Journal of Science: Advanced Materials and Devices 9 (2024) 100694

Contents lists available at ScienceDirect

Journal of Science: Advanced Materials and Devices

journal homepage: www.elsevier.com/locate/jsamd

Review Article

Applications of nanomaterial technology in biosensing

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ARTICLE INFO

Keywords:
Nanomaterials
Biosensor
Micromolecules detection

ABSTRACT

Nanomaterial technology is a comprehensive subject with strong intersections, and its related research content involves a wide range of modern scientific and technological fields. The science and technology in the area of nanomaterials has attracted the attention of many research groups over the past few years. By its very nature, this topic has a lot of room for research, related to very tiny objects in the nanometer range. Nanomaterials refer to the sudden changes in the properties of substances when they reach the nanometer scale, resulting in special properties. In this paper, we introduce various nanomaterials commonly used in the field of biosensing, and briefly explain the advantages and disadvantages of nanoscale biosensors. At the same time, we also explain the working principles of various types of biosensors based on nanomaterial technology, including electrochemical biosensors, optical biosensors, and piezoelectric biosensors. In addition, we also introduce the sensing targets of common biosensors, such as enzymes, DNA, microorganisms, etc. Finally, we discuss the challenges and prospects for the application of nanomaterials technology in biosensing, and analyze the current trends and future directions.

1. Introduction

Materials with structural properties that fall between those of atomic and bulk materials are referred to as nanotechnology. Nanomaterials are defined as basic units, which are similar to densely packed atoms at a scale of 10–1000, or as at least one dimension in three dimensions at a nanometer size (1–100 nm). A material's properties at the nanoscale differ from those of bulk materials or ordinary atoms because of the surface effect, macroscopic quantum tunneling effect, quantum size effect, and small size effect. Their physical and chemical characteristics will be distinct. This also means that as long as the structural properties of nanomaterials are correctly controlled, new products, technologies, and scientific equipment can be developed. In recent years, research attention on nanomaterial technology has been dramatically increased because of the emergence of new methods for synthesizing nanomaterials and tools for manipulation. To better understand the size-dependent electrical, optical, and magnetic properties of nanostructures, a number of cutting-edge techniques for creating nanoparticles, nanotubes, and their constituent parts are available.

Here, the integrated use of biosensing and nanomaterial technologies is our primary concern. An integrated, self-contained device that analyzes data from a biometric element connected to a signal transduction moiety is called a biosensor. Biosensors are used to identify a wide range of compounds, such as gasses, heavy metal ions, carbohydrates, amino acids, and molecules linked to disease. The initial biosensors were only capable of achieving simple target detection, while with their continuous development and optimization, today's biosensors have been able to achieve detection with lower cost, higher sensitivity, better stability, and simpler operation. In this evolution, nanomaterials are indispensable. The primary purposes of utilizing nanomaterials in biosensors are to increase sensitivity and amplify signals. Functionalized nanomaterials can also be used to enhance other biosensor properties as robustness, stability, linearity, repeatability, biocompatibility, resolution, and response time. Increasing effective surface area, effectively immobilizing biomolecules, catalyzing electrochemical and optical events while reducing activation energy, accelerating electron transfer, separating biomolecular conjugates and pre-concentrating analytes, and labeling biological receptors are just a

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Peer review under responsibility of Vietnam National University, Hanoi.

https://doi.org/10.1016/j.jsamd.2024.100694
Received 4 December 2023; Received in revised form 18 February 2024; Accepted 21 February 2024
Available online 2 March 2024

few of the significant roles played by nanomaterials in biosensors [1]. At present, the research of biosensors pursues higher sensitivity and selective real-time response and reduces its interference on this basis [2]. In recent years, nanotechnology has become more and more significant in the development of biosensors. Biosensors' sensitivity and performance are enhanced by the use of nanomaterials, but more significantly, the application of nanomaterials has led to the introduction of numerous new signal transduction methods in biosensors. With the ability to detect or manipulate atoms and molecules in biomolecular identification, pathogen diagnosis, and environmental monitoring applications, nanomaterial-based biosensors – a combination of materials science, molecular engineering, chemistry, and biotechnology – can significantly improve the sensitivity and specificity of biomolecule detection.

In this paper, we mainly discuss the application of nanomaterial technology in biosensing. In the first part, we list and introduce various types of nanomaterials. Secondly, we explain the advantages and disadvantages of nanoscale biosensors, including their detection limit, response time, and non-specific detection properties. In Section 3, we enumerate various types of biosensors and briefly describe their working principles. Finally, we analyze and prospect the future application and development of nanomaterial technology in biosensing. This article aims to provide a comprehensive and up-to-date review of the application and development of nanomaterial technology in biosensors.

2. Classification of nanomaterials

Biosensing applications using novel nanomaterials are a fast-growing field. Scientists are now investigating a range of nanomaterials to ascertain their characteristics and potential uses in biosensors. Nanomaterials can be easily categorized into zero-dimensional, one-dimensional, and two-dimensional categories based on their spatial scale. In this section, we have briefly introduced the typical materials among the various nanomaterials mentioned above.

2.1. Zero-dimensional nanomaterials

Zero-dimensional nanomaterials refer to materials where the size of each dimension is constrained within the nanoscale. Electrons cannot move freely within zero-dimensional materials. There are various zero-dimensional nanostructured units, including nanoparticles, quantum dots, etc. Due to the significant increase in surface density of states of such materials, they exhibit significant quantum effects and are crucial in various research and applications.

2.1.1. Nanoparticles

Because of their size, nanoparticles (NPs), which are separable elements with sizes ranging from 1 to 100 nm, have completely distinct physical, electrical, and chemical properties from bulk materials. Numerous nanosensors have made extensive use of a variety of nanoparticle types, such as oxide, semiconductor, and metal nanoparticles (MNPs). For example, magnetic nanoparticles play a role in biosensors as supports and carriers. In the research in this field, biological entities do not show any magnetic effect, so they do not generate noise and interference signals. The number of biosensing applications based on NPs has grown in recent years, and their primary functions are also diverse.

First of all, NPs have the characteristics of high specific surface area and high surface free energy so that they can realize the immobilization of biomolecules. There is no denaturation or loss of biological activity throughout this process. Biomolecules become immobile primarily as a result of covalent bonding and electrostatic interactions. In certain uses, the researchers increased the active surface area of metal electrodes by adding MNPs in order to promote electrical interactions between solid surfaces and biomolecules. Furthermore, nanoparticles (NPs) have remarkable catalytic activity, which can be used to adjust and improve electrode catalytic performance. Additionally, due to their exceptional stability, nanoparticles can lower the overpotential of a variety of significant electrochemical reactions. Another crucial role of NPs is to label biomolecules. Biomolecules including DNA, antibodies, and antigens can all be labeled to preserve their biological activity and ability to interact with other biomolecules. In high-sensitivity biosensors, this function is essential. The use of Au-NPs and other nanoparticles in conjunction with fiber optic sensors has grown significantly in popularity in recent years. A variety of biomolecules, including uric acid, glucose, and cholesterol, can be detected using this kind of sensing technology [3]. This kind of sensor makes use of AuNPs' broad specific area, biocompatibility, and simplicity of manufacturing. LSPR rises when a local dielectric environment is created on AuNPs, increasing the sensor's sensitivity [4]. In addition, NPs also have functions such as enhancing electron transfer and acting as reactants, and their applications require further research and exploration.

