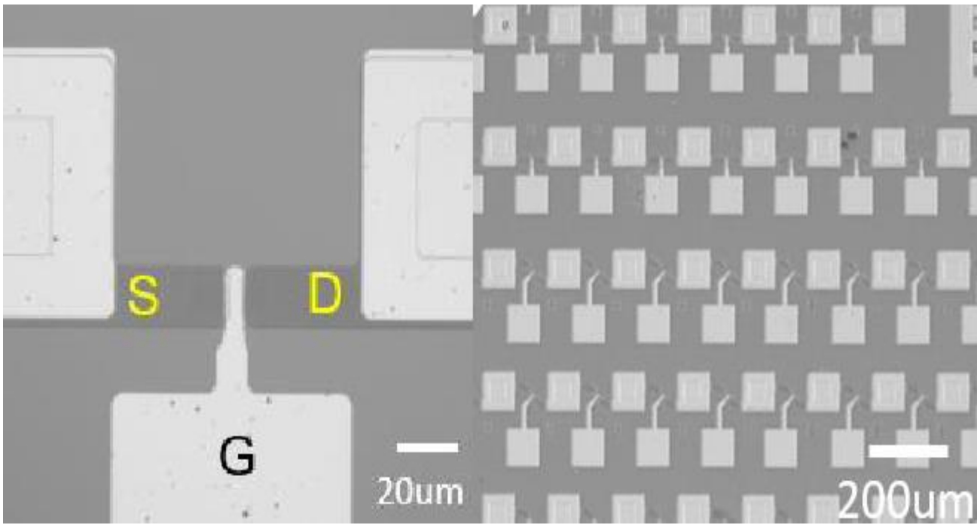
MASTER THESIS NO. 2022:10

College of Engineering

Department of Electrical and Communication Engineering

BIOSENSOR DEVICES BASED ON GRAPHENE AND 2D MATERIALS

Suhada Poovathy



November 2021

United Arab Emirates University

College of Engineering

Department of Electrical and Communication Engineering

BIOSENSOR DEVICES BASED ON GRAPHENE AND 2D MATERIALS

Suhada Poovathy

This thesis is submitted in partial fulfillment of the requirements for the degree of
Master of Science in Electrical Engineering

Under the Supervision of Dr. Amine El Moutaouakil

November 2021

Declaration of Original Work

I, Suhada Poovathy, the undersigned, a graduate student at the United Arab Emirates University (UAEU), and the author of this thesis entitled "*Biosensor Devices Based on Graphene and 2D Materials*", hereby, solemnly declare that this thesis is my own original research work that has been done and prepared by me under the supervision of Dr. Amine El Moutaouakil, in the College of Engineering at UAEU. This work has not previously formed the basis for the award of any academic degree, diploma or a similar title at this or any other university. Any materials borrowed from other sources (whether published or unpublished) and relied upon or included in my thesis have been properly cited and acknowledged in accordance with appropriate academic conventions. I further declare that there is no potential conflict of interest with respect to the research, data collection, authorship, presentation and/or publication of this thesis.

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Abstract

Nanomaterial offered new improvements and developments to the bio sensing field due to their unique physical and chemical properties. Unique and exceptional electronic properties, such as the ultrahigh surface-to-volume ratio and the excellent electrical properties of the 2D materials like in graphene, made these materials promising for future smaller and faster electronics, but extensive amount of research is still needed. This thesis is concerned with the study of integration of 2D material graphene in the development of sensitive and rapid biosensors. The main objective of this thesis is to understand features and characteristics of graphene, evaluate the scope of graphene in electronic biosensing, and the design and analysis of biosensors based on graphene. Epitaxial growth of graphene is done using Gas Source Molecular-Beam Epitaxy (GSMBE) and Mono Methyl Silane (MMS) as a single source gas on the 3C-SiC (110) surface. A field effect transistor was fabricated with this graphene as channel material using top gate technology. The change in output response of the fabricated sensor was evaluated by applying a biological solution RPMI to the graphene channel.

Keywords: Nano materials, 2D materials, Graphene, Nano-biosensors, GFET.

Title and Abstract (in Arabic)

الأجهزة الحيوية على أساس الجرافين ومواد ثنائية الأبعاد

الملخص

قدمت المواد النانوية تحسينات وتطورات جديدة في مجال الاستشعار الحيوي نظرًا لخصائصها الفيزيائية والكيميائية الفريدة الخصائص الإلكترونية الفريدة والاستثنائية، مثل نسبة السطح إلى الحجم العالية جدًا والخصائص الكهربائية الممتازة للمواد ثنائية الأبعاد مثل الجرافين، تجعل هذه المواد واعدة للإلكترونيات لامستقلاية الأصغر لاالأسرع لالالالا لا تزال هناك حاجة إلى قدر كبير من البحث. تهتم هذه الأطروحة بدراسة تكامل مادة الجرافين ذات الأبعاد في تطوير أجهزة بيولوجية نشطة وحساسة. الهدف الر ئيسي من هذه الأطروحة هو فهم ميزات وخصائص الجرافين، وتقييم نطاق الجرافين في الاستشعار الإلكتروني الحيوي، وتصميم وتحليل أجهزة الاستشعار الحيوية القائمة على الجرافين. يتم النمو فوق المحاور من الجرافين باستخدام (Epitaxy) الشعاع الجزيئي لمصدر الغاز(GSMBE)، كغاز مصدر واحد على سطح 3-C SiC (110). تم تصنيع ترانزستور ذو تأثير ميداني باستخدام هذا الجرافين كمواد وسيلة تسويق بوابة العلوية . تم تقييم التغيير في خرج المستشعر المصطنع من خلال تطبيق محلول بيولوجي (RPMI) على قناة الجرافين.

مفاهيم البحث الرئيسية: مواد النانو، المواد ثنائية الأبعاد، الجرافين، أجهزة الاستشعار الحيوية النانوية.

Acknowledgements

I would like to thank God for giving me the blessing, the strength, the chance, and endurance to complete this study. My first thanks go to my guide Dr. Amine El Moutaouakil, Department of Electrical engineering, who helped me in the work through the two years of research. I would like to thank him for providing the precious time to pursue my research goals.

In addition, I would like to thank the co-coordinator Dr. Mahmoud F. Al Ahmad, and all the faculty and technicians in the Electrical Engineering Department for their co-operations and support throughout the course.

Special thanks go to my parents, my beloved husband, friends, and my children who helped and supported me along the way.

Dedication

To my beloved parents and family

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List of Abbreviations

2D	Two Dimensional
AFM	Atomic Force Microscopy
AuNPs	Gold Nanoparticles
FET	Field Effect Transistor
GCE	Glassy Carbon Electrode
GFET	Graphene Field Effect Transistor
GO	Graphene Oxide
LOD	Limit Of Detection
MoS_2	Molybdenum Di-Sulfide
NP	Nano Particle
rGO	Reduced Graphene Oxide
SEM	Scanning Electron Microscope
SiC	Silicon Carbide
SPRF	Surface Plasmon Resonance Frequency
TEM	Transmission Electron Microscope

Chapter 1: Introduction

1.1 Overview

Two-dimensional materials (2D) are crystalline single layer sheets with covalently-bonded intra-layer atomic bonding and weak van der Waals interlayer and layer–substrate bonding. The isolated 2D materials showed exceptional and unique electronic properties from the parent material, which make it suitable in various applications like sensors and other biomedical applications. Integration of 2D nanomaterial like graphene with biosensors provided great opportunity for researchers in the development of ultra-sensitive and new generation biosensors (Bolotsky et al., 2019). The very high surface to volume ratio and outstanding electrical properties of 2D materials, along with many other unique propertied made them excellent candidate for electronic sensor circuits. Isolation of graphene, an allotrope of carbon, in 2004 by Geim and Novoselov, helped in achieving great progress and rapid development of variety of biosensor devices. Graphene-based biosensors, like Graphene Field Effect technology (GFET) offers outstanding sensing performance and allows the micro fabrication of the device at the nano scale (Li et al., 2020; Chauhan et al., 2017).

Biosensor devices are analytical devices for detecting the presence or amount of analyte such as biomolecule or pathogens, and comprise of a biological sensing element and a transducer (Yoo & Lee, 2010). First biosensors used by Professor Leland C Clark in 1962 were oxidase enzyme electrode for glucose detection ,but now they are extensively used in disease detection, drug delivery, environmental detection, and biosecurity (Castillo-Henríquez et al., 2020). Despite the significant advances in the health care system, current pandemic situation teaches us the need for a simple, sensitive solution for rapid identification of these pathogens. From ancient times onwards, different variants of viruses caused severe epidemiological and pandemic issues like Severe Acute Respiratory Syndrome (SARS) in 2002, swine flu in 2009, Ebola breakout in 2014, and Covid -19 break out in 2019 (Guilbault et al., 2004; Vermisoglou et al., 2020; Bolotsky et al., 2019).

There should be an easy and reliable detection method for identification of pathogens such as bacteria, viruses and parasites, to select the correct treatment strategies, protocols, and procedures (Bar-Haim et al., 2019; Kosack et al., 2017). Current laboratory methods are mentioned in Figure 1, like immunology-based methods, Polymerase Chain Reaction (PCR), electrochemical methods, and Enzyme-Linked Immunosorbent Assay (ELISA) are time consuming, need high cost reagents, laboratory conditions, well-trained staffs, high-accurate instruments (Döscher & Reiss, 2021; WHO, 2016).

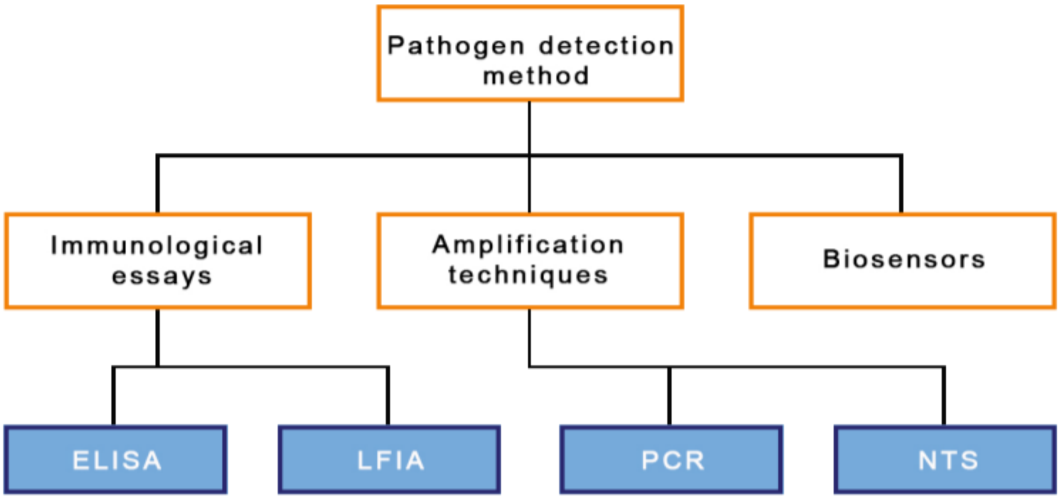


Figure 1: Different methods of bacterial detection. Adapted from (Priyanka et al., 2016)

1.2 Theory

1.2.1 Biosensor and Its Architecture

Biosensors can simply define as analytical method to detect or convert biological reactions into corresponding physiochemical signal proportional to analyte concentration. It normally consists of mainly three modules: a biological recognition component as sensor element for signal acquisition, a transducer for signal conversion, feeding to a signal processing and display unit (Figure 2). The bio receptor recognizes the biomolecules like enzymes, antibodies, DNA, RNA, and cells (Guilbault et al., 2004).

