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Review of the Recent Advances in Nano-Biosensors and Technologies for Healthcare Applications †

M.W.Aqra [1] and A.A. Ramanathan [2,*]

[1] National Center for Research and Development, Amman-11941, Jordan; maha.aqra@ncrd.gov.jo
[2] Department of Physics, University of Jordan, Amman-11942, Jordan
* Correspondence: amallahmad@gmail.com

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Abstract: The growing human population and the discovery of new diseases and emerging pandemics have increased the need for healthcare treatments and medications with innovative design. The emergence of nanotechnology provides a platform for novel diagnostic and therapeutic in vivo non-invasive detection and treatment of ailments. It is now the era of IOT (internet of things) and data acquisition and interpretation from various parts of the human body in real time is possible with interconnected sensors and information transfer devices. Miniaturization, low power consumption and price with compatibility to existing network circuits are essential requirements in IOT. Biosensors made from nanostructured materials are the ideal choice due to the unique structural, chemical, and electronic properties of these materials with the advantage of large surface to volume ratio which makes them very successful for use as sensors for detection of diseases, drug carriers, filters, fillers and reaction catalysts in healthcare applications. In this mini review, we will review the recent progress made in research and applications of biosensors in health and preventive medicine. The focus of the article will be on biosensors made from layered nanomaterials like graphene and its structural analogs molybdenum disulphide (MoS_2) and boron nitride (BN). We will discuss and highlight the present capabilities of the different nano forms of these materials in the detection and analysis of diseases. Their efficiency in terms of detection limits, sensitivity and adaptability to different environments will also be discussed. In addition, the challenges and future perspectives of using nano-biosensors to develop efficient diagnostic, therapeutic and cost effective monitoring devices with smart technologies will be explored.

Keywords: electronic tongues and noses; 2D materials; nanopores; preventive medicine; non-invasive

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1. Introduction

The detection of biological molecules, ions or species of interest (analyte) through the measurement and analysis of signals proportional to the concentration of the analyte is the basic function of a biosensor. The biological/chemical information needs to be transformed into readable outputs through the transducer. The biosensors used in the detection and prevention of diseases need to be non-invasive, highly selective, flexible and sensitive [1-3]. In addition in order to acquire and interpret signals from different parts of the body with interconnected or multifunctional sensors, the sensor design needs to be innovative and compatible with smart technologies that can transfer data with high speed and accuracy [4, 5]. Moreover, several constraints such as biocompatibility, reliability, stability, comfort, convenience, miniaturization, costs need to be considered [6]. The last decade has seen tremendous research on 2D materials like graphene, graphene oxide, MoS_2 etc in different nano forms for sensing applications in the health care, environment and other sectors [7-14].

Graphene (Gr) the first 2D material discovered with its one atomic layer honeycomb structure has remarkable electronic, mechanical and optical properties and has seen a multitude of applications [15-17]. Gr analogs MoS_2 and BN also have the honeycomb lattice and layered structure that allows for easy fabrication of 2D and other nanostructures due to the weak inter layer Van der Waal interactions.

A lot of research has been going on in the area of Gr and beyond Gr nanomaterials (NM) during the past decade and it is necessary to put into perspective and highlight the progress of Gr, MoS_2 and BN nanostructures in biosensing for the healthcare sector. This is a rapidly changing and highly researched field with new discoveries and innovation and requires frequent update of the progress and challenges. This motivates us to present a focussed review with literature survey of the recent developments (last five years) on Gr and its structural analogs MoS_2 and BN in the detection and analysis of diseases in terms of efficiency, detection limits, sensitivity and adaptability to different environments. We will discuss and highlight the present capabilities of the different nano forms of these materials. In addition the challenges and future perspectives of using nano-biosensors to develop efficient diagnostic, therapeutic and cost effective monitoring devices with smart technologies for healthcare and preventive medicine will be explored. The article is arranged under the main headings: Introduction, Nano-Biosensors, Smart technologies and Challenges OR opportunities.

