Nanomaterials for Biosensing Applications in the Medical Field

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Abstract The combination of nanotechnology and biotechnology has emerged as an integrated technology for medical applications. Over the world, day by day, numerous researchers are developing novel materials using the suitable platform to detect pathogenic, mutagenic, or toxic compounds or any biological effect. This chapter addresses the classification of biosensors, especially for medical applications based on the two most important parameters: bio-recognition element and signal transduction. Furthermore, several grooming biosensing technologies are also addressed. Subsequently, more emphasis has been added to nanomaterial classification employed in the biosensors based on their chemical contents and structural dimensions. Additionally, more insight into the current challenges in the application of nanomaterials in biosensors, especially for medical applications, has been demonstrated.

Keywords Biosensors · Biomedical detection · Nanomaterials · 2D materials · Carbon materials

1 Introduction

The alarming rise in several pandemic and epidemic diseases like severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), black fungus, cancer, etc., has forced the researcher to think up more advanced biological detection and monitoring systems

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to detect carcinogenic, mutagenic, and toxic elements [1–4]. Although modern technologies and industrialization have simplified our lives to a new level, others left behind several environmental issues leading to serious health issues [5]. Thus, it is highly desirable to design and explore the challenges in developing advanced detection and monitoring systems, especially bio-detection and bio-monitoring systems, to better human health. The potential of biosensors in various functional fields is schematically presented (Fig. 1). The technology that highly depends on genetically modified organisms can be treated as biosensor technology which is emerging in advancement. The research in biosensor had drawn attention when Gary Sayler's group reported the report of the genetically modified microbial biosensor in the early 1990s [6]. According to van der Meer and Belkin biosensor [7], a device detects the chemical and biological changes in the system and transforms them into a measurable signal when the biological materials interact with this engineered device. Based on the type of biological materials interacting with the bio-reporter, the sensor is nomenclatured by different names. When the biological material is an antibody or whole-cell or nucleic acid, it is termed as an immunosensor or microbial biosensor, or DNA aptamer [8], respectively. Basically, there are four major components in the biosensor namely; (i) bio-receptor, (ii) transducer, (iii) a signal processing unit, and (iv) a display or interface unit that showcases the output signal (schematically shown in Fig. 2).

