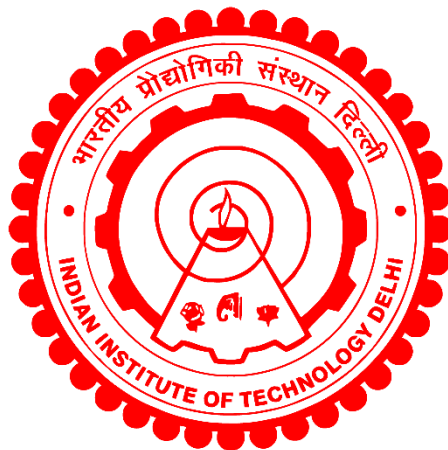


DEVELOPMENT OF SENSITIVE AND SELECTIVE FIELD EFFECT TRANSISTOR BASED BIOSENSORS

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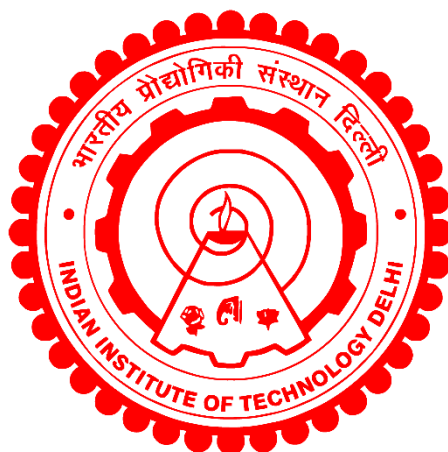
By

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Submitted

*in fulfillment of the requirements of the degree of Doctor of Philosophy
to the*



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JULY 2024

*Dedicated to my
Family*

CERTIFICATE

This is to certify that the thesis entitled, “**DEVELOPMENT OF SENSITIVE AND SELECTIVE FIELD EFFECT TRANSISTOR BASED BIOSENSORS**” being submitted by **Mr. SUMIT SHARMA** to the Indian Institute of Technology Delhi for the award of the degree of “**Doctor of Philosophy**”, is a record of bonafide research work carried out by him under our guidance and supervision.

In our opinion, the thesis has reached the standard of fulfilling the requirement of all the regulations regarding to the degree. The results contained in this thesis have not been submitted, in part or in full, to any other university or institute for the award of any degree or diploma.

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Sumit Sharma

Abstract

The use of biosensors for early stage disease detection and disease prognosis is becoming more and more popular every day. Among the different available biosensing platforms, Field Effect Transistor (FET) based sensors are the most popular nowadays for their various applications. The FET based biosensors offer the advantage of high sensitivity, low concentration of analyte detection, real-time sensing capability, quick response, and most importantly ease of integration with the integrated circuits (ICs). The wide usability of FET biosensors lies in the variable working characteristics such as working in chemical and physical medium and the variety of materials that are available for its fabrication. FET based biosensors have possibility of scalability and commercialization because they follow standard complementary metal-oxide semiconductor (CMOS) compatible fabrication process steps. This work majorly focusses on the development of highly sensitive biosensors based on the FET technology for saliva and plasma-based biomarker detection on a real time basis and the prospects of their batch fabrication.

In this work, a highly responsive FET biosensor based on tungsten trioxide (WO_3) thin film to detect physiological concentration of total ammonia (ammonium NH_4^+ and NH_3) in human body fluids is presented. The elevated level of ammonia in the body fluids indicates improper functioning of organs, mainly liver. Thus, real-time monitoring of ammonia concentration in human body fluid acts as a prognostic marker for liver disorders. It has been observed that the fabricated FET device shows reliable and accurate results towards ammonia sensing with the peak response of 498 at 100 μM and a limit of detection (LoD) of 6 μM . This is also capable of real-time detection of very low concentration of ammonia (2 μM) with a wide detection range from 2 to 100 μM . This study demonstrates a unique and stable sensing platform, that is capable of direct detection of ammonia concentration in human plasma, without any preprocessing of sample for point of care applications.