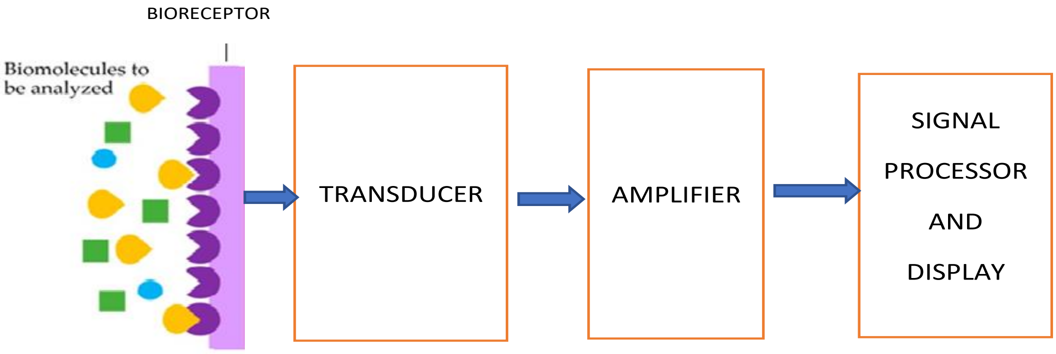


Figure 2: Block diagram of a typical biosensor. Adapted from(Suvarnaphaet & Pechprasarn, 2017).

Different types of biosensors are available as seen in Figure 3, based on the biological element used or the type of transduction principles. DNA, enzymes, antibodies, microorganisms, tissues, are different types of biological elements used (Kizek et al., 2015). The different types of bio transducers are electrochemical, piezoelectric, optical, electronic, pyro electric and magnetic biosensors. Field Effect

Transistor (FET) based biosensors provided highly sensitive, and accurate sensors which can be easily integrated with other electronic modules, such as signal amplifiers and processors.

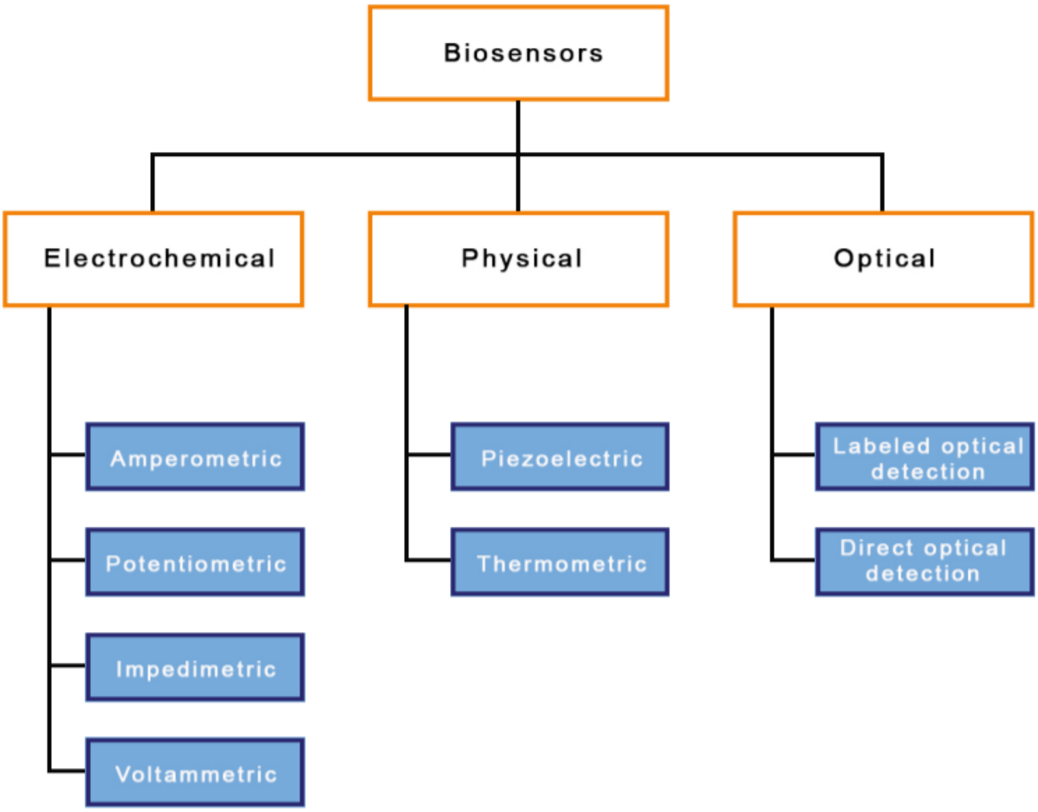


Figure 3: Different types of biosensors. Adapted from (Lazcka et al., 2007)

Extensive research is taking place in the biomedical field and healthcare; to detect pathogenic microorganism, in medical implants, and to assist in drug delivery. Also, highly sensitive label-free biosensors are essential for consumer genetics, in diagnosis and treatment of cancer, for controlling serious pandemics and drug development field. After its first invention by Professor Leland C Clark, immense scientific researches were carried out in the development of biosensor technologies that can surpass conventional in vitro diagnostics for disease detection and health care monitoring.

The performance of a biosensor is characterized mainly by following parameters like sensitivity, selectivity, range, response time, Reproducibility, Limit of Detection (LOD), Life time and Stability. These characters are explained in Figure 4.

Biosensors field is highly interdisciplinary, researches in surface chemistry provide fascinating new elements for biomaterials, and nanofabrication technologies offer miniaturization and integration with a better perspective for developing specific and sensitive biosensors.

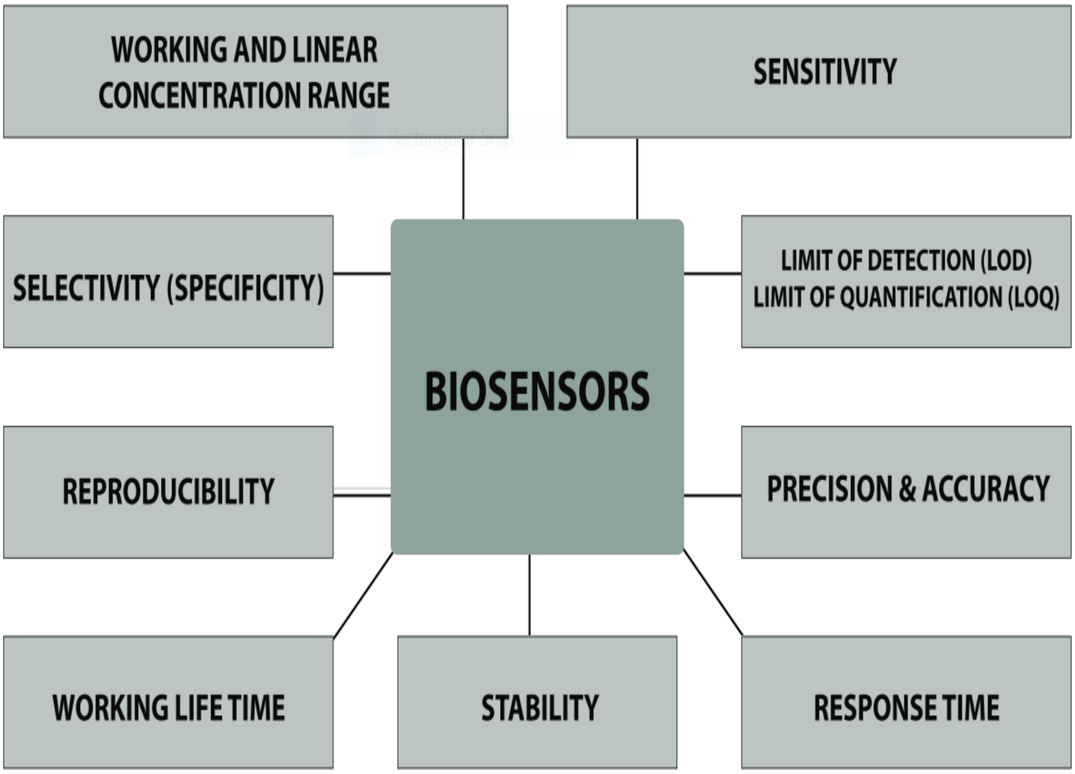


Figure 4: Characteristics of a biosensor. Adapted from (Preda et al., 2011)

1.2.2 Graphene and Other Two-Dimensional Materials

Graphene is an allotrope of carbon, with a single layer of sp2 hybridized carbon atoms in a hyper-dimensional (1D, 2D, or 3D) structure, as shown in Figure 5, with a carbon-carbon bond length of 0.142 nm. It has unique properties like electron mobility, thermal conductivity, large surface area of 2630 m^2/g and high electrical conductivity, with electrical conductivity of synthetic and natural graphene is around 1,000 siemens per meter and measured thermal conductivity in the range of 3000-5000 W.m-1. K-1. Its high mechanical strength, Young's modulus of order ~1.0 TPa, large surface area, tunable band gap and tensile strength made it an attractive component in future biosensors (Xie et al., 2017; Kim & Jeong, 2018).

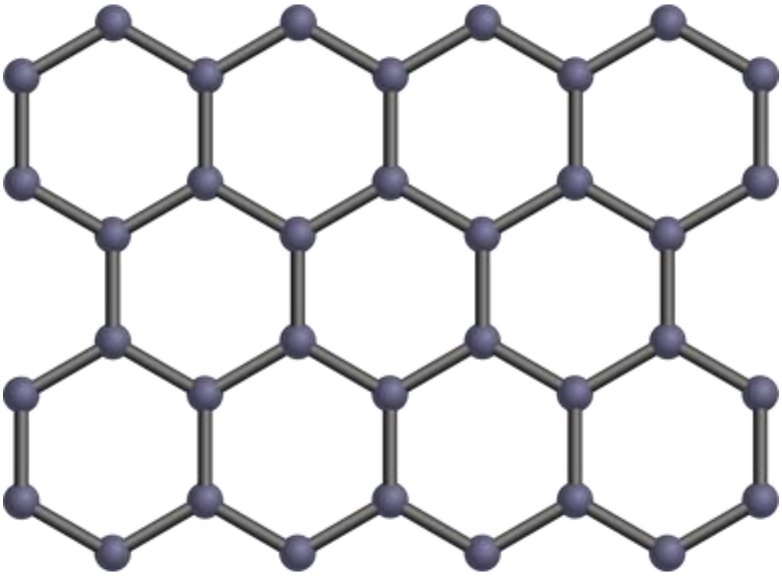


Figure 5: Structure of 2D materials. Adapted from (Šiškins et al., 2020)

1.2.3 Features and Characteristics of Graphene

2D material graphene is an atomically thin carbon crystal with Dirac-particle carriers, this 2D crystal is arranged with intralayer covalent bonding and interlayer van der Waals bonding in honey comb lattice structure. They exhibit high surface area, very high electron mobility (~20,000 $cm^2 V^{-1} s^{-1}$), excellent thermal conductivity, high optical nonlinearity and light weight.