Synthesis of nanoparticles. Typical synthetic methods for NPs is shown in Fig. 1. Methods for synthesizing metal nanoparticles can be divided into two categories, namely "top-down" and "bottom-up". "Top-down" refers to the decomposition of bulk materials into colloids or nanoclusters. Metal vapor deposition, for example, is a more general method suitable for laboratory-scale nanoparticle fabrication. The "bottom-up" approach, forms nanoclusters by decomposing organometallic precursors. Specifically, neutral nanoclusters can be obtained by reducing metal ions using suitable reducing agents, and such a method can obtain small and uniform nanoparticles, increasing the possibility of distinguishing nanoparticle sizes.

Likewise, the preparation procedures of magnetic nanoparticles are also diverse. First of all, physical methods include the vapor deposition and the electron beam lithography. The chemical preparation methods include the chemical co-precipitation method, the electrochemical method, oxidation method and the biochemical decomposition reaction. At last, there is the microbial approach, which enables the control of composition and geometry in a simple and versatile way.

Functionalization of nanoparticles. The functionalization of nanoparticles is to achieve better stability, biocompatibility, and functionality, thus enabling their application in the biological field. Currently, existing functionalization strategies include surface encapsulation, in-situ synthesis, and self-assembly, which can appropriately customize and trim the surface of nanoparticles. These days, a wide range of materials, including silica, artificial polymers, biopolymers, and small molecules, have been used to functionalize nanoparticles. Firstly, one of the most effective methods for giving nanoparticles stability, biocompatibility, and surface functioning for biological applications is to coat them with silica [5]. Emelianov et al. showed that silica-coated gold nanorods could produce photoacoustic signals that were around three times stronger than those of uncoated gold nanorods in their research. In addition, silica-coated MNP can be used as MRI reagents[6]. In addition to silicon dioxide, titanium dioxide is a commonly used chemical coating with significant photochemical properties [7].

Secondly, as one of the commonly used functionalization methods, synthetic polymer coatings can dissolve hydrophobic inorganic nanoparticles and introduce multiple functionalities onto their surfaces while maintaining their stable state. To dissolve nanoparticles in aqueous solutions, surface coatings frequently do not need to replace coordination ligands on the particles. This is essential to preserving their special qualities and shielding their center from environmental interaction. Poly (vinyl alcohol) (PVA), polyethylene glycol (PEG), and polylactic acid (PLA) are examples of commonly used polymers. PEG is one of them that is frequently utilized to modify the surface of AuNPs in order to give them colloidal stability. These functionalized AuNPs are suitable drug carriers because they can attach to cell membranes and penetrate target cells [8]. In order to offer biocompatibility, improve selective absorption, prolong cycle time, and

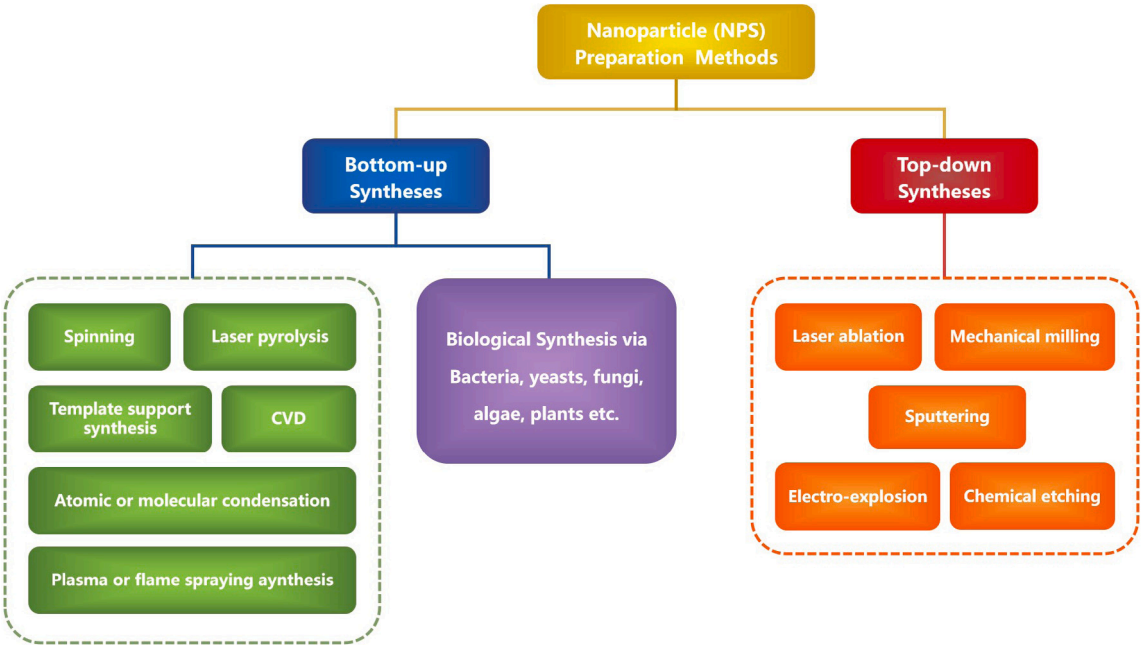

Fig. 1. Commonly used synthetic techniques for NPs in both the top-down and bottom-up methodologies.

avoid protein adsorption and aggregation in the biological environment, linearly produced polyether PEG can be employed for in-situ coating and grafting of nanoparticles. Excellent application value has also been demonstrated by other polymers in areas like cancer treatment and drug delivery. In general, the properties of nanoparticles coated with synthetic polymers can be altered while retaining some of their original characteristics. Furthermore, there are numerous benefits to using biomimetic monolayer coating for nanoparticles in vivo distribution and tumor targeting. These benefits include a longer cycle time, simpler bioconjugation and functionalization, a reduction in nonspecific binding, and a decreased long-term toxicity. Furthermore, by improving particular interactions with biological molecules, surface-functionalized nanoparticles can take part in biological processes. For different types of nanoparticles, a common natural conjugation technique is the covalent interaction of biomolecules with them. In addition to covalent bonding, biomolecules can also be directly attached to nanoparticles by noncovalent electrostatic interactions. Nanoparticle-based biosensor components can generate helpful outputs through integrated signal transduction systems while recognizing and combining analytes. Sensitive biomolecules like proteins, nucleic acids, peptides, and small molecules can be conjugated to the surface of nanoparticles to form biosensor components. In addition to their surface characteristics, nanoparticles must be able to bind to biomolecules by controlling their stability, activity, and orientation. This is necessary for their biological uses.

2.1.2. *Quantum dots*

Quantum dots (QDs) are semiconductor nanoparticles with diameters in the nanometer range. SThe small size of charge carriers, which shows unique electrical and optical qualities like tunable photoluminescence and long-term photostability sex, is constrained by the fact that it is very close to the exciton Bohr radius. In past research, quantum dot bioconjugates have received significant attention in bioanalysis, biomedicine, and biophysics. Specifically, quantum dots are often used as a substitute for molecular probes because of their better brightness and photostability, and the ability of quantum dots to absorb broad-spectrum light and emit narrow-spectrum light makes them the best choice for simple fluorescent intensity probes in biosensors.