Apart from ammonia, the second most common analyte associated with the improper functioning of human organs is hydrogen sulphide (H_2S). Human plasma and saliva normally contain 10 μM to 100 μM of hydrogen sulphide, variation in this concentration range has been linked to various disorders. Owing to the advantages of layered transition metal dichalcogenides (TMDs) like high surface to volume ratio and good charge transport characteristics, an ultrasensitive field-effect transistor using layered TMDs is demonstrated to detect dissolved H_2S in plasma and saliva. The developed biosensor effectively utilizes a

few layers of MoSe₂ as a channel material for the FET device. The fabricated biosensor exhibits the highest response of 78 at the lowest H₂S concentration of 1 μ M and a wide linear dynamic range (between 1 μ M and 1 mM). With the lowest detection limit of 1 μ M, the fabricated biosensor is appropriate for quick and real-time detection of H₂S in plasma and saliva for point-of-care applications.

Layered TMDs show promise for sensing due to their high surface to volume ratio but lack in selectivity. To address this issue, an innovative hybrid structure is proposed for precise bioanalytes detection. So, this work focusses on the organic/inorganic hybrid transistor structure for biosensing application. Organic polymers are crucial for the interfacial characteristics of the sensors as organic polymer film have redox sensitivity, bio-immobilization potential, and ion-to-electron charge transportation make it appealing for analyte sensing. With the excellent electron transport capability of inorganic 2D TMDs and high surface sensing capability of organic polymers via electron to ion transport, MoSe₂/P3HT hybrid transistor has been fabricated. This hybrid FET device is used for ammonia detection in saliva and plasma in the concentration range of 0.5 μ M to 1 mM. This hybrid sensor shows improved response and more stable output towards the ammonia detection as compared to only inorganic or organic FET device.

Eventually, the device architecture of WO₃ FET device was further optimized and fabricated to demonstrate its applicability in another biosensing application. The channel surface of WO₃ FET device is modified with different bio linkers to make it specific for particular biomarker detection. In the first step of this work, WO₃ thin film channel layer is modified with (3-Aminopropyl) triethoxysilane (APTES) cross linker to bind the CYFRA 21-1 antibody with the channel layer, next the surface is modified with the bovine serum albumin (BSA) blocking agent to avoid any nonspecific interaction at FET channel surface. At last, CYFRA 21-1 antigen in artificial saliva interacted at the channel surface to detect oral cancer biomarker in saliva. The presented work demonstrated the detection capability of different CYFRA 21-1 concentrations in artificial saliva to detect oral cancer biomarker and showed a response in real-time. In this work, the FET sensors fabrication is demonstrated over entire 2-inch wafer and the uniformity among the device is tested from the prospective of batch fabrication and scalability.

सार

प्रारंभिक चरण की बीमारी का पता लगाने और रोग के पूर्वानुमान के लिए बायोसेंसर का उपयोग हर दिन अधिक से अधिक लोकप्रिय हो रहा है। विभिन्न उपलब्ध बायोसेंसिंग प्लेटफार्मों में, फील्ड इफेक्ट ट्रांजिस्टर (एफईटी) आधारित सेंसर आजकल अपने विभिन्न अनुप्रयोगों के लिए सबसे लोकप्रिय हैं। एफईटी आधारित बायोसेंसर उच्च संवेदनशीलता, विश्लेषण का पता लगाने की कम मात्रा, वास्तविक समय संवेदन क्षमता, त्वरित प्रतिक्रिया और सबसे महत्वपूर्ण रूप से एकीकृत सर्किट (आईसी) के साथ एकीकरण में आसानी का लाभ प्रदान करते हैं। एफईटी बायोसेंसर की व्यापक उपयोगिता परिवर्तनशील कार्य विशेषताओं में निहित है जैसे कि रासायनिक और भौतिक माध्यम में काम करना और इसके निर्माण के लिए उपलब्ध सामग्रियों की विविधता। एफईटी आधारित बायोसेंसर में स्केलेबिलिटी और व्यावसायीकरण की संभावना है क्योंकि वे मानक पूरक धातु-ऑक्साइड अर्धचालक (सीएमओएस) संगत निर्माण प्रक्रिया चरणों का पालन करते हैं। यह काम मुख्य रूप से वास्तविक समय के आधार पर लार और प्लाज्मा-आधारित बायोमार्कर का पता लगाने के लिए एफईटी तकनीक पर आधारित अत्यधिक संवेदनशील बायोसेंसर के विकास और उनके बैच निर्माण की संभावनाओं पर केंद्रित है।