It is made up of carbon atoms, with two carbon (C) atoms per unit cell arranged in hexagonal lattice, with sp^2 hybrid-bonded carbon, occurs in thin sheets with Dirac cones. Graphene's lattice structure can be considered as two equivalent triangular sub lattices as in Figure 6. Dirac points are the intersection points where the two corresponding energy bands of the sub lattices meet. The graphene is a zero band gap semiconductor, because the dispersion relation near Dirac point in graphene is linear. The unique properties of this material is due to the electronic linear spectrum and the chiral nature of the electron's wave function (Peres, 2010; Late et al., 2019).

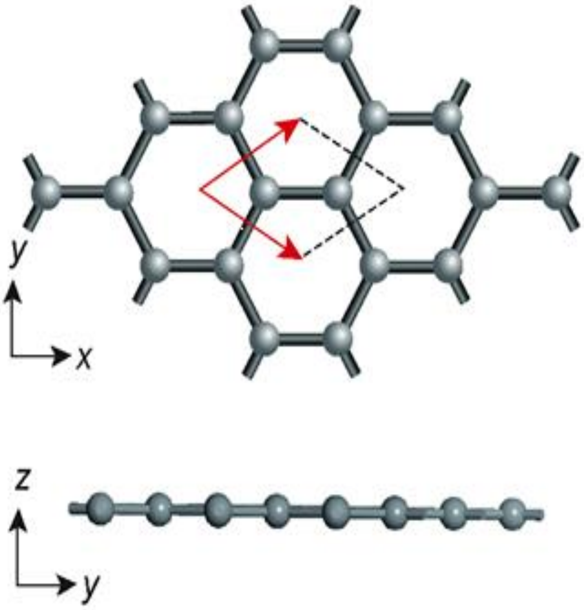
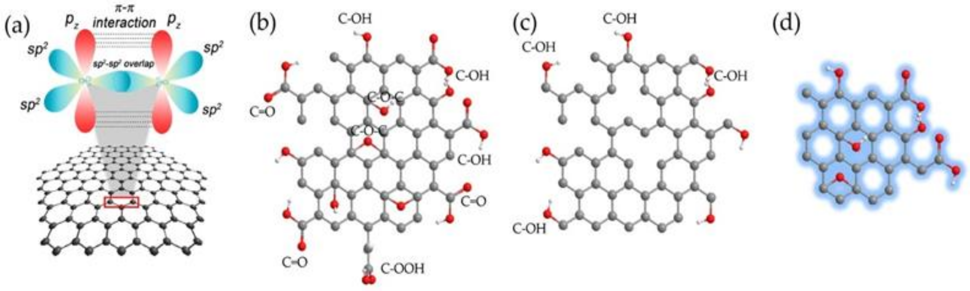


Figure 6: Atomic structure of graphene

1.2.4 Scope of 2D Materials in Biosensing

Biosensing requires detecting different compounds with high sensitivity and selectivity. The first 2D materials, graphene and its derivatives proved an excellent one in biosensing application. Graphene is a zero-gap semiconductor material with unique mechanical, physical, electrical, and optical properties. High mechanical strength, extreme conductivity, tunable bandgap, adjustable optical properties, large specific surface area are some of the most fascinating properties of graphene which make it a promising material in biosensor fabrication (Suvarnaphaet & Pechprasarn, 2017). It is conductive, transparent, and biocompatible, and hence can be used in the construction of biosensor in various transduction modes, like electrical ,electrochemical transduction and optical transduction (Krishnan et al., 2019).

Main types of graphene based materials used in biosensor application are shown in Figure 7, are pristine graphene, Graphene Oxide (GO), Reduced graphene oxide (rGO), and Graphene Quantum Dot (GQD) (Bolotsky et al., 2019).



Graphene
Graphene oxide
Reduced graphene oxide
Graphene-based quantum dot

Figure 7: Structure of graphene materials used in the biosensor. Adapted from (Suvarnaphaet & Pechprasarn, 2017)

1.2.5 Pristine Graphene

Graphene in pure and un-oxidized form where carbon atoms arranged in a honeycomb structure with sp^2-hybridization and connected with covalent bonds forms Pristine graphene , and Graphene Oxide (GO) is formed by oxidizing the carbon core structure, and reduced Graphene Oxide (rGO) by reducing the core structure with vacancy defects (Pei et al., 2015). The important properties of pure graphene are mentioned in Table 1.

Table 1: Important properties of graphene

Properties	**Value**
Specific surface area	2630 m^2/g
Young's modules	1 TPa
Electron mobility	10,000 $cm^2/(V.s)$
Mean free path	1000 nm
Current density	10^8 A/cm^2
Thermal conductivity	5000 W/m.K
Melting point	3800 K

1.2.6 Functionalized Graphene

The increased transducing area of the graphene provides large area for analyte attachment (Figure 8). Thus, strong and biocompatible graphene material exhibit high electron transfer rate and high optical transparency, which make it suitable to use in the development of highly efficient biosensor and optical sensors. Moreover, graphene can be combined with other metal compounds like gold or other nanoparticles and composites, to develop highly specific and sensitive sensors with low limit of detection.

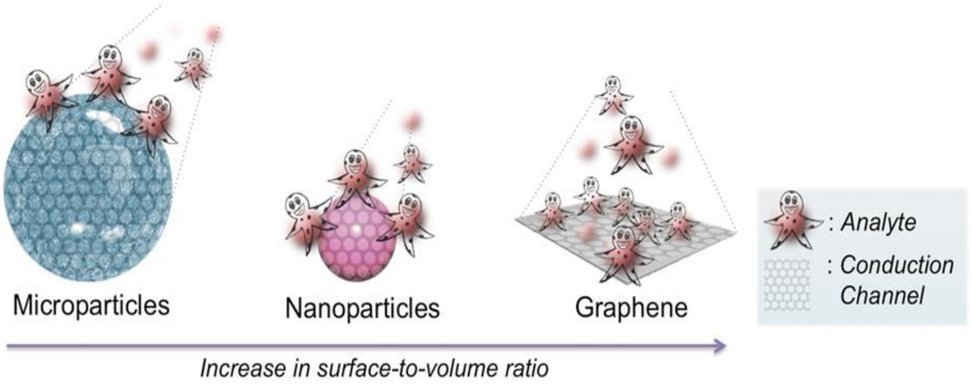


Figure 8: Concept of influence of surface-to-volume ratio. Adapted from (Chauhan et al., 2017)

1.2.7 Synthesis of Graphene

Several chemical and physical methods are used for the isolation of graphene. Different applications demand specific physical, mechanical, electrical properties and quality of material, and which in turn dependent upon the synthesis method adopted. The electrical and mechanical properties and quality of the materials depends on the amount of defects and impurities present in it. The main techniques used are mechanical exfoliation, epitaxial growth on SiC substrates, chemical reduction of exfoliated graphene oxide, chemical vapour deposition, unzipping carbon nanotubes, and liquid phase exfoliation (Figure 9). Each method have some advantages and limitations, whereas researches are still taking place to find improved approaches for large scale production of graphene with low-cost and high quality (Atta et al., 2015).

Among these, most common technique for the large-scale production is chemical vapor deposition, which is depositing gaseous reactants onto a substrate in a gas chamber, at high temperature of around 1000°C, where quality of produced graphene can be controlled by varying pressure and temperature of the system. The experimental setup is illustrated in Figure 10.

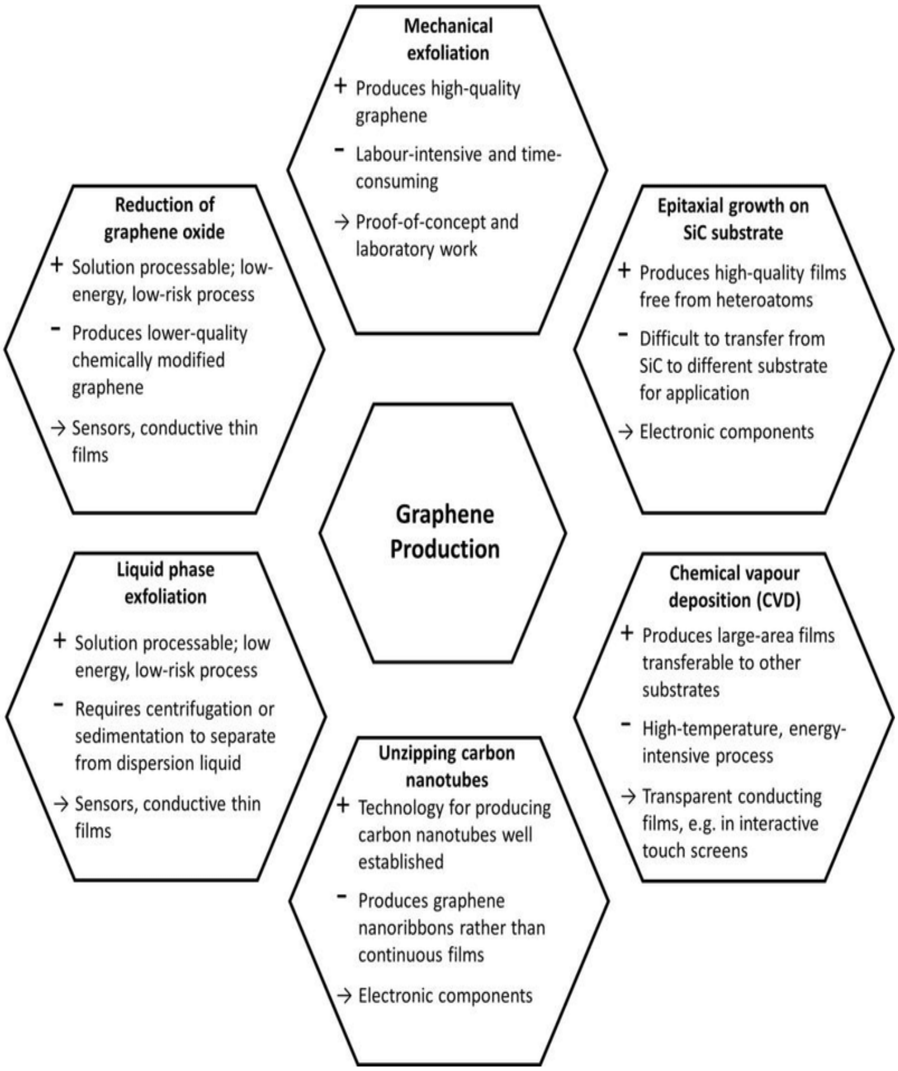


Figure 9: Various graphene synthesis methods. Adapted from (Hernaez et al., 2017)