2. Nano-Biosensors

2.1. Biosensor types

Biosensors are two component devices consisting of a receptor and a transducer. The receptor is a biological recognition element which could be an enzyme, microorganism, tissue, antibody or nucleic acid. The transducer converts the physiochemical change due to the interaction of the analyte with the receptor into an analytical output signal, which is coupled to an appropriate data processing system. A schematic diagram of the process is shown in Figure 1.

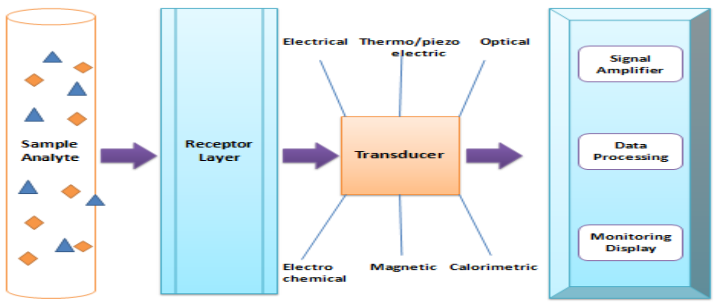

Figure 1. Schematics of a biosensor unit.

Electrical, optical, electrochemical, micromechanical, calorimetric, magnetic, thermoelectric, and piezoelectric transducers can be employed in biosensors and the choice depends on the sensing environment and needs. Materials have been researched widely by the materials science community for use to fabricate the best suited biosensor.

2.2. Nanostructured materials for biosensing

Gr and Gr like MoS_2 and BN NMs are the best materials so far for biosensing. The unique layered and honeycomb structure of these materials allows for easy synthesis of monolayers (ML), bilayers (BL), nano-flakes, nanotubes and hetrostructures with a wide range of bandgaps and a diverse variety of optoelectronic properties. In addition, due to the weak inter layer Van der Waals forces one can intercalate with atoms of different species and functionalize them easily to obtain the desired properties at will; moreover the NMs have the advantage of large surface to volume ratio which is important in efficient immobilization of receptors on the surface of the NM for good sensor performance [18]. All these factors make them prime candidates for use as biosensors in healthcare applications. In Figure 2 we give a graphical representation of the NMs for biosensing that best describes the scope of this review.

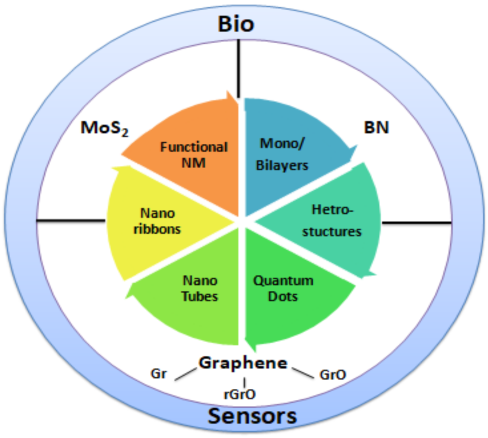

Figure 2. Graphical representation of nanostructured materials for biosensing.

2.2.1. Gr nano-biosensors

A Graphene layer has hexagonal symmetry with a honeycomb structure and the in plane C atoms are bonded by strong covalent sp^2 bonds with the nearest neighbours and an out of plane delocalised π bond as shown in Figure 3(a). It is the delocalised π electrons that are responsible for the extremely high room temperature mobility of 15,000–200,000 cm /Vs, [19]. Moreover Gr has excellent mechanical strength on account of the strong covalent bonding and is optically transparent and highly flexible [20, 21].