इस काम में, मानव शरीर के तरल पदार्थों में कुल अमोनिया (अमोनियम NH_4^+ और NH_3) की शारीरिक एकाग्रता का पता लगाने के लिए टंगस्टन ट्राइऑक्साइड (WO_3) पतली फिल्म पर आधारित एक अत्यधिक उत्तरदायी एफईटी बायोसेंसर प्रस्तुत किया गया है। शरीर के तरल पदार्थ में अमोनिया का उंचा स्तर अंगों, मुख्य रूप से यकृत के अनुचित कार्य को इंगित करता है। इस प्रकार, मानव शरीर के तरल पदार्थ में अमोनिया एकाग्रता की वास्तविक समय की निगरानी यकृत विकारों के लिए एक रोगसूचक मार्कर के रूप में कार्य करती है। यह देखा गया है कि निर्मित एफईटी डिवाइस $100 \mu\text{M}$ पर 498 की चरम प्रतिक्रिया और $6 \mu\text{M}$ की पहचान (LoD) की सीमा के साथ अमोनिया सेंसिंग की दिशा में विश्वसनीय और सटीक परिणाम दिखाता है। यह 2 से $100 \mu\text{M}$ तक की विस्तृत पहचान सीमा के साथ अमोनिया ($2 \mu\text{M}$) की बहुत कम सांद्रता का वास्तविक समय का पता लगाने में भी सक्षम है। यह अध्ययन एक अद्वितीय और स्थिर संवेदन मंच को प्रदर्शित करता है, जो मानव प्लाज्मा में अमोनिया एकाग्रता का प्रत्यक्ष पता लगाने में सक्षम है, देखभाल अनुप्रयोगों के बिंदु के लिए नमूने के किसी भी पूर्वप्रसंस्करण के बिना।

अमोनिया के अलावा, मानव अंगों के अनुचित कामकाज से जुड़ा दूसरा सबसे आम विश्लेषण हाइड्रोजन सल्फाइड (H_2S) है। मानव प्लाज्मा और लार में आमतौर पर हाइड्रोजन सल्फाइड के 10

μM से $100 \mu\text{M}$ होता है, इस एकाग्रता सीमा में भिन्नता को विभिन्न विकारों से जोड़ा गया है। उच्च सतह से मात्रा अनुपात और अच्छे चार्ज परिवहन विशेषताओं जैसे स्तरित संक्रमण धातु डाइचल्कोजेनाइड्स (टीएमडी) के फायदों के कारण, प्लाज्मा और लार में घुलित H_2S का पता लगाने के लिए स्तरित टीएमडी का उपयोग करके एक अति संवेदनशील क्षेत्र-प्रभाव ट्रांजिस्टर का प्रदर्शन किया जाता है। विकसित बायोसेंसर प्रभावी रूप से एफईटी डिवाइस के लिए एक चैनल सामग्री के रूप में MoSe_2 की कुछ परतों का उपयोग करता है। निर्मित बायोसेंसर $1 \mu\text{M}$ की सबसे कम H_2S सांद्रता और एक विस्तृत रैखिक गतिशील सीमा ($1 \mu\text{M}$ और 1 mM के बीच) पर 78 की उच्चतम प्रतिक्रिया प्रदर्शित करता है। $1 \mu\text{M}$ की सबसे कम पहचान सीमा के साथ, निर्मित बायोसेंसर प्वाइंट-ऑफ-केयर अनुप्रयोगों के लिए प्लाज्मा और लार में H_2S का त्वरित और वास्तविक समय में पता लगाने के लिए उपयुक्त है।