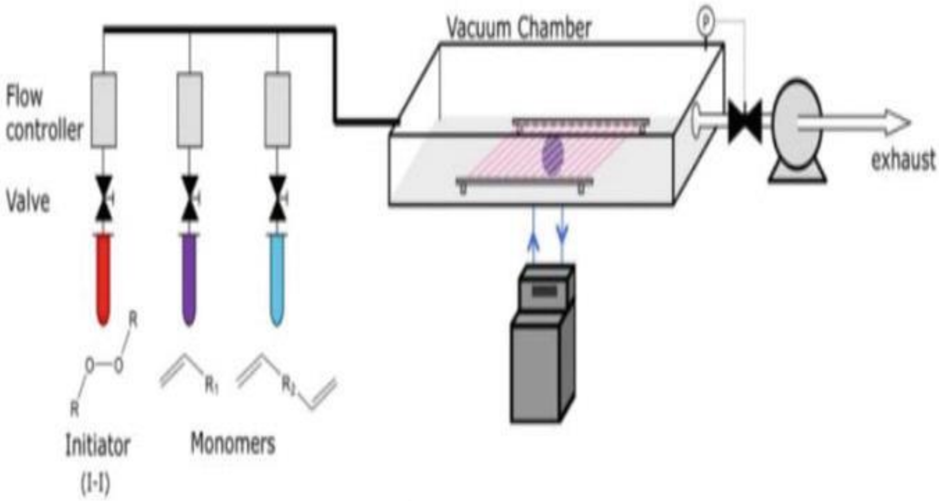


Figure 10: Experimental setup of CVD process. Adapted from (Rudrapati, 2020)

1.2.8 Analysis Techniques of Graphene and 2D Materials

The properties of synthesized graphene like size, shape, surface, and appearance are very significant in achieving the performance of the fabricating devices. Hence analysis and characterization of synthesized nanomaterials in several aspects, like the number, quality and defect of graphene layers requires sophisticated analytical techniques. Several methods are used to analyses the synthesized material like Electron microscopy, Atomic Force Microscope (AFM), X-ray Diffraction, Raman Spectroscopy, and so on.

1.2.8.1 Atomic Force Microscopy (AFM)

This is a surface study method where uniformity of the graphene layer can be measured. The electrical and mechanical properties of the material can be collected using a cantilevered mechanical probe, which operates in two modes: contact or tapping according to the tip movement. AFM allows analysis of nanoparticles with sub-nanometer resolution, with variable geometry, liquid medium and physical properties like magnetic field.

1.2.8.2 Raman Spectroscopy

Raman spectroscopy is an analysis technique which uses vibration, rotation, and other low frequency modes of the molecule to give the structural and chemical details about the material. Lasers or other monochromatic light are used to illuminate the sample and measures the inelastic scattering of photons called Raman scattering. The interaction of the laser light with electrons in the material result in a shift in energy of the laser photons, called Raman shift, which can be measured using spectrometer. A typical Raman spectrum of pristine graphene (Figure 11) shows the typical modes D band,G band and 2D band, where the D indicates structural disorder, G gives an idea about strain effects in the sp2 structure of graphene, whereas 2D indicates the number of graphene layers.

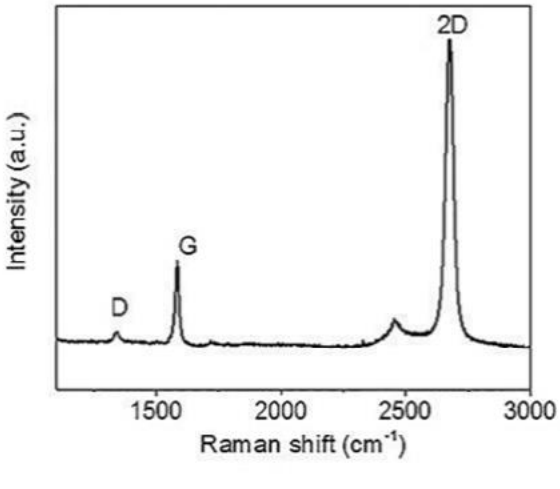


Figure 11: Typical Raman spectrum of pristine graphene. Adapted from (G-band, 2021)

1.2.8.3 Electron Microscopy

An electron microscope is used to provide high resolution images of the nanomaterial, where interaction of the electrons in the beam with the material result in various signals which gives idea about the nanostructure and chemical composition of the nanomaterial. Main two types are Scanning Electron Microscope (SEM) and Transmission Electron Microscope (TEM) based on the signal generation principles. In TEM interaction between a uniform current density electron beam and a thin sample is used, whereas SEM uses a focused beam of electrons to create images.

1.2.9 Designing and Analyzing Graphene-based Biosensors

Most types of biomolecules like antibodies, enzymes and DNA can be easily combined with graphene, which resulted in extensive research in development of graphene biosensor for various applications (Figure 12). The immobilization of specific analyte by adsorption, covalent binding, entrapment, or membrane confinement on to the bioreceptor results in change in the electrical properties, which in turn result in a measurable electrical response, hence, can identify the presence or concentration of analyte of interest (Thangamuthu et al., 2019; Chung et al., 2013; Penkala et al., 2017).

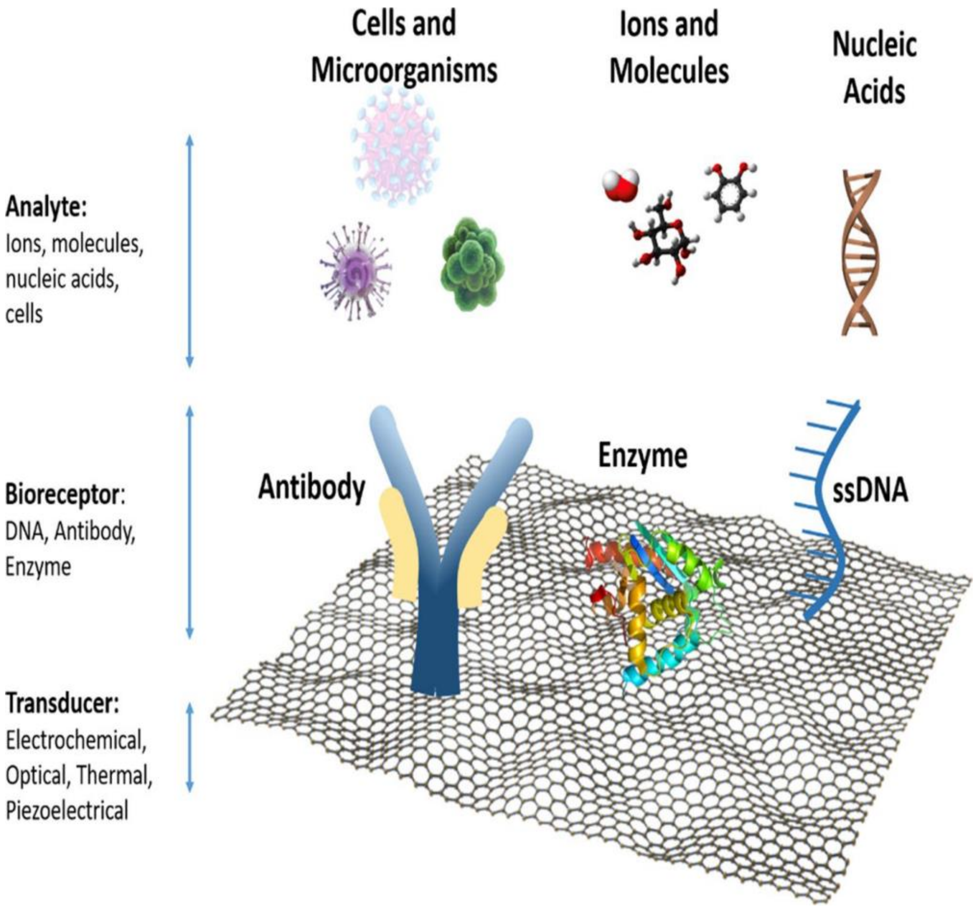


Figure 12: A graphene-based biosensors platform. Adapted from (Peña-Bahamonde et al., 2018)

1.2.10 Architecture of Graphene-Based Biosensors

There are mainly four approaches in graphene biosensors, they are:

1.2.10.1 Electron Transfer Materials

Graphene’s large surface area exposes all the carbon atoms to the analyte and hence can be used as electron transfer material for electrochemical biosensors. Direct electrical communication is facilitated by physically binding to analyte, and electrons in graphene have a very high mobility which ensures movement of electrons in the sensor.

1.2.10.2 Impedance Materials

The basic graphene atom forms three σ bond with each of its three neighbors and one π-bond, which forms π-π stacking interactions and hence other π-conjugated molecules can be easily attached to the electrode. So, graphene's surface can be easily modified without upsetting its electrical properties .

1.2.10.3 Photon and Phonon Transfer

The unique nature in phonon transport properties in graphene made possible its application in field of plasmonic and for coupling electromagnetic radiation in the terahertz frequency. Electrochemiluminescence and fluorescence are the main means for photon and phonon transfer, and hence used with Surface plasmon polaritons on metal films for improved biosensor performance. Surface Plasmons (SP) are coherent electrons that propagate along the interface between a metal contacting with a dielectric, and these waves quantize longitudinal plasma oscillations of free electrons near the metallic surface. Graphene based Surface plasmon resonance sensors are developed for direct and indirect pathogen detection with improved sensitivity than conventional methods. The sensitivity and strength of optical detection is enhanced by layering graphene on the top of standard metals like gold and silver. Thus, integration of graphene into the optical sensors and other types of sensors resulted in proposing and development of ultrasensitive biosensors for the detection of protein molecules at molecular level and hence the diagnosis and the treatment of variety of diseases like cancer, Alzheimer's (Bari et al., 2017).

1.2.10.4 Graphene Field Effect Transistor (GFET)

The thin silicon channel in the FET is replaced with a graphene thin film in graphene field effect transistor, to enable easy functionalization and binding of receptor molecules to the biosensor, and to provide thinner and sensitive channel region .(Figure 13). The surface of the GFET channel can be functionalized by binding receptors like proteins, bio-compounds, and DNA molecules to make sensors for various applications. Graphene shows high surface-to-volume ratio which enables identification of the smallest concentration of analyte, where binding of even a single analyte will create change in the electric field and properties of the system. GFET biosensors are thus useful for ultra-sensitive, rapid, label-free detection of pathogenic molecules such as virus and bacteria. They have fast response, ultra-sensitivity, and easiness of usage, and selectivity for analyte by attaching specific probes on the graphene channel (El Moutaouakil et al., 2011; Liu & Guo, 2012).

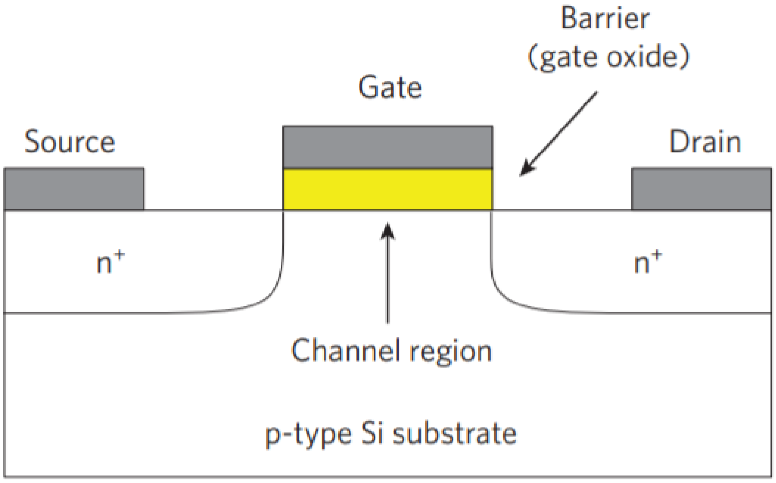


Figure 13: Schematic diagram of a typical GFET. Adapted from (Nishizawa, 1982)

There are typically three arrangements used in Graphene based Field Effect Transistors: (i) back gate, (ii) top gate, and both as (iii) dual gate (Figure 14). A dielectric is deposited on highly doped silicon substrate, and then graphene is deposited as a channel in the FET in back gate configuration.