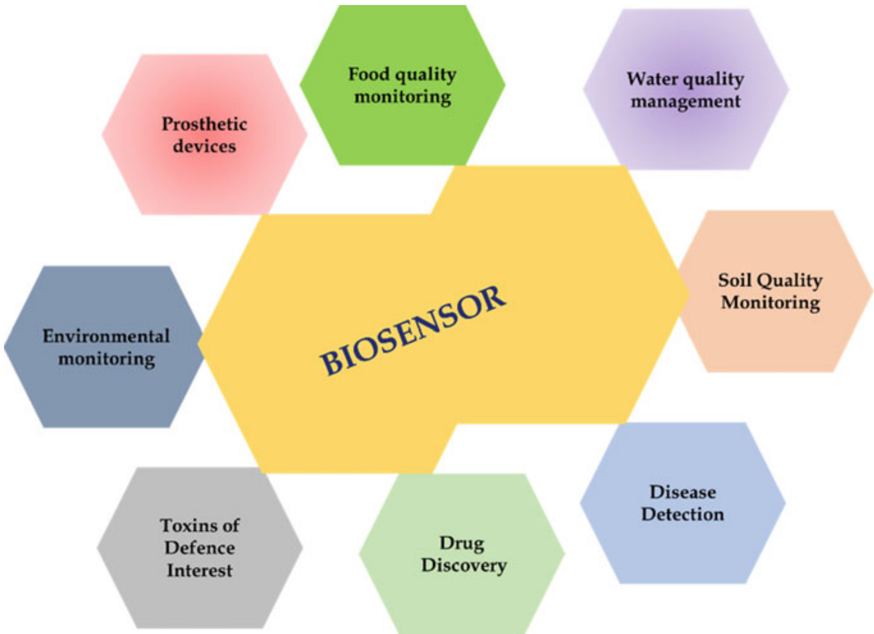

Fig. 1 Potential of biosensor in various fields of application in schematic form

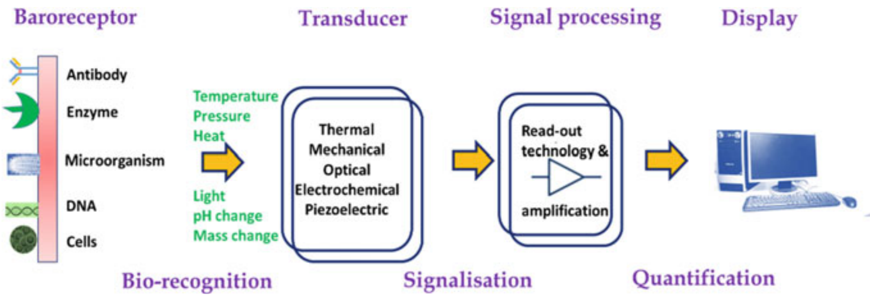

Fig. 2 Schematic of the biosensor

More research in experimental and theoretical aspects is timely required to use the biosensors as the first filter for pre-screening the samples. The potential of synergetic research in engineering with biology has an enormous potential in designing biosensors for advanced applications. Thus, it is highly desirable to understand the fundamental changes in the biological sensing behavior of living beings. Some of the natural examples are (i) vibration, tactile, and airflow sensors in spiders, (ii) fast response of the plants toward the change in luminous intensity, osmotic pressure, temperature, water availability, etc., (iii) the snapping system in venus flytrap, (iv) dogs possess a sense of smell far beyond the sensing behavior of the artificial sensor. More significantly, dogs can detection system is so sensitive that it can detect the concentration of parts per billion, and (v) the system for controlled bending of trees, etc. In the above, all cases functional outputs are highly correlated to materials behavior with biological needs.

The biosensing platform is expected to be mechanically robust, versatile, and high throughput that will simplify the life in developing individual medicine, in vivo-drug development, genomic-proteomic research, and point-of-care medical diagnosis [9]. Integrated technologies where nanotechnologies coupled with micro-fabrication technologies are able to develop new biosensors for medical applications [10]. However, the above type of advanced biosensor fabrication is in the embryonic stage and needs more research and development to enhance sensitivity, specificity, and high throughput. In this contest, designing the building blocks of the biosensor, i.e., the sensing materials in different scales and dimensions, has received considerable attention. Especially, nanomaterials in various dimensions and squeezing the atomic scale dimension have demonstrated fascinating bio-molecule detection behaviors. The work of Nam et al. [11] using nanoparticles and Liber et al. [12] using nanowires to design ultrasensitive biosensor is the pioneer in this area of research.

Several up-to-date sensor platforms are tested and proposed [13–16], especially for bio-molecule detection; additionally, few integrated technologies are in the next research phase before the medical diagnosis [10, 17–20]. In this chapter, the classification of biosensors based on bio-recognition elements and signal transduction has been described. The electrochemical, optical, thermal, and piezoelectrical sensors based on the signal transduction perspective are proposed. Additionally, the enzymatic, protein receptor, immunosensors, DNA aptamer, and whole-cell biosensors based on bio-recognition elements are expressed. In the next section of the chapter, the nanomaterials of different dimensions and compositions applied in biosensor design have thoroughly been elucidated. Very concisely, nanomaterials, especially the two-dimensional materials used in designing flexible energy harvest and sensing for biomedical applications, are presented. Further, the current challenge and future prospective design of nanomaterials for biosensing, particularly for biomedical applications, are outlined.

2 Biosensors for Medical Applications

Technically, the entire class of biosensors has been classified based on two critical perspectives out of several, i.e., signal transduction and biorecognition element. In the subsequent section, the above two prospectives are briefly elaborated as follows.

2.1 Signal Transduction Perspective

Based on the signal transduction perspective, biosensors are categorized as electrochemical, thermal, optical, and piezoelectric sensors [3]. The electrochemical sensors are the most advanced and vastly investigated sensors for vivo monitoring or on-site monitoring. Low detection limit, high sensitivity, and generalizability are the advantages of this sensor compared to other category sensors. This category of the sensor is miniaturized to a lab-on-chip. Based on the signal from the sensor measured, it is subcategorized as amperometric (measuring the current produced during oxidation and reduction of the electroactive species), voltammetry (measuring the change in voltage of the working electrode concerning the reference electrode), and conductometry (measuring the alteration in conductance due to biochemical reaction). During the ongoing COVID-19 pandemic, electrochemical biosensors have been considered a crucial tool for rapid, accurate, and large-scale diagnosis of severing acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) [2, 4, 21–23]. During the biochemical reaction, the absorbed or emitted photons are measured through an optical transducer. The optical phenomena studied to observe the alteration in biological responses include fluorescence, surface plasma resonance, and absorption. In parallel, the advancement of fiber optics technology has boosted optical sensor research to an extent level.