स्तरित टीएमडी अपने उच्च सतह से मात्रा अनुपात के कारण संवेदन के लिए वादा दिखाते हैं लेकिन चयनात्मकता में कमी है। इस मुद्दे को हल करने के लिए, सटीक बायोएनालिटिक्स का पता लगाने के लिए एक अभिनव वर्ण-संकर संरचना प्रस्तावित है। इसलिए, यह काम बायोसेंसिंग अनुप्रयोग के लिए कार्बनिक/अकार्बनिक वर्ण-संकर ट्रांजिस्टर संरचना पर केंद्रित है। कार्बनिक पॉलिमर सेंसर की इंटरफेशियल विशेषताओं के लिए महत्वपूर्ण हैं क्योंकि कार्बनिक बहुलक फिल्म में रेडॉक्स संवेदनशीलता, जैव-स्थिरीकरण क्षमता और आयन-से-इलेक्ट्रॉन चार्ज परिवहन इसे विश्लेषण संवेदन के लिए आकर्षक बनाते हैं। अकार्बनिक दो आयामी टीएमडी की उत्कृष्ट इलेक्ट्रॉन परिवहन क्षमता और इलेक्ट्रॉन से आयन परिवहन के माध्यम से कार्बनिक पॉलिमर की उच्च सतह संवेदन क्षमता के साथ, $\text{MoSe}_2/\text{P3HT}$ हाइब्रिड ट्रांजिस्टर का निर्माण किया गया है। इस हाइब्रिड एफईटी डिवाइस का उपयोग लार और प्लाज्मा में अमोनिया का पता लगाने के लिए $0.5 \mu\text{M}$ से 1 mM की एकाग्रता सीमा में किया जाता है। यह हाइब्रिड सेंसर केवल अकार्बनिक या कार्बनिक एफईटी डिवाइस की तुलना में अमोनिया का पता लगाने के लिए बेहतर प्रतिक्रिया और अधिक स्थिर परिणाम दिखाता है।

अंतर्था, WO_3 FET डिवाइस के डिवाइस आर्किटेक्चर को एक और बायोसेंसिंग एप्लिकेशन में इसकी प्रयोज्यता प्रदर्शित करने के लिए और अनुकूलित और निर्मित किया गया। WO_3 एफईटी डिवाइस की चैनल सतह को विभिन्न बायोलिंकर के साथ संशोधित किया जाता है ताकि इसे विशेष बायोमार्कर का पता लगाने के लिए विशिष्ट बनाया जा सके। इस काम के पहले चरण में, WO_3 पतली फिल्म चैनल परत को चैनल परत के साथ CYFRA 21-1 एंटीबॉडी को बांधने के लिए (3-एमिनोप्रोपिल) ट्राइथॉक्सीसिलेन (APTES) क्रॉस लिंकर के साथ संशोधित किया जाता है, इसके बाद सतह को एफईटी चैनल की सतह पर किसी भी गैर-विशिष्ट बातचीत से बचने के लिए गोजातीय सीरम एल्बुमिन (बीएसए) अवरुद्ध प्रतिनिधि के साथ संशोधित किया जाता है। अंत में, कृत्रिम लार में CYFRA 21-1 एंटीजन ने

लार में मौखिक कैंसर बायोमार्कर का पता लगाने के लिए चैनल की सतह पर बातचीत की। प्रस्तुत कार्य ने मौखिक कैंसर बायोमार्कर का पता लगाने के लिए कृत्रिम लार में विभिन्न CYFRA 21-1 सांद्रता की पहचान क्षमता का प्रदर्शन किया और वास्तविक समय में प्रतिक्रिया दिखाई। इस काम में, एफईटी सेंसर निर्माण पूरे 2-इंच वेफर पर प्रदर्शित किया जाता है और डिवाइस के बीच एकरूपता का परीक्षण बैच निर्माण और स्केलेबिलिटी की संभावना से किया जाता है।