Nonradiative energy transfer between the excited QDs and the quencher realizes fluorescence resonance energy transfer (FRET), a classic approach in quantum dot applications. FRET is mostly applied in optical DNA sensors and oligonucleotide sensors [9]. Another QD-based nonradiative energy transfer method is bioluminescence resonance energy transfer (BRET). This method eliminates the need for an external light source by using a protein that emits light to transfer energy to the quantum dots.

Along with the first two methods, charge transfer quenching and chemiluminescence resonance energy transfer (CRET) are the last methods that are most frequently used for QDs as optical probes in biosensing [10]. After identification, the quencher must be moved away from the QD in order to get sufficient sensitivity using these methods. Most QD-based biosensors are optical, with only a tiny percentage being electrochemical.

Synthesis of quantum dots. The basic structure of QDs is shown in Fig. 2. When people study the synthesis methods of quantum dots, they pursue simple, economical, large-scale, and size-controllable synthesis methods. Researchers have proposed and practiced many synthetic techniques, including organometallic synthesis, synthesis of quantum Dots, biosynthesis of quantum dots, etc. These methods have significant differences in scalability, quality, and applicability. The synthesis techniques for quantum dots can be classified into two groups: “top-down” and “bottom-up”. Using carbon quantum dots (CQDs) as an example, “top-down” techniques for processing macroscopic carbon structures primarily involve arc discharge, laser ablation, electrochemical oxidation, chemical oxidation, and ultrasonic synthesis. Making carbon quantum dots from chemical precursors using microwave synthesis, thermal breakdown, hydrothermal treatment, template wiring, and plasma is known as the “bottom-up” method [12]. In the “top-down” process, most are inexpensive but can be complex to manufacture because of the size of the QDs involved. The main drawbacks of this kind of technology are the impurities in the QDs and the patterning-related geometric flaws. Furthermore, the “bottom-up” approach-which may be broadly classified into the gas-phase and wet chemical methods—prepares colloidal quantum dots by allowing the solution to self-assemble following chemical reduction. Wet chemical techniques include the nucleation and regulated growth of nanoparticles, the preparation of saturated semiconductor solutions utilizing organic solutions, and the manipulation of pH or temperature to produce supersaturated solutions; nucleation can result in the production of tiny crystals. Changes in electrostatic double-layer thickness, temperature, and the ratio of cations to

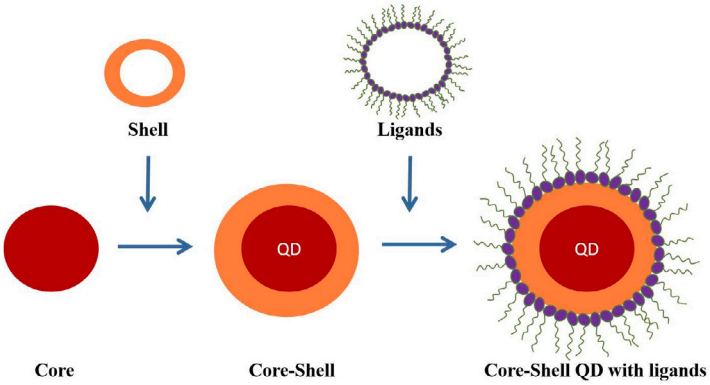

Fig. 2. Schematic illustration of Basic structure of Quantum dots (QDs) [11].

anion can all affect the size, shape, and structure of quantum dots. On the other hand, the gas-phase law relies on suppressing the epitaxial growth of highly strained materials, which are grown atom by atom, layer by layer. In the past two decades, experimental and theoretical studies on these nanoparticles have increased significantly to explore many of the fundamental properties of QDs and have been attracted by commercialization efforts.

Functionalization of quantum dots. Surface passivation is a necessary operation to make uncoated quantum dots useful for biological applications, and there are three factors related to this operation. The first is the surface properties of quantum dots. Uncoated quantum dots are subject to problems such as oxidation, metal ion penetration, and photochemical degradation, resulting in metal ion toxicity. Therefore, it is necessary to use capping agents to reduce surface defects and improve the performance and stability of quantum dots. Second, it is important to take into account how soluble quantum dots are in biological fluids and water. To control the size and avoid aggregation, a high-temperature process is typically used to create quantum dots from an organic solution. Hydrophobic groups are used to stabilize the solvent in advance. As a result, the intrinsic solubility of quantum dots in an aqueous solution is extremely poor, so hydrophilic ligands should be used to replace or cover the QDs. The main methods are amphiphilic combinatorial approaches, surface silanization, and ligand exchange procedures. The final influencing factor is the targeted delivery of quantum dots. Many quantum dot surface modification strategies for biomedical applications have been proposed in past studies to develop specific biosensors. Among these, the key point is to increase the choice of water-soluble ligand molecules, which can provide anchor points for further functionalization with various biomolecules.

As previously noted, biomolecules such as proteins, antibodies, and nucleic acids need to be applied to the surface of quantum dots in order for certain biosensor functions to be achieved. Either covalent binding or nonspecific adsorption can be used to complete this phase of binding to biomolecules. Biomolecules and ligands on the surface of quantum dots interact weakly chemically and electrostatically to facilitate nonspecific adsorption. It is mainly used for the functionalization of nanoparticles and biomolecules. Although this approach is very easy to use, it has certain drawbacks, including the inability to control the position of attached biomolecules and the weakening of the connection when other ligands are present on the surface of the quantum dots [13]. Biomolecules can achieve regulated localization and strong bonding on the surface of quantum dots by the use of covalent bonding. Attaching different ligands and forming functional groups on their surfaces is the basis of this technique. Generally, terminal carboxyl functional groups on proteins, peptides, or antibodies can be used to functionalize QD surfaces with free amines, creating amide bonds. The peptides can also be directly bound to the QD surface through the creation of disulfide bonds between the cysteine-containing peptides and the sulfur atoms on the QD surface. Nevertheless, there are limited yields when QD shells are combined with biomolecules' terminal alkyne or azide groups. Still, they increase the reactants' stability and can serve as connecting segments for other biomolecules. In such a case, we can obtain multiple functionalizations on one QD, enabling accurate checks in stoichiometry.

2.2. One-dimensional nanomaterials

A material with one of the three dimensions outside the nanoscale is called a one-dimensional nanomaterial. According to the specific shape, it can be divided into tubes, rods, wires, etc. Usually, those with a small aspect ratio are called nanorods, while those with a large aspect ratio are called nanowires.

2.2.1. Carbon nanotubes

In 1991, scientists made the discovery of carbon nanotubes (CNTs) [14], which possess special mechanical, chemical, and physical properties. Carbon nanotubes are the appropriate materials for chemical and biological sensing because of their optimal nanoscale size, biocompatibility, and electrical characteristics. Consequently, there is enormous room for advancement for carbon nanotubes in a variety of domains, including biomedical engineering, biosensing, and nanoelectronics. Depending on how many rolled layers they have, carbon nanotubes can be broadly divided into two types: single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs). Both kinds of nanotubes have already been used in biosensors [15]. Single-walled carbon nanotubes are cylindrical nanostructured tubes with a diameter ranging from 0.4 to 2.5 nm, formed from a single graphite sheet. Conversely, multi-walled carbon nanotubes consist of several layers of stacked graphene sheets and have a diameter of approximately 100 nm. Carbon nanotubes can act as scaffolds to immobilize biomolecules on their surfaces, and this function, combined with its intrinsic properties, enables the transduction and the recognition of various analyte or metabolite-related signals.