A thermal sensor, the most basic version, is a thermometer that is used to measure body temperature. However, the temperature range and toxicity of mercury limit its uses. Modern thermal sensors or enzyme thermistors are designed with a principal component called a sensitive thermistor based on similar working mechanisms. The function of the thermistor is to accurately estimate the change in enthalpy of the system during the biochemical reactions [24]. The piezoelectric sensor reciprocates the relationship between the resonant frequency change with respect to the mass of the molecule absorbed or desorbed on the crystal surface. The direct, label-free interaction with analyte mode is an efficient way of piezoelectric sensing platform. It is observed that the antibody or antigen is the best bio-molecule to be compatible with the piezoelectric sensor surface [25, 26].

2.2 Bio-recognition Perspective

Based on the bio-recognition perspective, the biosensors are categorized as enzymatic, protein receptor, immunosensor, DNA aptamers, and whole-cell biosensors. Each of the categories is elaborated as below.

a. Enzymatic biosensors

This type of sensor enzyme is the primary component that recognizes and reacts with the analyte to produce the electrochemical outcome. The brief sketch consists of analytes, receptors, an electrochemical transducer, and a signal amplifier. Here, the enzyme acts as a catalyst. And the function of the electrochemical transducer is to convert the chemical signal from the bio-reaction into a measurable physical signal which is further amplified by an amplifier. Most enzyme-catalyzed reactions release oxygen, carbon dioxide, and residual ionic species, measured by a transducer [27]. Two types of analytical enzymes such as hydrolases and oxidoreductases are used in the enzyme biosensor.

b. Protein receptor-based biosensors

The role of protein is opposite to enzyme as discussed previously in enzyme sensor. In this case, the protein present in the cell membrane acts as a receptor and reacts in a non-catalytic way with the signal from the transducer and produces the detectable signal by the process of metabotropic receptors through enzyme secretion or ionotropic receptors. Optical transduction has a significant role in this type of sensing platform [28, 29].

c. Immuno-sensors

This is a solid-state device wherein the immunochemical reaction is coupled to a transducer which is a basic design to detect the direct binding between antibodies to an analyte. Due to direct detection, faster and more cost-effective detection is possible using this type of sensor. A most exciting feature of immune-sensor is their selective and sensitivity in detecting multiple analytes by designing new recombinant antibodies [30].

d. DNA aptamers biosensor

Aptamers are short, single-standard DNA or RNA, and less than a hundred nucleotides are arranged/assembled in a specific sequence. This aptamer can interact selectively with superior specificity and affinity forms bonding with a particular type of analyte, virus, bacteria, proteins, small molecules, toxins, hormones, etc., by hydrogen or Van der Waal binding force for biosensing. The beauty of these aptamers is that they can rearrange to form a variety of shapes and dimensions [31, 32]. Compared to immune sensor, DNA aptamer sensor is more specific, stable, and has a simple detection ability and also the cost is relatively lower. Due to its high stability, low cost, and superior specificity the DNA aptamer sensor is considered an alternative to antibodies.

e. Whole-cell biosensor

This type of sensor consists of two working components, i.e., the sensing element and reporter. The reporter element is a gene or gene cassette that has catalytic as well as non-catalytic functions. Catalytically, it accelerates the biochemical reaction to a detectable signal, and in a non-catalytic way as coding for the genes for metabotropic or ionotropic signal generation. The sensing element observes the gene or sets of gene's transcription initiation point similar to a promoter. The microbial sensor is the widely used whole-cell biosensor [33, 34]. Functional information rather than analytical information can be obtained using the whole-cell biosensor. The functional information can be obtained from the living cells by understanding the stimulus on a living system which can be applied in pharmacology, toxicology, cell biology, and many more. For example, the bacteria whole-cell biosensors can be genetically modified to sense mercury, nitrogen oxide, and hydroxylated polychlorinated biphenyls in urine and serum.