Contents

<i>Acknowledgements</i>	i
<i>Abstract</i>	iii
<i>Contents</i>	ix
<i>List of Figures</i>	xiii
<i>List of Tables</i>	xv
<i>List of Abbreviations</i>	xvii
CHAPTER – 1 Introduction	1
1.1 Overview	3
1.2 Field Effect Transistor-based Biosensors.....	7
1.2.1 Background of Field Effect Transistor Devices	7
1.2.2 Working Mechanism of FET-based Biosensors.....	8
1.2.3 Metal Oxide-based FET Biosensors	10
1.2.4 Two-dimensional Transition Metal Dichalcogenide based FET Biosensors	11
1.3. Choice of Biomarker	15
1.3.1 Plasma as a Biofluid for Biomarker Identification.....	16
1.3.2 Saliva as a Biofluid for Biomarker Identification	16
1.4. Biosensor Characteristics	17
1.4.1 Response.....	17
1.4.2 Response Time	17
1.4.3 Selectivity	17
1.4.4 Limit of Detection (LoD)	18
1.4.5 Stability.....	18
1.5 Motivation	19
1.6 Objectives.....	19
1.7 Thesis Organization.....	19
1.8 References	22

CHAPTER – 2 Highly Sensitive Tungsten Oxide Thin Film-based Field-Effect Transistor for Real Time Monitoring of Dissolved Ammonia in Human Plasma33

2.1 Introduction	35
2.2 Experimental Section	37
2.2.1. Device Fabrication.....	37
2.2.2 Ammonia Sample Preparation in Plasma	38
2.3 Structural Characterization of WO ₃ Nanostructure.....	39
2.4 Results and Discussion.....	41
2.4.1 Electrical Characterization	41
2.4.2 Real-time Detection and Response of Ammonia in Plasma.....	42
2.4.3 Detection Mechanism	44
2.4.4 Selectivity Test	45
2.5 Ammonia Detection by Standard Ammonia Kit Assay	46
2.6 Scalability and Stability	48
2.7 Summary	49
2.8 References	50

CHAPTER – 3 Highly Sensitive, Rapid And Real-Time Detection Of Hydrogen Sulphide In Human Blood Plasma And Saliva Using MoSe₂ Field-Effect Transistor55

3.1 Introduction	57
3.2 Device Fabrication	59
3.3 H ₂ S Sample Preparation in Plasma and Saliva.....	60
3.4 Results and Discussion.....	61
3.4.1 Structural Characterization	61
3.4.2 Electrical Characterization	62
3.5 Biosensor Characterization	63
3.5.1 H ₂ S Detection in Plasma.....	63
3.5.2 H ₂ S Detection in Saliva	64
3.5.3 Real-time Detection of H ₂ S in Plasma and Saliva.....	64

3.6 Detection Mechanism.....	66
3.7 Summary	68
3.8 References	68
CHAPTER – 4 Hybrid MoSe₂/P3HT Transistor for Real-Time Ammonia Sensing In Biofluids	73
4.1 Introduction	75
4.2 Hybrid FET Fabrication	78
4.3 Ammonia Sample Preparation in Artificial Saliva and Human Plasma.....	78
4.4 Device Characterization	79
4.5 Results and Discussion.....	80
4.5.1 Hybrid Structural Characterization.....	80
4.5.2 Electrical Characterization MoSe ₂ and MoSe ₂ /P3HT FET	81
4.5.3 Ammonia Detection in Saliva and plasma for MoSe ₂ /P3HT FET	84
4.5.4 Ammonia Detection in Saliva and Plasma for MoSe ₂ FET.....	87
4.6 Selectivity and Stability Test.....	88
4.8 References	91
CHAPTER – 5 Scalable WO₃ FET Biosensor for Oral Cancer Detection in Saliva	99
5.1 Introduction	101
5.2 Scalable WO ₃ Thin-film FET Biosensors Fabrication	103
5.3 Artificial Saliva and CYFRA 21-1 Antigen Sample Preparation in Saliva	103
5.4 Experimental Section	105
5.4.1 WO ₃ Surface Functionalization with APTES.....	105
5.4.2 WO ₃ Surface Functionalization with anti-CYFRA 21-1	106
5.4.3 WO ₃ Surface Functionalization with BSA	106
5.5 Results and Discussion.....	107
5.5.1 Structural Characterization of Biofunctionalized WO ₃ Surface.....	107
5.5.2 Electrical Characterization of WO ₃ FET Device.....	111