While the functionalization procedure that is carried out affects the capacity of carbon nanotubes to trap various proteins, researchers introduced the unique properties of CNTs by defining a wide number of CNT biosensors based on alternative transduction techniques. The most widely utilized of them is called electrochemical transduction, and it works by immobilizing proteins and enzymes to take advantage of their catalytic activity and improve the attachment of various kinds of molecules to CNTs. In addition, proteins can also provide biocompatibility and solubility for CNTs. They can be organized according to the size or the chirality, and detecting other proteins can also be achieved. Among the enzymatic electrochemical biosensors, carbon nanotubes' special electrochemical characteristics and large specific surface area are frequently utilized to address the issue of the need for a medium in the electrochemical enzymatic reaction. Based on the great

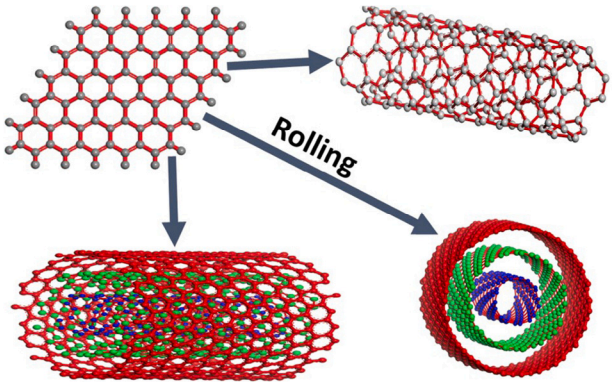

Fig. 3. Graphite layer is rolled into single- and multi-walled carbon nanotubes [20].

specificity of antibody–antigen interactions, immunosensors also make use of nanomaterials, including carbon nanotubes (CNTs) combined with antibodies, to improve the antibodies' capacity to bind and produce detectable signals. Analogously, DNA electrochemical biosensors, which employ covalent or non-covalent techniques to combine DNA with carbon nanotubes, leverage the distinct characteristics of CNTs and the distinct recognition capacity of DNA. They find extensive application in the fields of genetics, infectious disease diagnosis, genome mutation detection, etc [16]. Because CNTs have tubular and fibrous structures and are easy to functionalize with nucleic acids, peptides, and proteins. Based on this, CNTs can be functionalized appropriately and employed as nanocarriers to deliver proteins, genes, and anticancer medications for chemotherapy [17,18]. Furthermore, in order to directly eradicate cancer cells, they can also be employed as mediators for photodynamic therapy (PDT) and photothermal therapy (PTT). Apart from this, optical transduction is another major branch of CNT-based biosensors. Previous studies have shown that semiconducting SWCNTs have the properties of effective nano-quenchers when used as fluorophores. Yang et al. [19] designed fluorescent probes which can measure in the nanomolar range. SWNTs also show near-infrared photoluminescence and exhibit strong Raman scattering, so they can also be used as near-infrared fluorescent labels or as multicolor Raman labels.

Synthesis of CNTs. The basic single-layer and multi-layer carbon nanotube structures are shown in Fig. 3. Previously, the synthesis technology of carbon nanotubes mainly referred to a gas phase process in a high-temperature environment, but now low-temperature chemical vapor deposition (CVD) has replaced it. Studies have found that the latter can achieve more accurate control over the length, direction, diameter, purity, and density of carbon nanotubes.

Few specific examples have been developed to illustrate the synthesis technology of carbon nanotubes. The first one is the arc discharge technology, which synthesizes carbon nanotubes through the arc vaporization of two graphite rods. In this technology, the cathode is made of large graphite rods, and the anode is made of thin graphite rods, placed end-to-end in a temperature and pressure-specific environment. Using catalyst precursors in this process can also reduce structural defects and enable the synthesis of MWCNTs into SWCNTs. The second one is laser ablation, a gas-phase process at high temperatures. Various factors affect the properties of carbon nanotubes in this method, including the composition of the target material, gas flow, gas pressure, and laser characteristics. The advantage of laser ablation is that it can create reasonably high yields of high-quality SWCNTs with low metal impurity concentration [21]. Still, the disadvantage is that it is too expensive. At last, the chemical vapor deposition technique is presented. This involves covering the substrate with a layer of metal catalyst, nucleating the catalyst through thermal annealing or chemical etching, and then injecting a carbon-containing gas mixture to diffuse the carbon atoms into the carbon nanotubes in the substrate. This method can obtain high-purity CNTs on a large scale and is easy to control. Various CVD methods have emerged today, and this technique is the most widely used in the fabrication of multi-walled carbon nanotubes [22].

Functionalization of CNTs. The functionalization process of carbon nanotubes improves their dispersibility in biological systems and, thus, their biocompatibility. This allows for the combination of carbon nanotubes with other materials and their modification with certain functional groups. These days, covalent bonding of molecules, private adsorption of molecules, and embedded functionalization are the primary techniques for functionalizing carbon nanotubes (CNTs). Among a number of covalent processes, functionalizing CNTs by oxidation is the most used method. Specifically, this process requires the participation of an oxidant to form carboxyl groups at the ends of carbon nanotubes and the defects in the tube wall. However, covalent oxidation has its disadvantages: its specificity is low, and if it is over-oxidized, it will affect the structure and conductivity of CNT. The oxidized carbon nanotubes will spontaneously absorb biological molecules not explicitly bound to the tube wall. But at the same time, this method can make carbon nanotubes hydrophilic and reduce toxicity. Another more commonly used covalent reaction is related to the 1,3-dipolar cycloaddition of the azomethine ylide, which, unlike the former, operates on the aromatic sidewall [23]. The advantage of such a method is that the damage to the CNT structure is much less, and it can bind reactive groups with high specificity to biomolecules.

Second, the hydrophobic surface of the carbon nanotubes interacts with appropriate complimentary molecules as well as biological macromolecules both inside and outside the carbon nanotubes to produce non-covalent interactions. The process is simple and quick, and the specific steps include filtration, centrifugation, and sonication. In general, maintaining the structure of sp^2 nanotubes and their electronic properties is very important, so one can choose to functionalize the wall of SWCNTs by non-covalent methods. The advantage of this functionalization method is that it is easy to evaluate the characteristics of CNTs before and after the biomodification. Still, the disadvantage lies in low specificity, and the biomolecules may be destroyed during the adsorption process under certain circumstances.

The ultimate functionalization method is based on the encapsulation of molecules in the inner cavity of nanotubes; ex-situ and in-situ nanotube filling are the two types of nanotube filling. When filling occurs in-situ, it happens during growth; when filling occurs outside of the plant, the encapsulating stage happens after synthesis. The two ex-situ filling methods are solution filling and melt-phase filling. In general, the first one works well with biological chemicals, although the carbon nanotubes' surface functionalization or outer wall may be harmed by the corrosive liquid environment [23]. In contrast, the second one requires high temperatures and is used for metals, semiconductors, etc. The problem with CNT applications is their toxicity. Nanoparticles and nanomaterials may interact with biological systems to induce unintended toxicological consequences, but researchers can use different techniques to reduce or eliminate such phenomena depending on specific applications [24].