2.3 Limitations of Bio-based Biosensor

The major limitations that lag behind the bio-based biosensor are

1. First, low sensing performance with the low sensitivity and high limit of detection value of the designed sensor.
2. Due to limited active catalytic sites and surface area, bio-based biosensors have less chemical and catalytic activity.
3. The mechanical and cyclic performance stability and work life span of this type of sensor are very low.
4. Relatively low diffusivity of the bio-based biosensors. Especially in the electrochemical sensing case where the rate change of Faradic current is proportional to the diffusivity of the analyte on the electrode probe surface.

The above short-coming of the bio-based biosensors are tactically overcome by the use of engineered nanomaterials in the biosensor. Nanomaterials based biosensors are the rapidly growing research, especially for biosensor applications. Nanomaterials are basically used as transducer materials in biosensor development.

3 Nanomaterials in Biosensors

3.1 Metal Oxide Nanostructures

The beauty of the metal oxide nanostructures lies in their inherent functional biocompatibility, abundant active surface area in absorbing the bio-molecules, and high catalytic property in immobilizing the biomolecules in a non-toxic way to enhance electron-transfer kinetics for effective sensing characteristics. Various metal oxides from metals like Fe, Zn, Ce, Mg, Zn, Cu, Ti, and Zr are extensively explored in the literature for biosensor applications (shown in Fig. 3) [35–37]. These oxides of different morphologies and dimensions are synthesized using various synthesis methods like hydrothermal, sol–gel, radio frequency sputtering, soft chemistry, etc. [3].

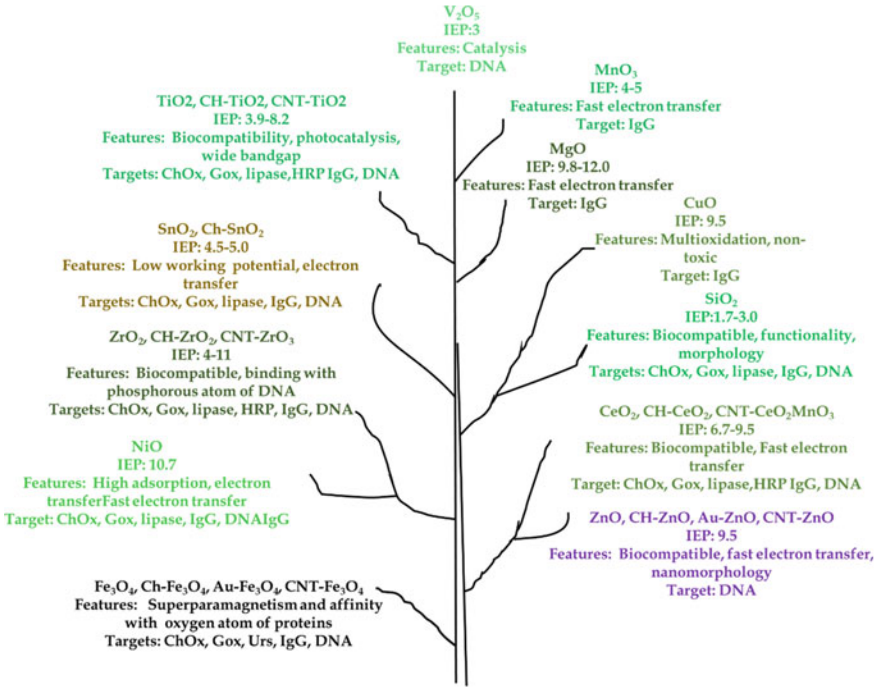

Fig. 3 Typical metal oxide nanostructures and their biosensing characteristics. The abbreviations in this picture can be read like this IEP as iso-electric point; ChO_x as cholesterol oxidase; GO_x as glucose oxidase; HRP as horseradish peroxidase; IgG as immunoglobulin G; Urs, as urease (adopted from Solanki et al. [35])

3.2 Chalcogenide Nanostructures

In biosensors, to enhance the optical, opto-electrical, electrical, and magnetic properties of the semiconducting oxides are deliberately used with metal oxide as a hybrid structure. Additionally, several semiconducting sub-atomic scale particles demonstrate fascinating biosensing characteristics. The use of semiconductor and semiconductor chalcogenide nanostructures is reported in optical transduction. As reported in the literature, semiconducting quantum materials are deliberately used in biosensing applications due to their superior photo-stability, size-dependent photoemission, and broad absorption. However, the structural defects in fine quantum dots enhance the radiative recombination leading to inaccurate emission estimation.

Several soft techniques are adopted to overcome such defects and make the transducer more sensitive toward analyte detection and bio-immobilization. Those are as follows.