5.5.3 Electrical Characterization of Biofunctionalized WO ₃ FET	112
5.5.4 Efficient Capture and Selective Detection of CYFRA 21-1 Antigen in Saliva.....	113
5.5.5 Real-time CYFRA 21-1 Antigen Detection in Saliva and Buffer	114
5.5.6 Detection Mechanism	118
5.6 Scalability and Stability Test.....	118
5.7 CYFRA 21-1 Detection by ELISA Kit and Comparison with FET Device	119
5.8 Summary	122
5.9 References	122
CHAPTER – 6 Summary, Conclusion and Future Scope.....	129
6.1 Summary of Research Work	131
6.2 Conclusion of the Thesis	133
6.3 Future Scope of the Work	133
List of Publications and Key Achievements	135
<i>Biography</i>	139

List of Figures

Figure 1. 1 Schematic representation of biosensors and different components of biosensors. .4	4
Figure 1. 2 Schematic showing potentials of FET based biosensors for point-of-care applications.7	7
Figure 1. 3 Working mechanism for FET biosensor includes design and corresponding output signals.8	8
Figure 1. 4 Advantages of choosing Metal-oxide and 2D TMDs semiconductors as a sensing layer in FET biosensors.9	9
Figure 1. 5 Metal-oxide thin-film based FET biosensors.10	10
Figure 1. 6 Layered TMDs based FET biosensors12	12
Figure 1. 7 MoS ₂ based FET biosensors for DNA detection.13	13
Figure 1. 8 Pictorial depiction of biofluids collected from different body parts.15	15
Figure 1. 9 Biosensor performance characteristics.17	17
Figure 2. 1 Fabrication process flow of WO ₃ thin film FET biosensor.39	39
Figure 2. 2 Material characterization by spectroscopic techniques40	40
Figure 2. 3 Material characterization by microscopic techniques41	41
Figure 2. 4 Electrical characterization of fabricated FET device.42	42
Figure 2. 5 Biosensor characterization for dissolved ammonia.43	43
Figure 2. 6 Band diagram at different stages of device i.e., before biasing, after biasing and after plasma ammonia interaction.44	44
Figure 2. 7 Selectivity test with common interfering analyte.45	45
Figure 2. 8 Dissolved ammonia characterization using standard ammonia assay kit.46	46
Figure 2. 9 Uniformity characterization.48	48
Figure 3. 1 Fabrication process flow.60	60
Figure 3. 2 Material characterization.60	60
Figure 3. 3 Electrical characterization.63	63
Figure 3. 4 Biosensor characterization with dissolved H ₂ S concentration in plasma.63	63
Figure 3. 5 Biosensor characterization with dissolved H ₂ S concentration in saliva.64	64
Figure 3. 6 Time-based spectra for dissolved H ₂ S sensing.65	65
Figure 3. 7 Conduction mechanism for dissolved H ₂ S sensing.66	66
Figure 4. 1 (a) Schematic illustration of back gated hybrid FET device device (b) Optical image of hybrid FET device.79	79