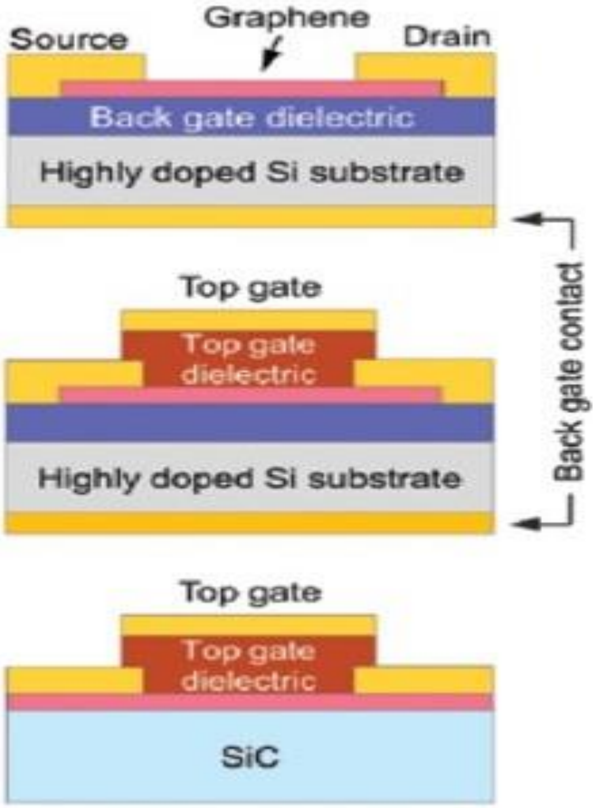


Figure 14: Different gate configurations in GFET. Adapted from (Klekachev, 2013)

The gate controls the electron and holes flow through channel, the high sensitivity of GFET is achieved because all current flows through this one atom thick graphene channel. The GFET shows ambipolar behavior, where negative bias result in hole carrier conduction, and electron carrier conduction is possible by positive bias. Dirac point is where both conduction curves meet (Figure 15).

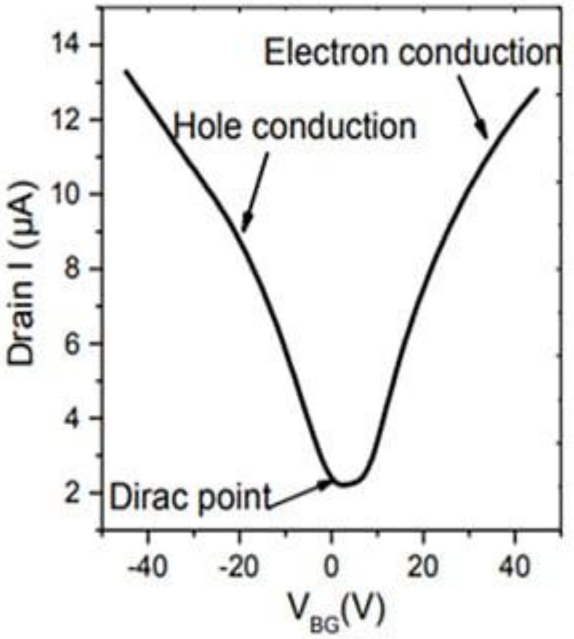


Figure 15: Transfer characteristics for GFET under a back gate bias. Adapted from (Smith et al., 2014).

Even though the GFET has many advantages over silicone FET, there are some limitations also. The main limitation is lack of band gap. The advantages and development of graphene inspired exploring similar materials. Other 2D materials which have similar structure of graphene are graphitic Carbon Nitride (g-C3N4), Boron Nitride (BN), transition metal oxides, and Transition Metal Dichalcogenides (TMDs). Recent development of these more versatile and tunable 2D nano-sheets opens new opportunities in developing more multifaceted functional nanostructures and biosensors (Vaidyanathan et al., 2020; Li et al., 2020; Ping et al., 2015).

1.3 Statement of the Problem

Infectious diseases are among the main reasons for serious pandemics and contagious infections; hence, they cause thousands of fatalities and economic losses annually. The currently available clinical laboratory methods are time consuming and complex, which necessitates development of a rapid, low-cost, and sensitive detection method to upgrade the living standards of humans. Present pandemic scenario of covid-19 emphasis the necessity of developing highly sensitive, rapid, simple and real time biosensor devices.

These newly emerging class of 2D nanomaterial provided exceptional promise for rapid research in developing ultra-fast and highly sensitive biosensors at nano-scale. The isolation of graphene and other 2D materials opened a new frontlet in developing highly sensitive and label-free biosensors. Although a lot of research have been dedicated in this field in recent years, only limited number of products are commercially available in the market. For the successful implementation of these proposed models, several scientiifc and engineering problems should be.undertaken, and more studies should be conducted in this field of 2D nanomaterial.

This thesis mainly focuses on following things:

1. To study and understand features and characteristics of 2D material graphene.
2. Evaluate the scope of graphene in electronic biosensing.
3. Design and analyze biosensors based on graphene materials.

1.4 Thesis Outline

This thesis begins with Chapter 1 titled “Introduction”; where some basics about the biosensors are explained. Different types and architecture of a typical biosensor device were mentioned. Different types of 2D nano materials and why they should be used as biosensor materials are also explained. Next Chapter is “Literature Review”, which present an integrative update of graphene-based nano-biosensor. Chapter 3 explains design and analysis of graphene based field effect transistor biosensor. Chapters 4 and 5 discuss the result and conclusion, and the remarks and suggestions for further research and practical application.

Chapter 2: Literature Review

2.1 Introduction

The journey of biosensors began in 1962, with invention of first generation biosenor by Leland C. Clark Jr. and Cham Lyon (Guilbault et al., 2004). Since then, tremendous research took place in this field. Figure 16 gives an idea of various publications and researches from 2000 to 2014 years. Developments in nano-science and 2D materials opened a promising tool for biosensor fabrication due to its many interesting properties (Saylan et al., 2019). This chapter focuses on different researches and developments in the application of graphene as biosensor, mainly on sensor for pathogen detection based on simple graphene and hybrid/advanced graphene structures (Suvarnaphaet & Pechprasarn, 2017; Krishnan et al., 2019). Figure 17 shows various application of graphene in recent years, and this review focus only on graphene based biosensor for pathogen detection and healthcare system (Huang et al., 2019; Lawal, 2018). Biocompatibility and toxicity aspects of graphene material on human body and environment have to be considered (Hudu et al., 2016).

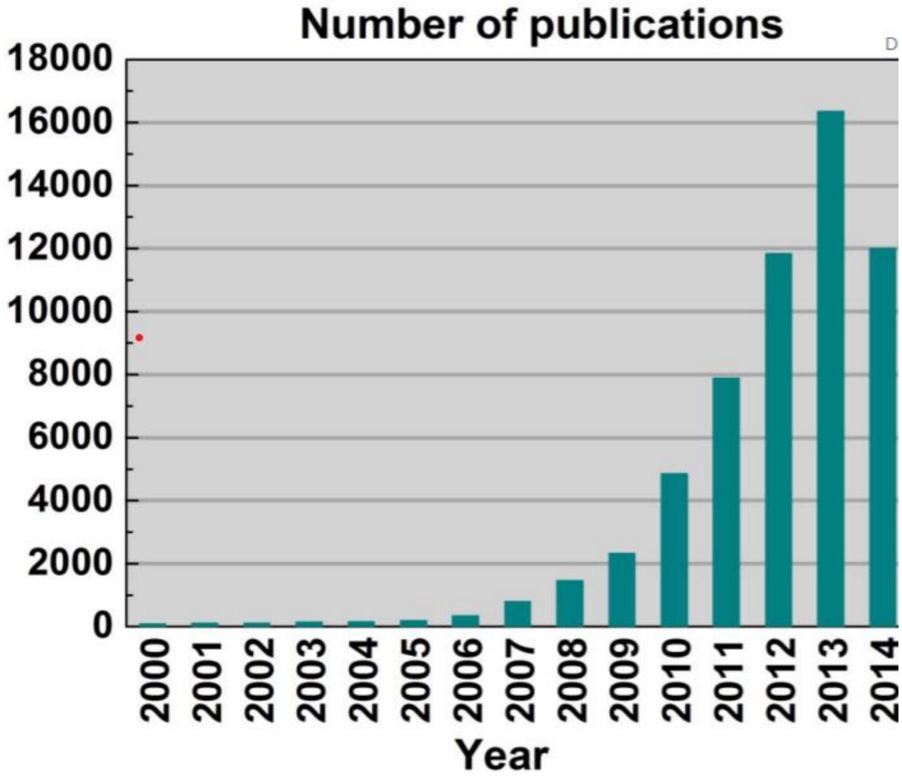


Figure 16: Number of publications of graphene from 2000 to August 2014. Adapted from (Veerakumar et al., 2018).

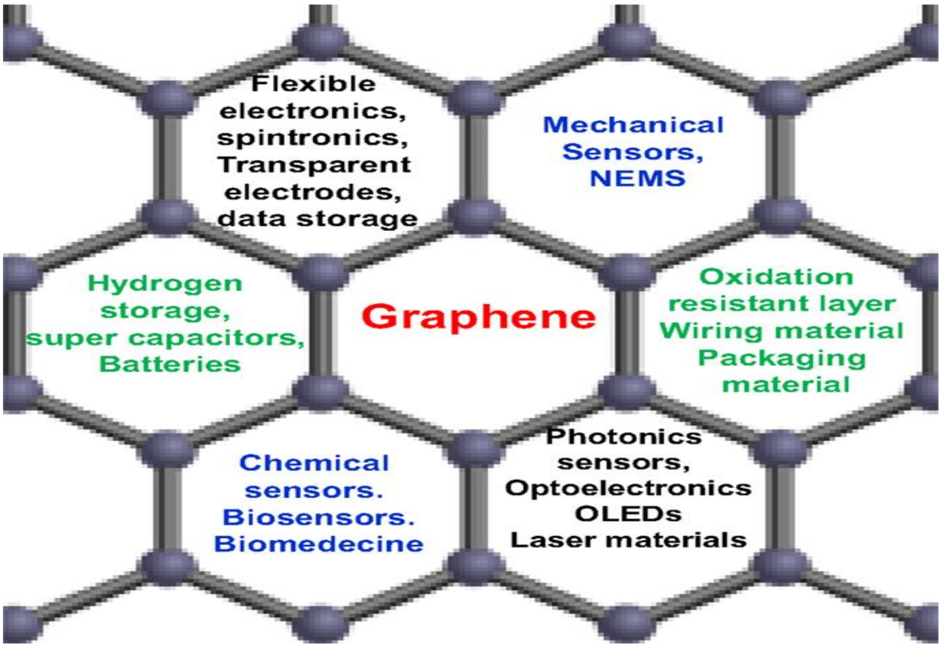


Figure 17: Different recent application of graphene. Adapted from (Aïssa et al., 2015).