(i) In the case of CdS, a layer of ZnS is coated on the surface to form a core–shell structure which acts as a photo-quencher: *Encapsulation*
(ii) Functionalization of the quantum dots to enhance biomolecule immobilization and minimize the chance of toxicity with a broad idea not to hamper the photophysical recombination: *Ligand exchange*
(iii) An extension of the previous step where the quantum dots are coated with silica to enhance the stability: *Silanization.*

This type of non-radiative or Fluro-quenched nanostructures is used as Förster/fluorescence Resonance Energy Transfer (FRET), especially for detecting optical DNA and oligonucleotides. Recently, two-dimensional nanomaterials and their derived quantum structures have demonstrated high potential donors in FRET-based sensing applications. These materials are graphitic carbon nitride (g-C_3N_4) [38], perovskite materials [39], selenium [40], 2D metal–organic/covalent organic frameworks [41], and their derived 2D quantum structures [42, 43]. The details of the above materials are tabulated in Table 1.

Bioluminescence resonance energy transfer (BRET) is another type of biosensing technique where semiconducting quantum nanostructures are used as the acceptor. It is a distance-dependent non-radiative energy transfer from a bioluminescent donor to a fluorescent acceptor through resonance energy transfer. Using this technique, the blood glucose level can be estimated from teardrops. Bioluminescence donors are natural enzymes collected from marine animals. Certain donors have specific functions based on their structural arrangement. Some of the BRET donor–acceptor pairs reported in the literature are listed below in Table 2. Recently, several quantum dots are used as the acceptor in BRET sensors due to their distinct advantages. Mattoussi et al. [60] tunable emission from Ag: ZnInSe QDs can be obtained by varying the In/Zn feeding ratio. This Ag: ZnInSe QDs demonstrates robust behavior in terms of tuning the emission to align the protein emission in the BRET sensor for several cycles. Some of the reported functionalized semiconducting quantum dots used in BRET sensors include polymer-coated CdSe/ZnS core–shell nanostructure [61],

Table 1 Summary of the FRET sensing applications of 2D nanomaterials as donors

Target analyst	Donor: acceptor pairs	Dynamic range	Detection limit	References
Bilirubin	MoS_2 QDs: bilirubin	0.5–10.0 μm	2.1 nm	[44]
MicroRNA	MoS_2 QDs: FAM-MBs	5–150 nm	0.38 nm	[45]
EP	MoS_2 QDs: $P_{EP\text{-}PEI}$ copolymers	0.2–40 μm	0.05 μm	[46]
AA	MoS_2 QDs: $P_{EP\text{-}PEI}$ copolymers	0.5–40 μm	0.2 μm	[46]
6-MP	MoS_2 QDs: DAP	0.5–70 μm	0.29 μm	[47]
BSA	MoS_2 QDs: RGO	5–50 nm	Not mentioned	[48]
Dopamine	MoS_2 QDs-aptamer: MoS_2 nanosheets	0.1–1000 nm	45 pm	[49]
BSA	MoS_2 QDs: polyaniline	10–70 nm	9.86 nm	[50]
GSH	MoS_2 QDs: R6G	5–50 nm	2.7 nm	[51]
Nitrite	MoS_2 QDs: BSA-Au NCs	0.5–20 mg/l	0.67 nm	[52]
NFZ	WS_2 QDs: NFZ	0.17–166 μm	0.055 μm	[53]
DNA	BP QDs: Dabcyl-L probe	4–4000 pm	5.9 pm	[54]
GSH	g-C_3N_4: MnO_2	NM	0.2 μm	[38]
H_2O_2	g-C_3N_4: MnO_2	0–130 μm	1.5 μm	[55]
Glucose	g-C_3N_4: MnO_2	0–150 μm	1.5 μm	[55]
Ricin	g-C_3N_4: MnO_2	0.25–50 μg/ml	190 ng/ml	[56]
Riboflavi	g-C_3N_4: riboflavi	0.4–10 μm	170 nm	[57]
Metronidazole	g-C_3N_4: metronidazole	0.01–0.10 μg/ml	0.008 μg/ml	[58]
Dopamine	BSA-Au NCs/g-C_3N_4: dopamine	0.05–8.0 μm	0.018 μm	[59]
Hg(II)	Perovskite: RBED	20–90 μm	2.36 μm	[39]

semiconductor polymer nanoparticles with poly[2-methoxy-5-((2-ethylhexyl)oxy)-p-phenylenevinylene] (MEH-PPV) [62], carboxylated quantum dots (Qd-625) [63], annexin V·RLuc-QDs [64], and glutathione-coated CdSeTe/CdS QDs [65].