2.2.2. Silicon nanowires

Silicon nanowires (SiNWs) are one-dimensional nanostructures that have sizes between 1 and 100 nm. More so than other nanomaterials, SiNWs are an appealing alternative for biosensing applications due to their high surface area ratio, optical properties, biocompatibility, and tunable electrical properties. SiNWs' nanoscale size is comparable to that of biological and chemical species, which can also increase the detection limit and ensure the high sensitivity of the sensors. SiNWs' distinct electrical characteristics are primarily influenced by their size, morphology, surface conformation, and growth orientation. SiNW biosensors are often employed as FET devices with a change in SiNW surface charge density serving as the sensing mechanism. In a

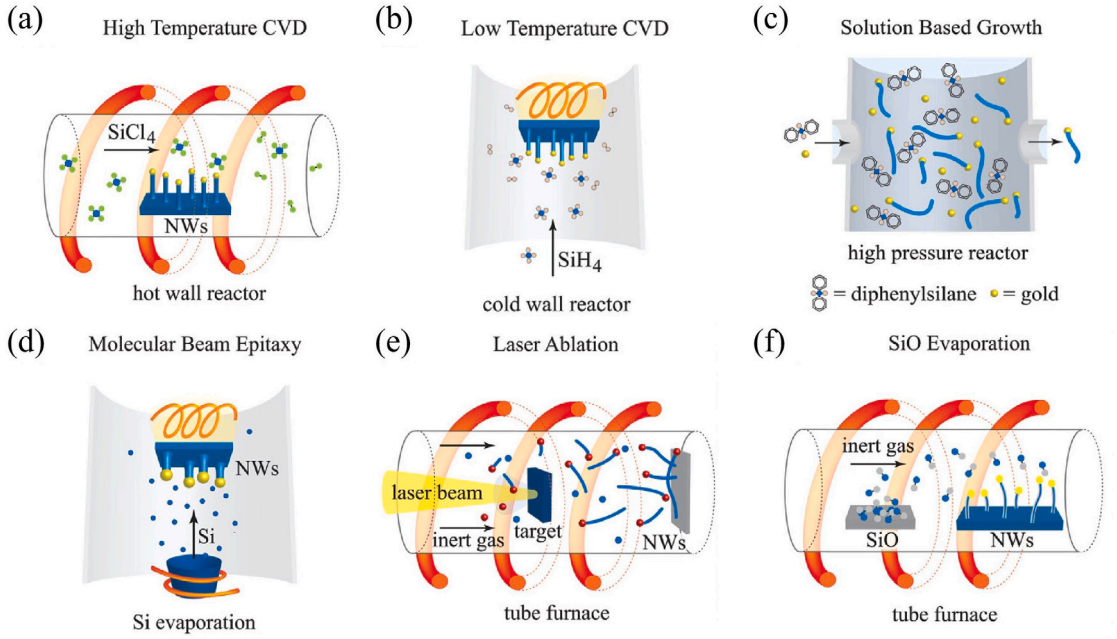

Fig. 4. (**a**) Schematic setup of high temperature CVD. (**b**) Schematic of a low temperature chemical vapor deposition reactor. (**c**) Schematic setup for solution-based growth of Si nanowires. (**d**) Schematic of MBE Si nanowire growth. (**e**) Schematic of a laser ablation setup. (**f**) Schematic of a setup of nanowire growth via SiO evaporation [27].

semiconductor channel, they are connected between the source and the drain. SiNW-FETs have become a fantastic technology for biological research because of its good physical properties, such as high carrier mobility [25], high current switching ratio, and virtually optimum subthreshold slope. These materials are also offered at a reasonable price. They have been effectively used to identify particular proteins, DNA, or RNA as indicators of cancer or cells. SiNW-FET biosensors provide distinct detection strategies for various compounds of interest. When PNA probes are used instead of DNA probes, SiNW-FET biosensors may detect DNA with a better sensitivity. This technique can be used for virus detection, sickness diagnosis, and pharmaceutical therapy. SiNW-FET biosensors can be combined with reversible surface modification techniques based on disulfide bonds to detect microorganisms such as viruses and bacteria. Furthermore, antigen antibody/biotin avidin-specific SiNW-FET biosensors can identify proteins. Multichannel 3D design, chip integration, and sample pre-treatment could all increase the detection sensitivity. Li et al. [26] developed a multi-channel dual gate SiNW-FET device for dual channel detection of BC tumor markers. By coating different SiNW surfaces on monoclonal CA15-3 and CEA antibodies, respectively, SiNW-FET can be utilized for dual channel specific detection of breast cancer tumor markers CA15-3 and CEA, respectively. According to experimental findings, the multi-channel design approach improves the source leakage current signal over the conventional SiNW-FET, suppresses internal transistor fluctuation noise efficiently, and promotes detection system stability. Recently, SiNWs and biosensors based on surface-enhanced Raman scattering (SERS) spectroscopy have attracted a lot of attention as well. SiNW arrays functionalized with silver nanoparticles and silver-coated SiNW arrays have been developed to enhance SERS detection. Furthermore, SiNWs are fully employed in fluorescent biosensors. In this instance, SiNWs' high aspect ratio allows them to produce a larger surface, which improves the loaded biomolecules' ability to immobilize. The novel biosensors made with nanomaterials have nanoscale dimensions that enable measurements in the smallest settings, which will be very useful for future study.

Synthesis of SiNWs. In Fig. 4, several commonly used methods are discussed for producing SiNWs. Similar to other nanomaterials, SiNW nanofabrication technology can be categorized into two groups: "top-down" and "bottom-up". The "top-down" method entails shaping the large silicon into the required dimensions. The "bottom-up" strategy, on the other hand, describes the formation of SiNWs from smaller building components. It encompasses methods like metal-assisted chemical etching, oxide-assisted growth (OAG), and vapor–liquid–solid (VLS). VLS technology requires metal catalysts deposited on silicon substrates in a tube furnace. Deposition of metal catalysts on silicon wafers can generate metal–silicon alloy droplets, and the silicon dispersed on the metal nanoparticle catalysts is supersaturated and precipitated from the metal–silicon alloy droplets. This technique can effectively control the diameter and the arrangement of SiNWs. While the OAG technology is implemented based on a thermal evaporation process, many SiNWs can be synthesized. Shao et al. [28] promoted the growth of SiNWs using SiO_2 as the alternative metal catalyst, leading to a notable increase in the yield. The final metal-assisted chemical etching process operates in two stages: first, the silicon wafer must be electrolessly plated, and then the chemical etching is carried out in a solution containing fluoride ions. This low-cost and simple "bottom-up" SiNW array fabrication technique produces SiNWs up to 3–5 nm in diameter. But in manufacturing, they need to be aligned in a spatially defined way so that they can be used to manufacture various other devices.