2.2 Biosensors Based on Simple Graphene Structures

In early application,2D nanomaterials were generally used as electrode modified materials. Single bacterium and DNA detection devices were achieved by immobilizing GO sheets on silica substrates with pre-deposited or post-deposited gold electrode using chemically modified graphene. The developed sensor exhibited highly sensitive detection, where the detection of single cells showed a remarkable increase in the device's conductivity. An ultra-specific graphene biosensors were fabricated by immobilizing a monoclonal antibody (anti-Zika NS1) to detect the Zika virus. (Figure 18) (Afsahi et al., 2018). A significant change in the channel current and gate capacitance (20% increase) was observed on detecting the target virus. (Figure 18). An electrochemical biosensor was made using graphene for the detection of rotavirus; A graphene film synthesized from a GO film was utilized in the sensor fabrication (Pant et al., 2017). The electrode surface was immobilized with pyrene derivatives and antibodies of the rotavirus. When the target binds to the antibodies, an anodic and cathodic current peak takes place, which can be observed using the cyclic voltammetry process (Hashwan et al., 2015).

Another sensor model is using a graphene field-effect transistor in which detection of Escherichia coli (E. coli) bacteria is by measuring transistor output voltage and current. The output reading of the transistor experience a sudden change in conductance when exposed to E. coli bacteria (Akbari et al., 2015; Liu et al., 2018).

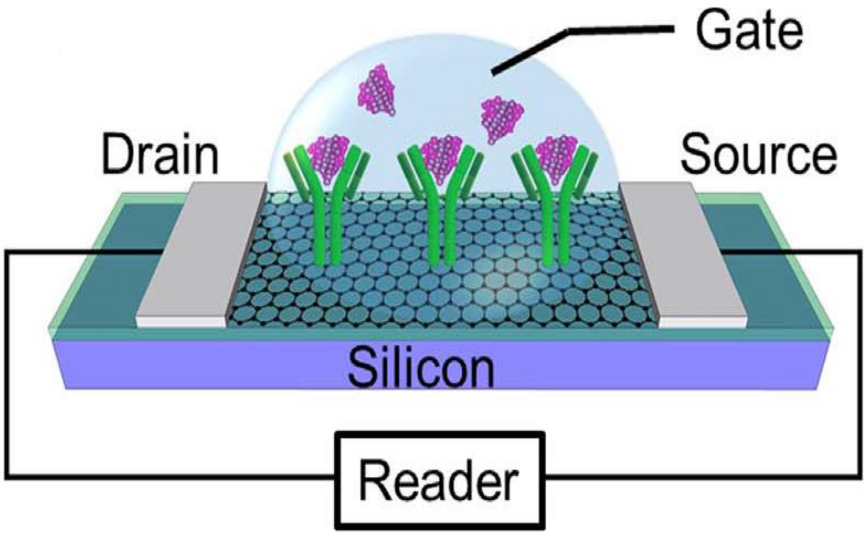


Figure 18: Graphene channel biosensor for Zika virus detection. Adapted from (Afsahi et al., 2018).

For the case of highly dangerous epidemic disease, such as Ebola, whose early detection is vital to prevent serious outbreaks, several graphene-based sensing solutions were reported; For instance: rGO material was used as a conducting channel to develop an FET sensor for Ebola detection (Chen et al., 2017). An Al_2O_3 layer (as a passivation layer and top gate oxide), gold nanoparticles (AuNPs; to fix the probes), and anti-Ebola antibodies were immobilized to the channel, as shown in Figure 19. This provides a real-time detection of the Zaire-strain of the Ebola virus with a very low detection limit of up to 1 ng/mL; hence, this achievement can definitely be a stepping stone in the early diagnosis and eradication of Ebola.

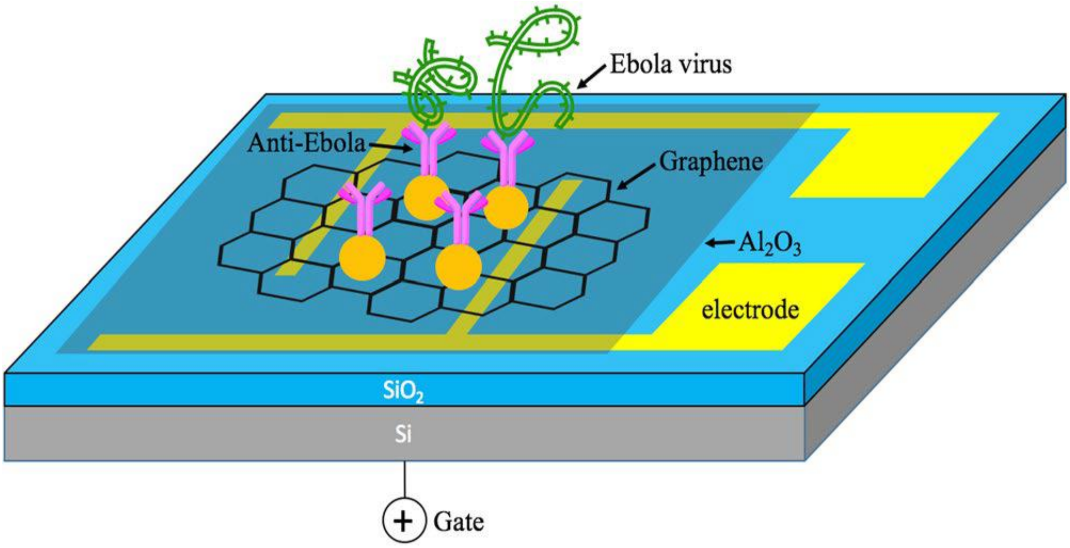


Figure 19: Reduced GO-based FET for detecting Ebola virus. Adapted from (Chen et al., 2017).

Graphene-based sensors were used not only in detecting human diseases but also in environmental, food, agricultural, and aquaculture industries. One such method was reported for detecting the white spot syndrome virus, which is a deadly virus in the aquaculture field; Modified GO was used to fabricate the device, where methylene blue and primary and secondary antibodies were anchored to its surface, which resulted in a quick sensitive detection within nearly 35minutes (Natarajan et al., 2017).

Other researchers used polymer matrix composites with nanomaterials for the quantitative and qualitative detection of pathogens; A method for the detection of dengue fever by utilizing GO with a polymer composite material and electrochemical impedance was based on the coating of GO polymer mixture on a gold electrode. measurements were performed by plotting the impedance spectra. Here, the GO was used to make the copolymers electrically conductive, thus resulting in the dengue virus detection with a low detection limit of 0.12 Plaque-Forming Units (PFU)/mL (Vashist & Luong, 2015).

The analysis of the changes in the surface-charge density of diseased cells provides relevant information regarding the state of many diseases, including non-viral diseases such as malaria, which is considered a vector-borne disease. A microfluidic GFET sensor and flow–catch–release sensing was able to detect and analyze single malaria-parasites-infected cells. When an infected cell binds to the sensor, it creates changes in the drain-source conductivity of the channel, which drops down to nearly 10%.

Moreover, aptamer-based sensors use aptamers as bio-receptors or transducers, where aptamers are oligonucleotides that can bind to a specific molecule with relatively high affinity and specificity. Several graphene-based viral bio-detectors with aptamer-based interactions were proposed for improved performance because they are easy to synthesize and modify and can bind to a broad range of targets. The detection can also be done using optical principles, such as fluorescence or electrical properties (Singh et al., 2018; Weng & Neethirajan, 2017).

2.3 Viral Biosensors Based on Hybrid Graphene Structures

Not only standalone graphene-based nanomaterials holds promising sensing features, combining graphene with nanoparticles or metallic structures such as those used to increase terahertz coupling provides novel nanocomposites with more desirable properties (Penkala et al., 2017). These metallic nanoparticles can be palladium, antimony, silver, or gold. Among these, AuNPs are most widely used with graphene, as they have many unique characteristics, including biocompatibility, low toxicity, and electrical and catalytic features (Darwish et al., 2018).

In addition, graphene-based compounds are also used in SPR biosensors. Also, combining graphene with single-layered transition metal dichalcogenides provides a new platform for developing biosensors that can detect a wide variety of pathogens (Wang et al., 2015).

Among these, graphene–molybdenum di-sulfide hetero-structures and ZnO–graphene heterostructures have led to new research lines in photon-sensing devices. Biosensors using MoS_2–graphene hybrid structures exhibited a considerable increase in sensitivity with more MoS2 and graphene layers (Sajid et al., 2017).

Conventional methods such as ELISA and PCR was not reliable to detect Norovirus, a virus that cause food poisoning, hence several researchers proposed various bio sensing platforms. A fabricated screen-printed carbon electrode in a microfluidic platform, where a carbon electrode was modified with a graphene particle-AuNPs composite offered a stable substrate for aptamer immobilization. The norovirus detection was based on aptamer–target interactions, where the aptamer was tagged with ferrocene as a redox probe. When the norovirus binds to the aptamer, an increase in the capacitance of the electrode results in the detection of the virus within a total time of 35minutes in the spiked blood sample (Figure 20).

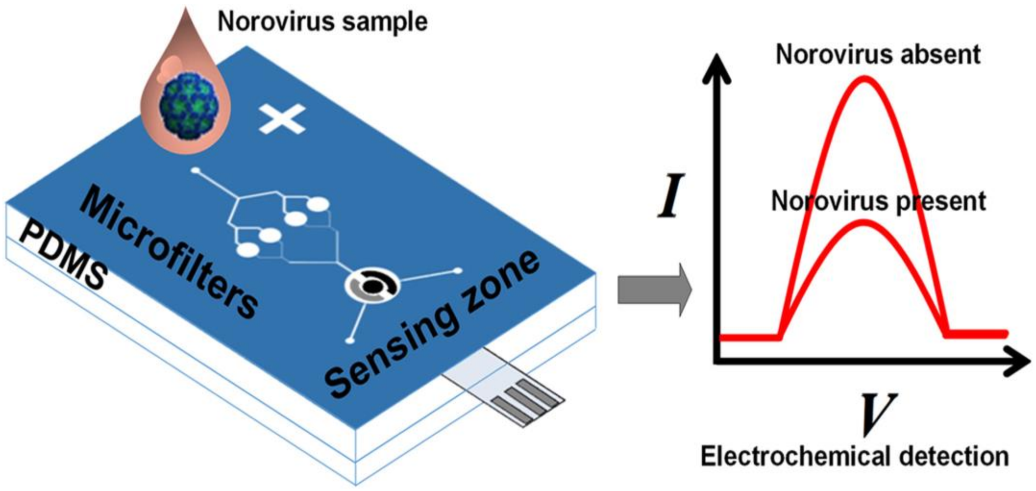


Figure 20: Norovirus detection using advanced graphene compounds. Adapted from (Sengupta & Hussain, 2021).