Table 2 Summary of bioluminescent proteins used in BRET sensing application

Bioluminescent proteins	Emission (nm)	Substrate	References
Vargula luciferase (Vluc) or Cypridina luciferase	460	Vagulin (Cypridina luciferin)	[66]
Bacterial luciferase (Lux)	490	$FMNH_2$ long-chain aliphatic aldehydehdacf	[67]
Gaussia luciferase (Gluc)	480	Coelenterazine	[68]
Metridia luciferase	480	Coelenterazine	[69]
Renillaluciferase (Rluc)	480	Coelenterazine	[70]
Aequorin	469	Coelenterazine	[71]
Firefly luciferase (Fluc)	562	D-luciferin	[72]
Nanoluciferase (Nluc)	460	Furimazine	[73]

3.3 Magnetic Nanoparticles

Intrinsic magnetic nanoparticles [74] and functionalized or coated nanoparticles have been applied in various biological applications like DNA [75] or cell separation [76], biological missiles [77], radio-immunoassay [78, 79], and in several varieties of biomolecule immobilization [80–87], especially for biosensor applications. Core–shell nanostructures of Fe_3O_4@polydopamine [88], Ferrocene-modified Fe_3O_4@SiO_2 nanoparticles [89], Au@Ni [90], Ag NPs@Fe_3O_4 [91], Fe_3O_4/Au @γ-Fe_2O_3/Au [92], etc., are designed for biosensor applications. Grancharov et al. [93] reported that the functionalized magnetic nanoparticles are used as biomolecular labels in magnetic tunnel junction-based biosensor. Chuang et al. [94] interpreted the time scale of Brownian relaxation of magnetic nanoparticles suspended in liquid obtained from the susceptibility variation as a function of frequency as a bio-magnetic target molecule sensor. Simultaneous detection of the magnetic field-assisted DNA hybridization is sensed using a spin valve sensor reported by Graham et al. [95]. Liu et al. [96] fabricated a phenol biosensor where carbon paste is used as the supporting substrate for chemically immobilized and functionalized core–shell magnetic nanoparticles.

Research on magnetic nanoparticle-based biosensors is limited to lab-scale devices and medical diagnosis instruments in miniature form for bedside medical diagnosis. Several NPs are used in medical diagnosis devices; their sensitivity, the minimum sample volume, and the analyte that can be detected using these instruments are listed in Table 3 which is adapted from Koh et al. [97]. One pioneer example is the μ-NMR designed by Weissleder et al. [10] using 39 nm functionalized iron oxide nanoparticles in the microfluidic network. Further, the improved version of the microcoils is embedded in PDMS to increase the filling factor and decrease the signal-to-noise ratio. Also, this instrument can detect a minimal amount of sample, i.e., 1 μl of the device [19, 20, 98].

Table 3 Magnetic nanoparticle used in different medical diagnosis instruments with their sensitivity [97]

	Analyte	Magnetic particle/instrumentation	Sensitivity	Sample volume (μL)	References
MRSw type I	Nucleotide	CLIO, benchtop relaxometer	Low nM-pM	300	[99]
	Proteins	CLIO, benchtop relaxometer	Low nM	300	[100]
	Virus	CLIO, MRI	50 virus/100μL	100	[101]
	Bacteria	Core/shell, DMR	20 CFUb/100 μL (membranefitered)	5	[20]
	Cancer cell	Mn-MNP, DMR	2 cells/1 μL	5	[19]
MRSw type II	Antibody	MP, bench top relaxometer	< 1 pM	300	[102]
AC susceptometer	Antibody	Iron oxide nanoparticles	< 1 nM		[103, 104]
SQUID	Bacteria	Iron oxide nanoparticles	1.1 × 105 bacteria/ 20 μL		[103, 104]
	DNA	Magnetic bead	3–10 pM (signal amplification)		[105]
GMR	Protein	Cubic FeCo NP	2 × 106 proteins	2	[106]
	DNA	Antiferromagnetic NP	10 pM		[107]
	Protein	Iron oxide NP	2.4 pM		[108]