Figure 4. 2 Microscopic Characterization of hybrid nanostructure.	80
Figure 4. 3 Raman spectrum using 514 nm laser (a) MoSe ₂ (b) P3HT (c) MoSe ₂ /P3HT hybrid structure.....	81
Figure 4. 4 Electrical performance of MoSe ₂ and hybrid device.....	82
Figure 4. 5 Transfer characteristics for different devices before and after P3HT film coating	83
Figure 4. 6 Electrical characteristics of hybrid device at different ammonia concentration in saliva.	84
Figure 4. 7 Real-time biosensing measurements at different ammonia concentration in saliva and plasma.	85
Figure 4. 8 Uniformity test among device D2, D3, and D4.....	86
Figure 4. 9 Electrical characterization of MoSe ₂ device at different ammonia concentration and performance comparison with hybrid device.....	88
Figure 4. 10 Selectivity and Stability test.	89
Figure 5. 1 Schematic representation of fabrication process flow.....	104
Figure 5.2 Schematic representation of WO ₃ thin film FET at different surface functionalization steps.....	105
Figure 5. 3 Spectroscopic characterization of WO ₃ thin film.....	106
Figure 5. 4 Microscopic analysis of WO ₃ thin film.	107
Figure 5. 5 Microscopic analysis of WO ₃ thin film using AFM.....	108
Figure 5. 6 Spectroscopic analysis of WO ₃ thin film using XPS.....	109
Figure 5. 7 Fluorescence microscopic image of antigen (CYFRA-21-1) on sapphire substrate bound to BSA/anti-CYFRA-21-1/APTES/WO ₃ by using rhodamine 6G dye bound antibodies.	110
Figure 5. 8 Electrical performance of WO ₃ FET device.....	111
Figure 5. 9 Transfer characteristics of device after different biofunctionalization steps.....	112
Figure 5. 10 Electrical performance of WO ₃ transistor device with CYFRA 21-1 antigen.	113
Figure 5. 11 Selectivity test for CYFRA 21-1 antigen.	114
Figure 5. 12 Real-time sensing and response for CYFRA 21-1 antigen.	115
Figure 5. 13 CYFRA 21-1 antigen detection in PBS.....	116
Figure 5. 14 Band diagram representation of conduction mechanism WO ₃ channel layer at different stages of antigen sensing.....	117
Figure 5. 15 Stability and repeatability test.	119

List of Tables

Table 1. 1 FET based biosensor for different biomarker detection in biofluids.	6
Table 2. 1 Comparison of this study with previously reported biosensors for ammonia detection in plasma and whole blood.	49
Table 3. 1 Comparison of Fabricated FET Biosensor with Available Sensing Techniques for Dissolved H ₂ S Detection in Biofluids.....	67
Table 4. 1 Comparison of hybrid FET biosensor with previously reported techniques for ammonia detection for human health monitoring.	90
Table 5. 1 Validation of WO ₃ FET biosensor response using ELISA kit.....	120
Table 5. 2 Comparison of present study with previously reported biosensors for CYFRA 21-1 in saliva.	121

List of Abbreviations

AFM	Atomic Force Microscopy
AFP	Alpha Fetoprotein
APTES	3-Aminopropyl Triethoxysilane
BHF	Buffered Hydrofluoric acid
BSA	Bovine Serum Albumin
BUN	Blood Urea Nitrogen
CDC	Centre for Disease Control and Prevention
CMOS	Complementary Metal Oxide Semiconductor
CV	Cyclic Voltammetry
CVD	Chemical Vapor Deposition
DI	Deionized
DPV	Differential Pulse Voltammetry
EDX	Energy Dispersive X-ray Spectroscopy
EGFET	Electrolyte Gated Field Effect Transistor
EIS	Electrochemical Impedance Spectroscopic
ELISA	Enzyme-Linked Immunosorbent Assay
FESEM	Finite-Element Scanning Electron Microscopy
FET	Field Effect Transistor
FTIR	Fourier Transform Infrared Spectroscopy
GC	Gas Chromatography
HPLC	High Pressure Liquid Chromatography

ICNIRP	International Commission on Non-ionizing Radiation Protection
ISFET	Ion-sensitive Field Effect Transistor
KPFM	Kelvin Probe Force Microscopy
LOD	Limit of Detection
MOSFET	Metal Oxide Semiconductor Field Effect Transistor
NASH	Non-alcoholic Steatohepatitis
NHS	N-hydroxy Succinimide
NW	Nanowire
PBS	Phosphate Buffer Saline
PCR	Polymerase Chain Reaction
POC	Point of Care
PSA	Prostate-specific Antigen
RBC	Red Blood Cells
RCA	Radio Corporation of America
RF	Radio Frequency
RIE	Reactive Ion Etching
RPA	Renal Papillary Antigen
SAM	Self-Assembled Monolayer
SCCM	Standard Cubic Centimeter per Minute
SEM	Scanning Electron Microscopy
SERS	Surface Enhanced Raman Spectroscopic
Si	Silicon

SOI	Silicon on Insulator
SPR	Surface Plasmon Resonance
TMDs	Transition Metal Dichalcogenides
WBC	White Blood Cells
WF	Work Function
WHO	World Health Organization
XRD	X-ray Diffraction