Another promising biosensor is the fabricated carbon electrode-based biosensor, whose electrode was modified with AuNPs, graphene, and flower-like VS2 (AuNPs/Gr–VS2/glassy carbon electrode; GCE) and immobilized with aptamer for the detection of the avian influenza (H5N1) virus. The graphene provided a large surface area to hold more AuNPs, which in turn resulted in a highly sensitive virus detection with a low detection level of the order of 5.2×10^{-14} M (Chekin et al., 2018; Nehra et al., 2019). Other researchers investigated the integration of GCEs with porous rGO and MoS_2, which was immobilized with the human papillomavirus (HPV)-16 L1 specific aptamer for the selective detection of the HPV, and this method resulted in a low detection limit of 0.1 $ng.mL^{-1}$ (Navakul et al., 2017; Ping et al., 2015).

Other theoretical researchers found that the use of graphene on top of the gold films in SPR biosensors greatly increased the sensitivity and showed that the sensitivity of the sensor, with 20 graphene layers, increased up to 50% (Fu et al., 2015). Additionally, the examination of the change in the Surface Plasmon Resonant Frequency (SPRF) and sensitivity with respect to the target concentrations by increasing the number of graphene layers found that a greater number of layers contribute to higher values in SPRF and sensitivity (Chen et al., 2018).

Additionally, graphene and gold nanocluster incorporated into a GCE provided a good detection of human immunodeficiency virus with an improved detection limit. Moreover, graphene quantum dots were used as well with gold-embedded polyaniline nanowires in their highly sensitive impedimetric biosensor for the detection of the hepatitis E virus (Chowdhury et al., 2019).

Many researchers succeeded in developing highly sensitive graphene-based biosensors with Pico-molar limit of detection (Pumera, 2011). Graphene-based FETs are the most studied biosensors because they can be easily integrated with the commercially available read-out systems, but the leakage current that takes place in them due to the lack of the intrinsic bandgaps in graphene sometimes results in low sensitivity. Solving the leakage issue using proper doping and bandgap engineering techniques will contribute to the efficient implementation of the graphene biosensors.

Chapter 3: Materials and Methods

Different steps in the synthesis of the graphene are explained in this chapter. Also different fabrication steps and processes involved in the fabrication of GFET using the synthesized graphene as channel material are elaborated.

3.1 Graphene Synthesis

Epitaxial growth provides high quality single and multi-layer graphene films grown on silicon carbide (typically on 4H- and 6H-SiC). Among more than 200 polytypic of SiC, only cubic (3C-) SiC grows on the Si substrate. Here epitaxial growth of graphene is done using Gas Source Molecular-Beam Epitaxy (GSMBE) and Mono Methyl Silane (MMS) as a single source gas on the 3C-SiC (110) surface.

The first step is the cleaning of the starting sample B-doped, p-type Si (110) substrates, where it was polished to remove scratches and other defects, and then cleaned with acetone and isopropyl alcohol. The non-contact radiation heating was made possible by thin tungsten film placed on the rear face. Then it was cut to 7 × 40 mm^2 size, is moved to the reactor. Again, clean surface is achieved by degassing and flash-annealing in vacuum for several times at 1200°C, by bringing into an ultra-high vacuum MBE chamber. Mono Methyl Silane (MMS) (99.999%) as the source gas is introduced in to the chamber at a pressure of 3.3×10^{-3} Torr. First stage is a buffer layer formation (at 600°C for 5 min) and followed by SiC growth (at 1000°C for 120 min). The sample will then be annealed in vacuum (at 1200°C for 30 min) after withdrawing MMS from the chamber. The prepared sample can be evaluated using Raman-scattering microscopy (Renishaw, Ar 514 nm) (Nakazawa et al., 2000).

3.2 GFET Fabrication

The next step is fabrication of the field effect transistor with the graphene as channel material using conventional top-down lithography and processing techniques. The graphene channel interconnects the drain and source terminals, and a gate dielectric is used to isolate gate from the graphene channel. Here top gated technology is used to achieve field effect responses in liquid environment and to ensure good sensitivity of the analyte (Ma et al., 2012).

The device fabrication process includes photolithography or E-beam lithography, metal deposition, plasma etching, plasma dielectric deposition, and wire bonding. GFETs are fabricated on a SiC substrate with metal contacts. The first step is ohmic contact formation where the source and drain electrodes are made on the graphene layer with a source drain spacing of 10 micrometers. Here a 30 nm thick Ti and 100 nm thick Au are used as electrode material and are patterned by a liftoff process. Different steps in photolithography are explained below, and the different steps in lithography process are used to define the FLG (Few Layer Graphene) layer, then next step is removing the extra area, except the device active area which is done

using low energy oxygen plasma.

The different steps in photolithography process are:

1.Wafer cleaning: remove any impurities on the substrate.

2. Dehydration baking: remove any moisture on the surface.

3. Primer coating: coat the wafer with a primer.

4. Photoresist coating: coat the surface with a uniform photoresist layer.

5. Soft baking: remove the solvents from the resist layer.
6. Mask alignment: align the patterns on the mask with the wafer surface.
7. Exposure: expose the resist to an UV or DUV light.
8. Development: remove the unwanted resist on the surface by a developer.
9. Hard baking: harden the photoresist and improve the adhesion of the photoresist to the surface.

Figure 21 illustrates the different steps in the photolithography procedure.

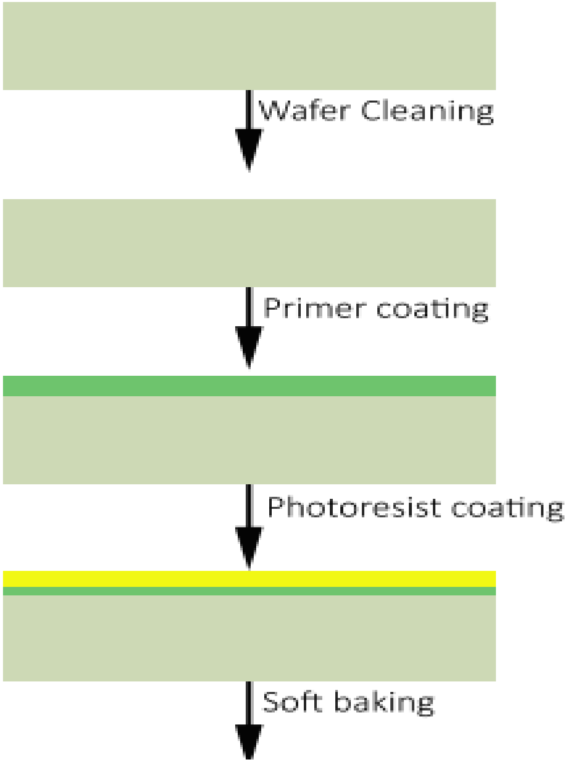


Figure 21: Different steps in potolithography. Adapted from (Aziz et al., 2012)

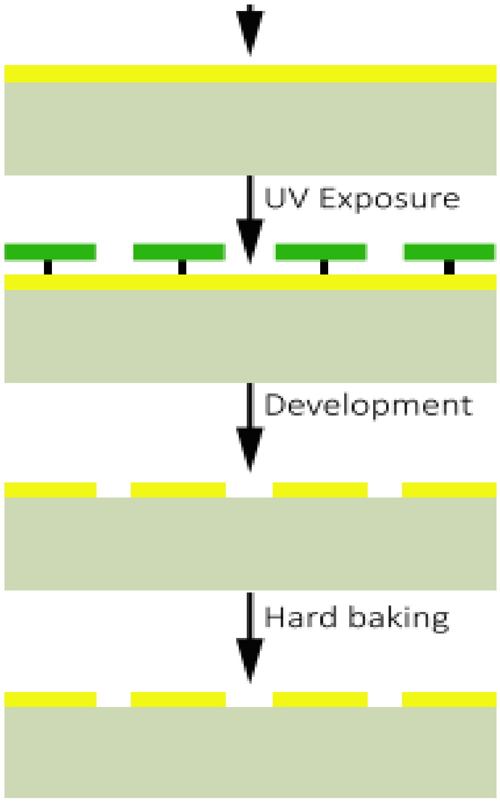


Figure 21: Different steps in photolithography. Adapted from (Aziz et al., 2012) (continued)

The different steps in fabrication procedure can be summarized as following:

1. Epitaxial graphene growth.

2. Deposition of metal contact Pd/Au.

3. PMMA spin coating and baking. (7% PMMA, spin speed: 5k RPM; baking:180ºC for 60 seconds).

4. 1st E-beam patterning on PMMA.

5. PMMA development.

6. RIE pure oxygen etching. (Power: 100 W; pressure: 100 mtorr; flow rate: 20 sccm; etching time: 60 seconds).

7. PMMA removal with acetone (30 minutes).

8. HSQ spin coating and baking.

9. 2nd E-beam patterning on HSQ to define the HSQ insulating layer over the graphene.

10. HSQ development (Developer: AZ300MIF; developing time: 60 seconds).

11. MMA/PMMA bilayer spin coating and baking. (Bottom layer: MMA, spin speed 5k RPM, baking: 150ºC for 60 seconds; Top layer: PMMA (3%), spin speed: 5k RPM, baking: 180ºC for 60 seconds).

12. 3rd E-beam patterning on MMA/PMMA bilayer to define the regions for top gate electrodes.

13. Deposition of top gate electrodes (60 nm Al) by an E-beam evaporator (Base pressure: 2×10−6 torr; evaporation rate: 1 A per second).

14. Liftoff of MMA/PMMA bilayer by acetone (30 minutes).

15. Wire bonding and preliminary electrical test.

Figure 22 shows the schematic diagram of the fabricated GFET biosensor, and Figure 23 shows the microscopic image of this GFET device.

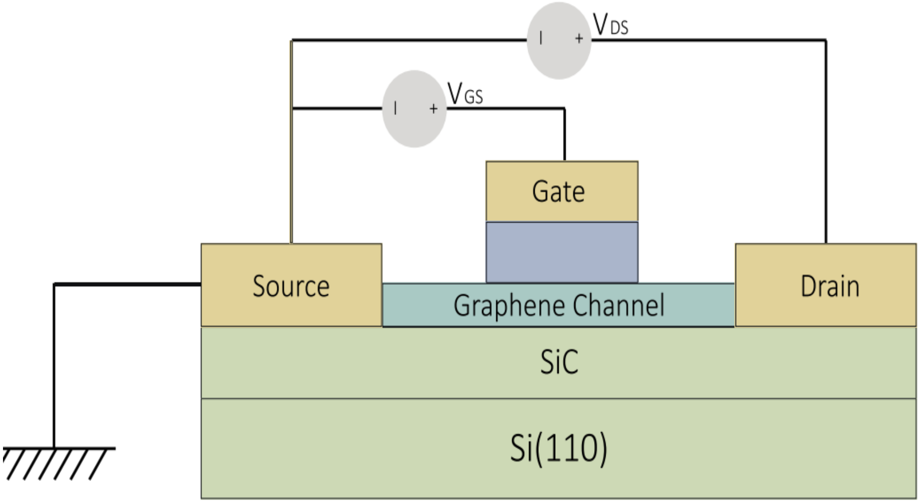


Figure 22: Schematic diagram of the fabricated GFET biosensor.