3.4 Carbon Nanostructures

The beauty of carbon-based nanomaterials from its bulk count part is

It is easy to electrochemically recognize a specific type of biomolecule (such as ascorbic acid and uric acid.) mixed with carbon nanomaterials and quantify it which is impossible with glassy carbon electrodes. In potentiodynamic analysis, carbon nanotubes act as an ion–to–electron transducer for biosensing analysis.

a. The outstanding electrical transport properties of carbon nanomaterials like carbon nanotubes and graphene. Intrinsic single-wall carbon nanotubes and graphene possess ballistic transport properties with high electron mobility which is necessary for high-speed biosensors.
b. Using carbon nanomaterial in particular single or bilayer defect-free graphene which has high conductivity with low thermal noise and due to fewer defects, the pink noise (*i*/*f* noise) is also very low and can be effectively utilized in designing ultrasensitive biosensors.
c. For flexible biosensor design, carbon-based nanomaterials are considered the best selection based on cost, stability, and performance.

d. Carbon nanodots/quantum particles are the best fluorescent centers for effective optical biosensor applications.

3.5 Hybrid Nanostructures

Hybrid nanomaterials are a promising platform for biosensor application, especially for the sensor in bio-medical diagnosis consisting of a unique conjugate of inorganic and organic components. The beauty of these hybrid nanomaterials lies in

a. Fine inorganic nanoparticles (< 100 nm) have an enormous potential to be applied in electronics, catalysis, bio-medical, etc. However, for bio-medical applications, the inorganic particles must be bio-compatible and have colloidal stability in the aqueous environment without agglomeration and degradation. Thus, the organic material is widely hybridized with this inorganic particle to improve bio-compatibility, processability, and chemical stability.
b. The organic/inorganic hybrids are mechanically robust and thermally more stable systems than individuals. Most importantly, the internal porosity of the hybrid can be tuned by anchoring the inorganic component which is highly desirable for ultrasensitive biosensor design and to increase the drug loading efficiency.
c. The biological fluid when interacting with finer in-organic particles, the protein corona forms on the surface of the inorganic nanoparticles. The size and surface properties of the nanoparticles are highly dependent on the protein corona formation and cell-nanoparticle interaction. Additionally, the selection of organic components of the hybrid especially for biomedical application needs depth understanding of the protein corona formation and growth for effective biomedical application of the hybrid nanomaterial.

Based on recent literature, we are citing some of the recent works on the use of hybrid nanomaterials in biosensing applications. The list of carbon materials in hybrid form, reported in the literature in tabulated form (adapted from [3]) is cited in Table 4.

4 Challenges and Future Perspectives

Most importantly, the modern biosensor device can be miniaturized to a portable form for bedside clinical applications with effectively high throughput. Some of the new detection techniques that sound well from a scientific point of view and technological importance are grooming as next-generation electronic sensing chips such as field-effect electrolyte–insulator-semiconductor (FE–EIS) sensors and capacitive FE–EIS. Recently, the application of 2D materials like nanocarbon, metal dichalcogenides, hexagonal boron nitride, black phosphorous, and metal oxides has highly impacted the research in the FE–EIS-based sensors. However, there remain several challenges

Table 4 Represents the list of carbon and carbon-based hybrid nanomaterials employed in the development of biosensors (Adopted from Ref. [3])