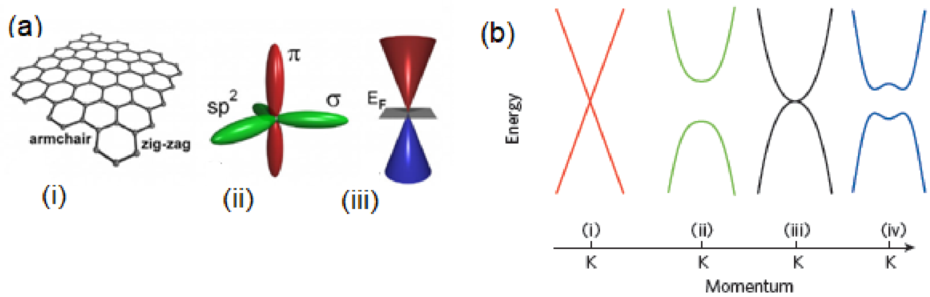

Figure 3. (a) (i) Graphene geometry (ii) bonding, and (iii) related band diagram [19] (b) (i) Schematic diagram showing the Dirac Fermi cone (ii) the modification of the band by chemical or geometry restrictive doping (iii) the modification of the band by bilayer graphene; (iv) and finally, the modification of the bands in doped bilayer graphene [22].

The high electrical and thermal conductivity, mechanical strength, flexibility, optical transparency and ultrathin (one atom thickness) of Gr are ideal characteristics for sensing applications. Sensor selectivity plays a very important role in its design and this is very closely related to the NM senor characteristics, so selectivity can only be improved by fine tuning the NM properties. The NM interacts with target bio-molecules by either a Physisorption or Chemisorption process. Physisorption, although fast, is a non covalent bonding reaction and is not preferred as the bio-molecules do not bind completely thereby affecting the sensitivity. Chemisorption can be brought about by the presence of defects, vacancies, doping and chemical functionalization, all of which increase the reactivity and enhance the selectivity to the target species. Figure 3(b) depicts band structure changes of Gr by changing the geometry, thickness and doping mechanisms. Graphene oxide (GrO) 2D material produced by the oxidation of Gr is semiconducting and has a finite gap as compared to Gr. It has the advantage of being stable in water and other solvents and can be easily functionalized. Reduced graphene oxide (rGrO) is obtained by the removal of the oxygen functional groups and has the advantages of Gr and GrO; being conducting and having chemically active defect sites. Bandgap engineering and chemical functionalizing of Gr through use of graphene derivatives like graphene oxide (GrO) and reduced graphene oxide (rGrO) and composites have proved to work well as sensors (including wearable sensors, and implantable devices) for human health monitoring as reported in Table 1. Body temperature is an important indicator of abnormal body functions and its measurement is one of the first lines of action in suspicious cases. We see ample evidence of this during the current Covid19 pandemic. It is also linked to our biological clock and can be used to monitor an individual's sleep patterns, which is important in determining the overall health and mental fitness. Table 1 gives a summary of the various Gr based sensors along with body functions tested, the mechanism of sensing, sensitivity & range when available and the reference to the corresponding work.

Table 1. Summary of details of graphene based sensors in health monitoring.

NM	Body function	Sensing mechanism	Sensitivity	Range	Ref.
Freestanding single rGrO; 3D Gr-PDS composite	Body temperature	Resistance based	- -	- -	[23] [24]
Gr/PDMS; Graphene	Body movements	Piezo-capacitive strain; textile strain	0.24 kPa^{-1} 0.0078 kPa^{-1}	0–10 kPa 10–100 kPa	[25] [26]
Inkjet printed Gr	Heart rate	Electronic	-	-	[27]
	Wrist pulse	Strain;pressure	-	-	[28] [29]
Gr-rubber composite; rGrO	Body movements +Respiration rate	Strain	- -	- -	[30] [31]
Gr porous network	Blood pressure	Pressure+strain	-	-	[32]
3D Nano implant; Nano hybrid fiber	Blood glucose Sweat glucose	Electrode Electrocatalytic	- -	- -	[33] [34]
3D Gr Scaffold	ECG	implant	-	-	[35]
Gr; Porous Gr	EMG	Electronic skin	- -	- -	[36] [37]
3D Gr Scaffold; Gr	EEG	Implant Electronic skin	- -	- -	[35] [36]

2.2.2. MoS_2 and BN nano-biosensors

Similar to Gr in honeycomb structure 2D MoS_2 and hBN have all the advantages of Gr for sensing mentioned in the previous section. These Van der waal structures exhibit unique optical and electronic properties that make them very appealing for biosensing [38]. Moreover, they have the added advantage of bandgaps unlike Gr which has a zero gap; this improves the sensitivity of sensor devices made from these materials especially in sensors.