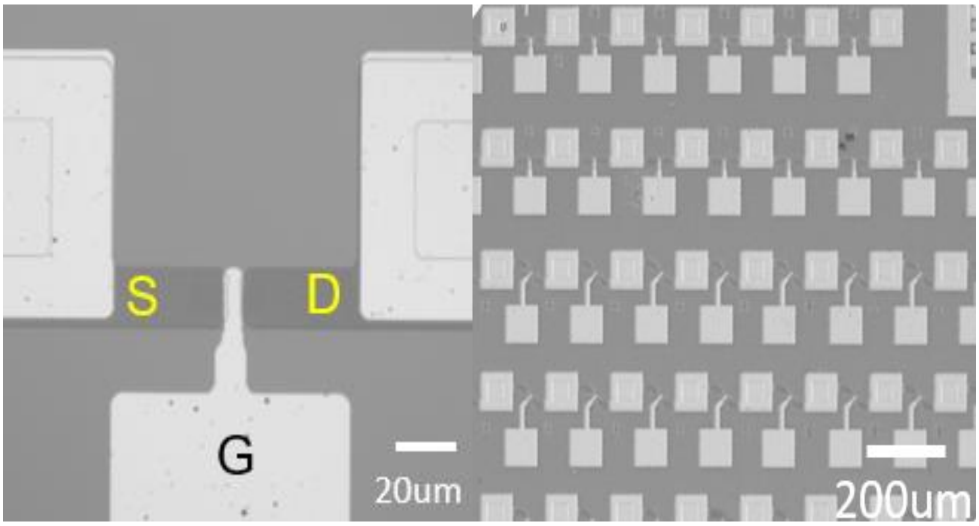


Figure 23: SEM image of the GFET biosensor.

Chapter 4: Results and Discussion

4.1 Electrical Measurements and Transfer Characteristics

In the field effect transistor, for a given drain-source voltage (V_{DS}) a current (I_{DS}) flows through the channel, from drain to source. This current can be modulated by applying a potential (V_{GS}) on the third terminal (the gate), which in turn can alter the charge of the channel (Figure 24). Biological events at the channel surface causes changes in the surface potential variation of the semiconductor channel and hence in the channel conductance.

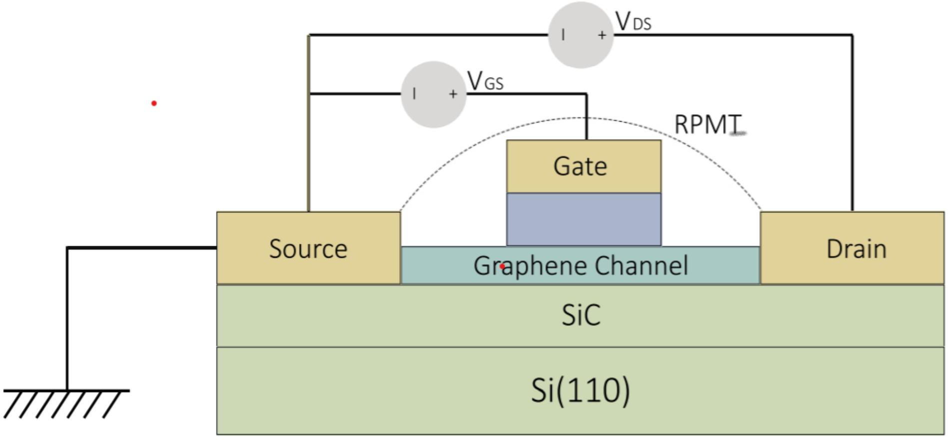


Figure 24: Electrical measurements in RPMI medium.

Several instruments like ammeter, multiple voltage sources and Model 2602B (Keithley Instruments) were used to record the voltage and current values. Figure 24 shows the I–V test configuration for the device. The drain current (I_{DS}) is depended on the voltage (V_G) applied to the gate terminal via an Ag/AgCl electrode.

The I-V characteristics recorded by varying the voltage V_D and corresponding I_D values are tabulated. Then the transfer characteristics is drawn using tabulated data (Figure 25). The recorded data and graph show that fabricated device didn't behave like typical biosensor. The electrical measurements were repeated by applying a biological solution RPMI to the graphene channel through a pipette. There were no significant changes in the I-V values with application of RPMI solution (Figure26).

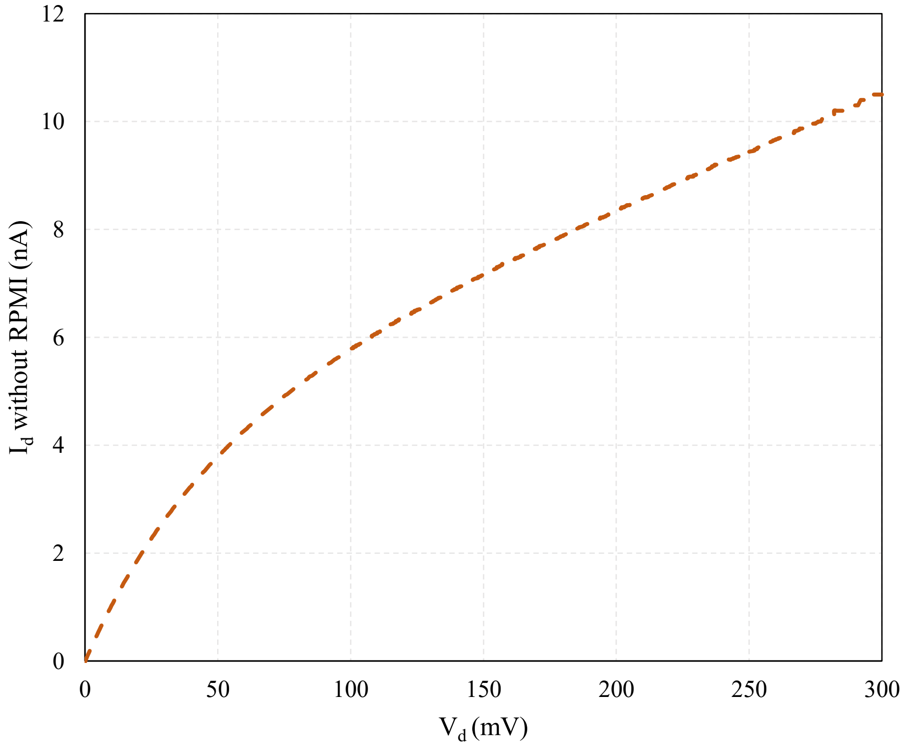


Figure 25: I-V characteristics of the GFET biosensor.

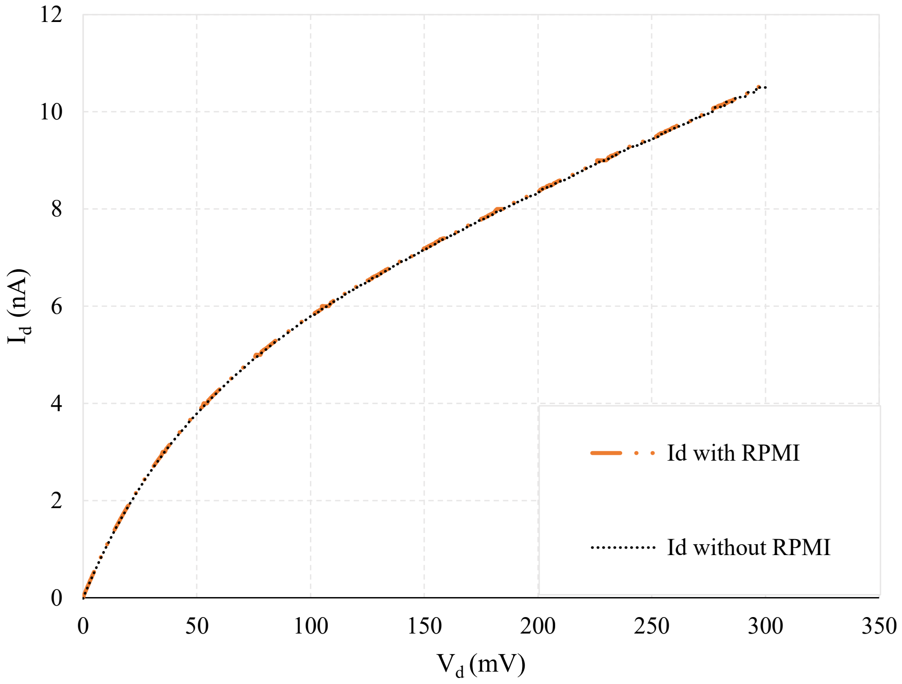


Figure 26: I-V characteristics with and without RPMI solution.

4.2 Discussion

The output I-V values indicate that the fabricated device didn’t behave like the typical GFET, this may be due to the improper establishments of the graphene channel or metal contacts during fabrication process. Also, if the graphene layer didn’t grow continuously and cover the channel region properly, it may result in wrong behavior of the device. The graphene is very small area between the drain and source with 10 micrometer size and mean channel width, and the SEM image shows that top gate contact is touching SiC area below the graphene. All these may be the reason for the inappropriate behavior of the fabricated device. Moreover, channel should be protected by a chemically resistant layer to ensure proper working in aqueous environment.

Chapter 5: Conclusion and Future Perspectives

5.1 Conclusion and Limitation of the Study

The discovery of 2D nanomaterial made a great impact in electronic industry and in biosensor field mainly due to their exceptional physical, electro-chemical, optical properties. Familiarized the features and characteristics of the first 2D nanomaterial graphene, and evaluated its scope in biosensing field. A GFET was fabricated using graphene as the channel material, and the transfer characteristics were plotted. The V-I characteristics were repeated with biological solution RPMI.

The research question mentioned in Section 1.3 was achieved successfully. The features and characteristics of graphene are explained in detail in Chapter 1. The scope of graphene in electronic bio sensing and the different architecture of graphene-based biosensors are also elaborated. The electrical measurements were repeated after introducing a biological solution RPMI in the channel region, but transistor didn’t show much difference in. This may be due to the. The performance of GFET depends on the graphene quality and the fabrication methodology of the device, and it is very important to have a high-quality defect free graphene for the device to perform properly.

5.2 Future Outlook

As a future work, the graphene or its derivatives can be functionalized with specific antibody to improve the current sensors. The immobilization of specific analyte by adsorption, covalent binding, entrapment, or membrane confinement onto the bioreceptor results in a change in the electrical properties. Highly sensitive and more linear response biosensors can be developed using hybrid or advanced graphene nano composite materials like gold Nano-Particles (AuNPs) or Magnetic Nano-Particles (MNPs). Research report shows graphene percolated with specific antigen can be used in various glucose sensors and to detecting SARS-CoV-2, or detecting other viruses, bacteria and cancerous tumors.

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UAE UNIVERSITY MASTER THESIS NO. 2022:10

This thesis is concerned with the study of integration of 2D material graphene in the development of sensitive and rapid biosensors. A GFET electronic biosensor with graphene as channel materials is designed and fabricated, and the transfer characteristics is plotted. The developed FET sensor with appropriate modification can be used in the sensitive detection of biomolecules.

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