Nanomaterial	Analyte	Transducer	Linear range	Detection limit	References
Ag@CQDs-rGO	Dopamine	Electrochemical	0.1–300 µm	0.59 nm	[109]
Ag NP-MWNT	Glucose	Electrochemical	0.025–1.0 mM	0.01 mM	[110]
Pd/Co-NCNT	Hydrazin	Electrochemical	0.05–406.045 µm	0.007 µm	[111]
Pd/CNF/$[M3OA]^+[NTF2]^-$	H_2		1.00–35.0 nM	0.33 nM	[112]
Cu NPs/Rutin/MWCNTs/IL/Chit/GCE	H_2O_2	Cyclic voltammetry	0.35–2500 µM	0.11 µm	[113]
Cu/rGO-BP	Glucose	Electrochemical	0.1–2 mM	11 µm	[114]
Ni/Cu MOF	Glucose	FET	1 µM–20 mM	0.51 µM	[115]
NiO/PANINS	Glucose	Amperometric	1–3000 µM	0.06 µM	[116]
MnO-Mn_3O_4@rGO	H_2O_2	Impedimetric	0.004–17 mM	0.1 µM	[117]
ZnO-rGO	Dopamine	Cyclic Voltammetric	0.1–1500 pM	8.75 ± 0.64 pM	[118]
MoO_3@RGO	Breast cancer	Electrochemical	0.001–500 ng mL^{-1}	0.001 ng mL^{-1}	[119]
Graphene QDs	Cu^{2+}	Electrochemical	0.015–8.775 µM	1.34 nM	[120]
Graphene QDs	Lung cancer$^+$	Fluorescence	0.1 pg mL^{-1}–1000 ng mL^{-1}	0.09 pg mL^{-1}	[121]
CdTe/CdS//ZnS core/shell/shell QDs	l-ascorbic acid	Fluorescence	8.0×10^{-9}–1.0×10^{-7} M	1.8×10^{-9} M	[122]
NSET amptamer@Fe_3O_4@GOD and MoS_2	Tumorcell(EpCAM)	Magnetic fluorescence	2–64 nM	1.19 nM	[123]
Au NPs@PDA@CuInZnS QDs	P53 gene	Electrochemiluminescenece	0.1–15 nmol L^{-1}	0.03 nmol L^{-1}	[124]
CaM/SiNW-FETs	Protein	FET	10^{-8}–10^{-6} M	7 nM	[125]
G/Au NR/PT	HPV DNA	Electrochemical	1.0×10^{-13}–1.0×10^{-10} m L^{-1}	4.03×10^{-14} m L^{-1}	[126]

(continued)

Table 4 (continued)

Nanomaterial	Analyte	Transducer	Linear range	Detection limit	References
Graphene-Au NRs	NADHEthanol	Amperometric voltammetric	20–160 μM5–377 μM	6 μM1.5 μM	[127]
LAC-CNTs-SPCE	Para-cresol	Electrochemical	0.2–25 ppm	0.05 ppm	[127]
Co_3O_4-CNT/TiO_2	Glucose	Photoelectrochemical	0–4 mM	0.16 μM	[128]
CNT thin-film transistor (TFT)	DNA	Thin film transistor (TFT)	1.6×10^{-4}–5 μmol L^{-1}	0.88 μg L^{-1}	[129]
GQDs-MWCNTs	Dopamine	Electrochemical	0.005–100.0 μM	0.87 nM	[130]
CNT/Au NPs	Choline	Amperometric	0.05–0.8 mM	15 μM	[131]
PAMAM dendrimer	DENV 2E	Optical fiber	0.1 pM–1 μM	19.53 nm nM^{-1}	[132]
SAM/NH_2rGO/PAMAM	DENV 2E	SPR	0.08 pM–0.5 pM	0.08 pM	[133]

in biosensor-based materials design, especially for medical applications which are as follows

a. In enzyme-based biosensors, the presence of fouling agents and endogenous interfaces present in the sample has significantly hampered the sensor's sensitivity and specificity. Though this issue was partially addressed by making hybrid biomaterial, still the interface effect persists.
b. Generally, doped semiconductor nanostructures have particular importance in biosensor design. However, the synthesis of doped semiconductor nanostructures is carried out in a harsh environment, and it isn't easy to achieve it on a large scale. Scale-up synthesis with high-quality control is highly desirable.
c. Real-time in-vivo monitoring in complex media such as tissues and blood is still challenging. Moreover, it is highly desirable to establish a robust detection platform for in-vivo analysis, especially from a pharmacokinetic and pharmacodynamics point of view.
d. Toxicity of the nanomaterials (carbon nanomaterials such as carbon whisker and carbon fiber.) in biosensors remains a significant challenge, especially for medical diagnosis.

5 Conclusions

This chapter comprehensively summarized the present scenario of nanomaterials in biosensors for medical applications. An attempt was made to summarize several chemical compositions and dimension nanomaterials applied in various biosensors in worldwide research. Additionally, the classification of biosensors based on the biorecognition and signal transduction mechanism was discussed. In recent decades, biosensors have demonstrated their potential to detect various quantitative and qualitative targets, especially for medical diagnosis. Due to the high stability and lower price, biosensors such as aptasensors and DNA-modified electrodes are being used as point-of-care devices for quick diagnosis of the SARS COVID-19 virus during ongoing pandemic emergencies across the globe. Modern biosensors have a vast perspective and high compatibility compared to conventional biosensors in medical applications due to their real-time diagnosis capability, high specificity, and sensitivity with minimal sample preparation.

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