Functionalization of SiNWs. When SiNWs are applied in biosensing, a necessary step to ensure their attachment to probe biomolecules capable of recognizing specific targets is the surface functionalization of SiNWs. Usually, there are two ways to achieve this: electrostatic adsorption and covalent bonding.

The first one is electrostatic adsorption, which refers to using electrostatic forces to adsorb ionic solutes on oppositely charged adsorbents. However, this method, although simple, is very demanding and is not feasible when neutral or weakly charged probes are used. The second one is the covalent binding method, which uses covalent bonds to attach biomolecules to the SiNW structure.SiNWs are frequently employed in electrochemical biosensors to alter the working electrodes. When SiNWs are functionalized with metal nanoparticles, enzyme activity is increased and electron transport is sped up. The modified electrodes also exhibit increased sensitivity at the same time. Moreover, SiNWs functionalized with oxides and amines exhibit pH-dependent conductance, which can be attributed to changes in surface charge during protonation and deprotonation. The small size and sensitive,

label-free, real-time detection of a wide range of chemical and biological species of antigen-functionalized SiNWs makes them useful for array-based screening and in vivo diagnostic applications, even though they also show real-time concentration-dependent detection and reversible antibody binding.

Specifically, different approaches using silane chemistry exploit the native oxide film on the SiNW surface, in which case alkoxy silanes (i.e. 3-aminopropyl trethoxy silane) are widely used as linkers molecules, providing amino groups on the SiNW surface. Many researchers have made research results in this field. Zhang et al. [29] immobilized peptide nucleic acid (PNA) on the surface of the SiNW device, which can directly recognize miRNA as a receptor without labeling the target miRNA. Furthermore, Zheng et al. [30] found that 3-(trimethoxysilyl)propanal (APTMS) generates an aldehyde-terminated SiNW surface, thereby enabling direct coverage of DNA, PNA, and antibodies. Additionally, they employ silicon nanowire field effect device arrays in clinical settings to detect telomerase and protein cancer indicators using extremely selective and sensitive multiplex electrical detection. Another idea presented by Cattani-Scholz et al. [31] refers to the biofunctionalization of silicon-based field-effect sensor devices using hydroxyl groups as a novel platform. This makes it possible for PNA, DNA, and antibodies to connect.

2.3. Two-dimensional nanomaterials

Two-dimensional nanomaterials refer to materials with only one dimension limited to the nanoscale and can be infinitely extended in the other two dimensions. They possess special physical and chemical features not found in other nanoscale materials because of their thickness at the nanoscale. Improved sensitivity and high detection accuracy are among the many advantages that 2D materials offer. These advantages stem from their huge surface area to volume ratio, exceptional optical transparency, strong mechanical and thermal conductivity, and high elasticity. So far, besides graphene, many other two-dimensional structures have been developed. Among them, in the field of biosensing, transition metal disulfides (TMDs) are the most prominent materials besides graphene[32,33].

2.3.1. Graphene materials

Graphene is a single-atom-thick planar sheet of sp^2-bonded carbon atoms organized in a flawless honeycomb lattice. Many unusual physicochemical properties of graphene, including high thermal and electrical conductivity, tunable optical properties, a huge surface area, and exceptional elasticity and mechanical strength, are a result of its unique structure. Furthermore, graphene's electrical structure is comparable to that of zero-gap semiconductors or semimetals, having a high charge density and stable, high mobility across a broad temperature range. With this property, graphene can fabricate high-performance FETs, which dissipate heat quickly and consume less energy. This unique material has quickly piqued the interest of researchers in a wide range of domains, including nanoelectronics, high-frequency electronics, energy storage and conversion, and field emission display.

In the last ten years, zero- and one-dimensional nanomaterials – such as quantum dots, nanoparticles, carbon nanotubes, nanowires, etc. – have become the main materials employed in the sensing area. These materials are all one-dimensional cylinders of carbon sheets. First isolated in 2004 [34], the graphene sheet has since demonstrated its usefulness in a number of novel sensors. The characteristics of graphene also make it a material that researchers are increasingly eager to use in the biosensing sector to create new kinds of biosensors. Since graphene oxide (GO) exhibits water solubility and stability and has the potential to enhance the hydrophilicity of the graphene layer, it is a graphene material deserving of further investigation. The main ingredients of graphene-based nanomaterials are graphene, graphene oxide (GO), and reduced graphene oxide (rGO). Graphene oxide (GO) differs from graphene in that it has a range of oxygen-containing functional groups, such as C=O, C–O–C, –COON, and –OH, which have favorable binding sites for further functionalization, high dispersibility, and strong reactivity. GO's oxygen-containing functional groups are eliminated chemically or thermally to generate rGO, which has enhanced mechanical properties, high electron mobility, strong thermal conductivity, chemical stability, and a large specific surface area [35]. It can also interact non-covalently with diols, amine groups, and phenyl groups in biomolecules via hydrogen bonding, $\pi - \pi$ stacking, and electrostatic interactions. This research can help identify biomolecules with great specificity. In some situations requiring electrochemical transduction, GO – which is also an electrical insulator – can be utilized as a label.

Graphene has the ability to immobilize biomolecules in electrochemical biosensor research, enhancing electron transport and enhancing surface interfaces to enhance the analytical capabilities of these biosensors. Govindasmy et al. [36] created a chemical resistance biosensor for the detection of cancer biomarkers (miRNA-21) in biological fluids using double-layer graphene made by chemical vapor deposition. The top graphene layer is treated with low damage plasma to improve the surface biocompatibility of graphene devices and allow DNA probe binding, while the bottom graphene layer maintains its conductivity. Direct creation of double-layer graphene has an advantage over layer-by-layer stacking of graphene thin films because of the strong interlayer coupling that improves the sensing power of the device. Furthermore, graphene has undergone testing in piezoelectric biosensors as a stationary platform. The use of graphene in biosensors can be investigated further through experiments and study.

Synthesis of graphene. The two types of graphene manufacturing processes that are now in use are top-down and bottom-up, as Fig. 5 shows. Bottom-up manufacturing techniques such as CVD, epitaxial growth, laser and thermal decomposition, and direct organic synthesis [38,39] can convert carbon precursors [40], including polymers, carbonaceous gases, and laser and thermal decomposition, into graphene. These processes are difficult because they typically require complex infrastructure and operating environments. The most popular method for producing carbon nanomaterials is chemical vapor deposition (CVD), which works well for large-scale manufacturing and is relatively simple to use. It can generate a uniform thermochemically catalyzed carbon atom layer, which is then deposited on metal surfaces or transferred on various substrates. However, this method is expensive as it requires complex instruments and is affected by the expensive and time-consuming graphene transfer process. Using silicon carbide (SiC) for epitaxial thermal growth is another graphene production method, but it is expensive and technically complex [37]. In comparison, the pyrolysis of graphene is a cheaper and more direct method [41]. Another bottom-up method that relies on assembling atomic or molecule components is the chemical or organic production of graphene. This process yields graphene with uniform nanostructures and atomic precision, which makes it excellent for producing repeatable and precise components for optoelectronic, nanoelectronic, and spintronic applications. The production parameters and the size and form of graphene can be accurately controlled by the bottom-up method. As a result, graphene made in this manner is of greater quality. It is difficult to scale up these methods for large-scale manufacturing, though.

