identifying target particles (SARS-CoV-2 Variants).

The electrical characteristics of the GFET biosensor were calculated using equation (4) from Wu et al. (5) in which the ΔI_{ds} represent the source-drain current change; ΔN change in the carrier density; w denoted as the width of the graphene channel; l is the length of the graphene channel; e represents the elementary charge, which is (1.602×10^{-19} C); μ is the carrier mobility; V_{ds} is the source-drain voltage.

$$\Delta I_{ds} = \frac{w}{l} \cdot e \cdot \mu \cdot V_{ds} \cdot \Delta N \qquad (4)$$

An increase in current was observed upon the attachment of Ab2E8a or Ab2E8b antibodies to the GFET sensor. The conductance of the channel was assessed according to the available charging carriers, which is potentially influenced by the voltage of the gate. When Ab2E8a or Ab2E8b antibodies bind to the RBD protein of COVID-19 variants

on the surface of the graphene, the conductance of the channel increased. This has led to an increase in current due to the enhanced electrons flow. The measurement of current originated from the flow of electron transfer from drain to source as shown in Figure 7.



4. CONCLUSION

This study designed a GFET biosensor and simulations to detect multiple variants of SARS-CoV-2. Two antibodies, namely anti-Delta (Ab2E8b) and anti-Omicron (Ab2E8a) were used in the simulation. These antibodies would specifically bind to the RBD surface antigen on SARS-CoV-2 Delta and Omicron variants. The conductive state track of the graphene layer was simulated to detect the presence of RBD SARS-COV-2 antigens. Each variant of SARS-CoV-2 was identified by the respective antibodies. If interaction occurs between the RBD and the antibodies, it results in an increase in the current flow in the GFET. Hence, this biosensor demonstrated the capability to detect multiple variants and is well-suited for application in the COVID-19 biosensor detection market. This technology is particularly valuable for identifying asymptomatic patients or individuals affected by SARS-CoV-2 variants.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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