MoS_2 is a prototype of a class of materials termed transition metal dichalcogenides (TMDs) and has markedly anisotropic properties, as seen from its electrical resistivity among other properties. The resistivity in a direction perpendicular to the planes is about 1000 times greater than in the parallel direction. Unlike Gr which is one atom thick, a ML of MoS_2 has three atomic layers Sulfur–Molybdenum–Sulfur. The physical properties of MoS_2 change markedly at the nanoscale. The bulk material has an indirect band gap of ~1.2 eV, while the ML has a direct and broader band gap of ~1.8 eV [39]. Hence, it shows thickness dependent band-gap properties, allowing for the production of tuneable optoelectronic devices with diversified spectral operation.

The electronic and optical properties of Gr and MoS_2 is complemented by hBN which is an insulator with a large indirect bandgap value of`~5.95 eV [40] in bulk form and in the ML limit crosses over to a direct bandgap material with a gap of 6.1eV[41]. The sensing mechanisms of these materials could be electrical-based sensing, through charge transfer which alters the resistance or optical sensing where due to the charge transfer, the surface Plasmon resonance (SPR) gets modified and can be detected; or the biomolecules are detected by their spectral fingerprints.

Hybrid structures of Gr, Mos2 and BN have also been highly researched to increase the scope of biosensing capabilities of these NM. This is the topic of the next section.

2.2.3. Hetrostructures

2D Gr, GrO, rGrO, MoS_2, hBN can all be used like Lego blocks to build interesting hetrostructures by mixing and matching for increased selectivity and sensitivity of the nano-biosensensors. This process of electrostatic doping by stacking of these Van der Waal structures can be used to obtain unique and tuneable electronic properties. Figure 4 shows a graphical representation of a hetrostructures that can be made with the basic single layers of Gr, hBN and MoS_2.

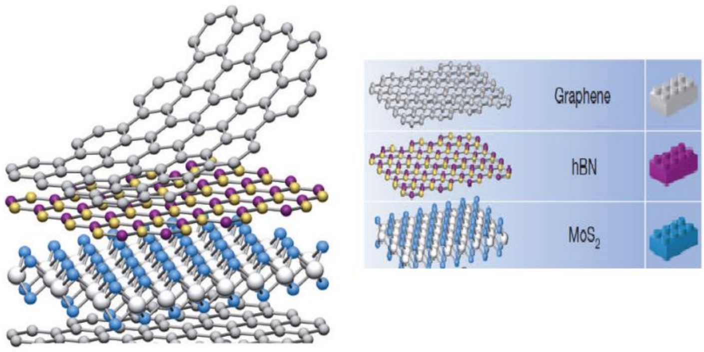

Figure 4. Graphical representation of possible hetrostructures that can be made by stacking multiple van der Waal layered structures in different orderings. Adapted from [42].

Hetrostructures although highly desirable, require careful considerations of lattice mismatch, misalignment of layers and introduction of unforeseen defects during the deposition and the epitaxial growth. Hexagonal BN is an insulating analogue of graphite with a small lattice mismatch (~1.8%), and so it is an ideal substrate for graphene and a key building block in many van der Waals hetrostructures. Graphene-hBN integrated devices have been recently used for DNA sequencing by current modulation [43] and distinguishing nucleotides in DNA [44]. SPR based biosensor consisting of graphene/hBN hybrid structure for the detection of biomolecules was reported in 2019 [45]. SPR technique was also used in a biosensor consisting of MoS_2/graphene hybrid structure with Au as a substrate was used to detect biomolecules using SPR [46]. Again in 2017, angle based SPR biosensor made of MoS_2 /Al film/MoS_2/graphene heterostructure was used to detect biomolecules [47]. In Table 2 we have summarized the various Nano biosensors made from MoS_2, hBN, Gr, Gr derivatives and hetrostructures of these NMs in the recent years. The table gives the nanomaterials used, the species detected, the sensing mechanism, sensitivity, detection range, the year of publication and reference to the publication.