Graphene is synthesized top-down from graphite via a combination of chemical redox, liquid phase exfoliation (LPE), electrochemical exfoliation, solid-state exfoliation, and arc discharge methods [40,42]. These top-down techniques are less expensive and simpler to use broadly. These technologies still have to overcome many obstacles, however. For instance, the most common way to make single-layer graphene is to mechanically peel highly oriented pyrolytic graphite (HOPG), a procedure that is not suitable for large-scale production. For example, the automated peeling method can produce graphene from a single layer to several layers, but using this technology to obtain the same structure is unreliable. Another top-down approach is LPE,

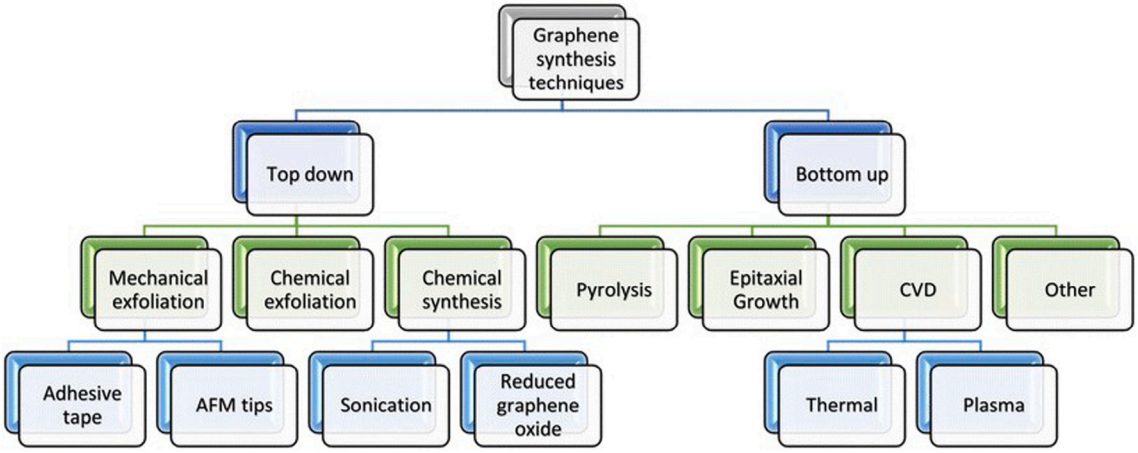

Fig. 5. A process flow chart of Graphene synthesis [37].

mainly studied by Coleman. By performing ultrasonic treatment on graphite in a specific liquid, graphite microcrystals are peeled off to obtain graphene nanosheets [43]. The one-step process, ease to operate, and environmental friendliness of this approach notwithstanding, there are still certain obstacles to its large-scale manufacture. The most common method of producing graphene is chemical redox, which involves first converting graphite to oxidized graphite and then reducing it to graphene by means of chemical, thermal, or electrochemical processes. Graphene can be produced top-down with great repeatability, little substrate transfer requirements, and ease of execution. Nonetheless, graphene is not widely produced today in the world and has a high production cost overall. Therefore, developing new methods and improving existing graphene production processes is necessary.

Functionalization of graphene. Graphene obtained using the above techniques still has many defects and oxygen-containing groups, which are the drawbacks in sensing applications. Therefore, various modification methods are needed to provide the characteristics required for biosensing, such as high water solubility and biocompatibility, to compensate for these shortcomings. Some of the unique properties of graphene can only be obtained by functionalizing organic groups such as amino, carboxyl, or hydroxyl groups. For example, graphene-based materials can achieve colloidal stability and dispersion in aqueous solutions after surface functionalization [44]. Certain graphene derivatives, such as graphene oxide (GO) and reduced graphene oxide (rGO), have functional groups that can help them interact with other molecules. Covalent and non-covalent bonding are the two methods that can be used to encourage the functionalization of graphene. First, non-covalent bonding allows graphene to retain its original characteristics. Among these, graphene self-assembly into other materials can be accomplished simply through electrostatic contact [45]. In addition, graphene can be functionalized by $\pi - \pi$ stacking to physically adsorb aromatic molecules on its surface [46,47]. However, although covalent interactions can improve graphene's mechanical properties and stability, they can disrupt its structure. For instance, graphene's band structure can change as a result of direct doping. Certain functional groups will stay in the structure if graphene is created by reducing GO, permitting covalent connections. In conclusion, polymers, metal nanoparticles, or biomolecules can be added to graphene-based nanomaterials to alter them [48]. The effective modification of graphene promotes the interaction between biomolecules and their surfaces, and the final biological binding compounds can be used as the primary sensing part of biosensors.

2.3.2. Two-dimensional transition metal dichalcogenides

TMDs, or transition metal dichalcogenides, are layered compounds of the MX_2 type, where X represents S, Se, and Te and M represents transition metal elements. Though some 8–10 TMDs have non-layered properties, solid covalent connections generated in-plane with weak interlayer contacts make up the majority of TMDs. The three multiple triple layers that comprise each layer of bulk TMDs are propelled by van der Waals forces. These layers each contain an atomic layer of transition metal and are positioned between two atomic layers of chalcogen. Changes in the structural phase and chemical composition of TMDs show many electronic properties relating to band structure characteristics, topological and correlated phases. Compared to their bulk counterparts, TMD nanosheets have distinct physical, chemical, optical, and electrical properties because of their incredibly thin thickness and two-dimensional structure. Two-dimensional TMD has numerous valuable and distinctive functions [49]. Because of their low toxicity, biocompatibility, and layer-dependent tunable band structures, 2D nanomaterials like TMD, hBN, Mxenes, and graphite nitride $(g - C)_3N_4$ are excellent choices for transducers in ultra-sensitive sensors. In contrast to graphene, the majority of TMDs have been extensively researched for potential use in integrated electronic circuits since they possess semiconductor electrical characteristics. Unique optoelectronic features are produced when multi-layer TMD is reduced to a single layer. The electrical band structure also shifts from indirect to direct, accompanied by high photoluminescence (PL) and a substantial exciton binding energy. Numerous applications, including gas sensing, biological imaging, light detection, luminescence, and drug administration, have been investigated with TMDs. Furthermore, its mechanical flexibility allows for integration with the upcoming generation of flexible wearable care point (PoC) devices [50]. The quantum confinement effect directly affects the band structure and leads to changes in atomic structure at ultra-small length scales. By altering fundamental characteristics including the quantum distribution of electronic states, continuous band to discrete level transitions, and size-dependent tunable band gaps, this method in TMDs will improve electrical properties, photoluminescence, and other aspects. TMDs have a large surface-to-volume ratio (S/V), a mechanical toughness, an adjustable band gap through layer number, and a high interaction with light [51,52]. They also have great charge transfer ability. They are also very straightforward to make and highly cost-effective. Because of its distinct form and functionality, TMD is a great option for the production of electrochemical sensing devices. Moreover, two-dimensional TMD nanosheets can directly interact with biomolecules to modify their surface, which can greatly increase the spectrum of applications for them in biosensing. Specifically, biological molecules can be highly physically adsorbed onto the surfaces of single-layer TMD nanosheets due to their huge surface area. Additionally, two-dimensional TMD nanosheets are a suitable platform for developing fluorescence-based biosensors due to their effective fluorescence quenching ability for fluorescent groups [53].