Table 2. Summary of Nanobiosensors with references and year of research.

NM	Analyte	Sensing Mechanism	Detection limit	Range	Ref.+year
MoS_2	DNA	Fluorescence quenching	500 pM	0-50 nM	[48]; 2014
MoS_2/Gr	Acetaminophen	Electrochemical	20 nM	0.1–100 μM	[49]; 2013
Gr/MoS_2	DNA hybridization	Photoluminescence	1 attomolar		[50]; 2014
MoS_2/Gr on Au	Biomolecule	SPR		10−6 RIU	[46]; 2015
MoS_2/Gr-Al hybrid	Biomolecule	Angle based SPR	190.83°/RIU		[47]; 2017
Gr	PMMA, PVP	IR transmission spectroscopy	-	-	[51]; 2014
Gr	ssDNA	Phase based SPR	1 attomolar	-	[52]; 2015
Gr	Glucose	FET	0.5 μM	-	[53]; 2015
Gr	Carcinoembryonic antigen (CEA)	FET	100 pg/ml		[54]; 2016
Gr	Protein	Acoustic Gr plasmons	-	-	[55]; 2017
Multi-channel Gr	DNA	FET	10 pM	-	[56]; 2017
rGrO + Trityl Organic Radical	Xanthine	Electrode based	0.52 nM	-	[57]; 2017
GrO	hCG	Angle based SPR	0.06 mM	-	[58]; 2017
hBN	Dopamine	Neurotransmittor	10 μM	-	[59]; 2016
hBN	CBP	IR vibrational spectroscopy	-	-	[60]; 2018
Gr/hBN	DNA sequencing	Current Modulation	-	-	[44]; 2017
Gr/hBN	DNA sequencing	Current Modulation	-	-	[43]; 2019
Gr/hBN	Biomolecule	SPR	4.207 μm/RIU		[45]; 2019

3. Smart technologies

Early stage detection and prevention of chronic and fatal diseases requires continuous monitoring. Data acquisition and interpretation from various parts of the human body in real time is possible with interconnected sensors and information transfer devices in today's era of internet of things (IOT). The unprecedented advancements in electronics and sensor technologies coupled with Big Data and AI offer exciting opportunities in the field of smart and sustainable healthcare. The stage is now set to shift from the old medical procedures and protocols and adapt smart integrated medical testing with nano-devices for diagnosis and therapeutics [61, 62]. We need to do away with costly and bulky equipment and old fashioned laboratories and embrace wearable and miniaturised sensors that use interstitial fluid (ISF) instead of blood to detect the minute changes in biomarkers with sweat, tears and breath analysis that contain a wealth of information about the body malfunctions [1-3]. Wireless, powerless nano-devices made from biocompatible materials that can be worn on the skin (patches, tattoos, watches etc), in textiles, in the eye, mouth, teeth (miniaturised implants) and other innovative means using non-invasive probes are the need of the day. Electronic Nose, Tongues and Skin are the new innovative smart technologies that are the future of health care monitoring and preventive medicine [63-67].

4. Challenges OR opportunities

A challenge, limitation or drawback is an opportunity for improvement, change in strategy or chance for innovation. Although, nano-biosensors research show that considerable improvements to health care monitoring can be made, commercial products are few and from small companies [68]. Before large-scale and widespread manufacturing of 2D and other nanostructured devices for health-related applications can be realized, uniformity and controlled synthesis is necessary to rule out device to device variability. This is crucial for large scale commercialization and the challenge has been met as indicated by the recent research and publications addressing this issue [69, 70].

In addition, in vivo and point of care diagnostics require biocompatibility and toxicity issues to be addressed. Precise control of the NM properties and biocompatibility are required especially in the local biological environment where the devices are to be used with a thorough understanding of the complex physiochemical interactions. The recent years has seen tremendous work in this direction with good progress [71-73].

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