Synthesis of 2D TMDs. TMDs have been produced thus far using a variety of techniques, such as hydrothermal/solvothermal procedures, chemical vapor deposition, liquid and chemical exfoliation, and mechanical cleavage. Top-down and bottom-up technologies are separated into two groups [54]. The most often used top-down technique is mechanical cleavage, which uses the sticky properties of scotch tape to produce high-purity single- or multi-layer structures from bulk materials. Etching the growth substrate to release the previously described crystals is the first step in the attachment of deposited polymer films to TMD crystals or the use of scotch tape to achieve TMD monolayer mechanical exfoliation [55]. Mechanical cleavage has been used to create a number of ultra-thin two-dimensional TMDs, such as TaS_2, MoS_2, ReS_2, and WSe_2[54]. Although mechanical cleavage is a simple and inexpensive method, the manufacturing scale is very slow, and the ability to control quality and thickness is limited. Second, chemical exfoliation is an additional technique that uses ultrasonic in water to place intercalators in the intermediate layer of a bulky crystal, significantly exfoliating the crystal. Typical examples of organic metal compounds used as intercalators are butyl lithium and naphthyl sodium. Nevertheless, this approach still has limitations, including high reaction temperature, time-consuming, and sensitive to environmental changes [56,57]. The three primary processes of liquid exfoliation are exfoliation, purification, and the dispersion of layered materials in a liquid environment [58]. With the use of certain solvents and ultrasonic, liquid exfoliation can produce good block crystal exfoliation. The primary function of these solvents is to prevent the reorganization of detached NS and maintain its stability. The most commonly used solvents are organic, such as N-methyl pyrrolidone and dimethylformamide. In short, this method is simple and can mass produce high-quality two-dimensional nanoparticles.

Furthermore, CVD technology is a useful technique in bottom-up techniques to manufacture large-sized and uniformly thick TMDs, which can generate high-quality layered TMDs on various substrates [59]. Under high temperature and pressure settings, the substrate in this approach affects the reaction precursors of transition metals and chalcogenide atoms [60]. Ultra-thin 2D TMDs are produced when the final reaction product is put on the substrate. Scalable TMD films with good quality, superior electrical characteristics, and adjustable thickness can be made using this technique. Additional techniques include the solvothermal and hydrothermal processes, which are two popular ways to create TMD colloids. The solvothermal method refers to the use of effective nucleation and growth procedures in high-boiling organic environments. In addition, organic ligands are required to regulate the size and shape of TMDs and improve their dispersion capacity. The solvothermal approach is highly suited for the synthesis of non-oxides and may successfully prevent oxidation [61]. Hydrothermal techniques are simpler and more widely applicable than solvothermal techniques [62]. The solvothermal method's precursor solution is often non-aqueous, which is the only distinction between the two. So far, different TMD nanostructures have been successfully prepared using hydrothermal/solvothermal processes, including MoS_2 hollow cubic cages, CuS microtubules, Ag_2Se nanoparticles, etc.

Functionalization of 2D TMDs. TMDS are not naturally biocompatible, despite having biological characteristics like moderate conductivity, fluorescence, and high photothermal response. Therefore, more functionalization is needed to enhance its sensitivity as a diagnostic tool or to add capabilities like contrast imaging, DNA sensing, or drug administration. Similar to graphene materials, TMDs have a large surface area to volume ratio, which facilitates their facile functionalization. They may or may not be covalent. When it is essential to preserve the intrinsic qualities of 2D TMDs or when the removal of the TMDs' functional groups is a part of the diagnostic/delivery mechanism, non-covalent functionalization is usually chosen. In order to achieve optimal loading and environmental interaction, the functionalization procedure requires the physical adsorption of the drug carrier or probe onto the relatively large substrate surface of TMDs. On the surface of TMDs, covalent functionalization will create chemical linkages with the functionalized chemical groups. In the case of sulfur-based TMDs, this can be accomplished using certain chemical methods, such as thiol chemistry. Covalent bonds change the physical or electrical properties of TMDs by securely attaching particular functional groups to their surface. Different materials introduce different properties. Polymers and small organic molecules can achieve covalent or non-covalent binding with TMDs for biosensing or other applications [63]. Composite materials consisting of biocompatible polymers and TMDs can be created by non-covalently adding the polymers to TMDs. Usually, these polymers are added to the solution as reagents when block-shaped TMDs are intercalated to create 2D nanosheets. These polymers will thus provide the produced TMD nanosheets with good functionality. These polymers can also act as loading centers to further absorb medicinal compounds. Smaller organic molecules can be chosen for functionalization because they are smaller in size than polymers. This allows for direct drug delivery to cells and cellular absorption for cell labeling. Other applications include using the host TMDs platform's electrostatic interaction with connected molecules to increase its electrocatalytic efficiency. Moreover, TMDs can be used to develop biosensors that rely on the external disturbance-induced quenching or recovery of functional molecular fluorescence. The contact and self-assembly of TMDs with DNA biomolecules can also be facilitated by van der Waals forces between the substrate surfaces of TMDs and DNA nuclear bases. Single-stranded fluorescent-labeled DNA functionalized onto TMDs can serve as probes because its luminescence is influenced by single-stranded hybridization with other DNA [64,65]. Adorned with metal nanoparticles is a further functionalization technique that can improve TMDs' electrocatalytic potential or function as contrast agents for imaging [66]. To increase the sensitivity of their detection, additional two-dimensional materials are stacked as part of another non-covalent functionalization technique. Moreover, TMDs can produce pores for DNA sequencing [67]. TMDs' response to changes in the environment can vary depending on how they are modified and how they interact with external chemical elements. This provides a strong basis for their potential use in biomedical applications.

3. Challenges of biosensor miniaturization into the nanoscale

In the past few decades, the research direction of biosensors has tended to achieve specificity and high sensitivity combined with fast response time, low cost, and portability. Currently, the development of biosensors miniaturized to nanoscale becomes a very attractive research topic, which has important value such as reducing the cost for both early diagnosis and regular health monitoring. However, the reduction in critical dimensions of biosensing elements has an impact on two important metrics, which are detection limit and response time. There are other important factors to consider including non-specific binding, ease of biofunctionalization, and manufacturing complexity for large-scale production.

3.1. Limit-of-detection and response time

At present, the difficulty for all nanoscale biosensors is to maintain equilibrium in the connection between response time and detection limit [68]. However, we need to talk about two processes: reaction transport kinetics and signal transduction efficiency, when examining the relationship between a biosensor's size and its detection limit. Among these, the least amount of analyte that needs to be bound to the sensor surface in order to obtain an appropriate signal-to-noise ratio is linked to signal transduction efficiency, and response transport kinetics is related to the amount of time required for capture. Biosensing systems' signal-to-noise ratios can be raised by increasing signal density and lowering background signal. The higher signal transduction efficiency must be weighed against the longer mass transfer time needed

to gather target analytes on the sensor surface. Different biosensing systems can be created to combine low detection limits and quick response times by utilizing various signal transduction pathways and reaction transport kinetics.

Biosensors are autonomous integrated devices that consist of biological recognition components and signal transduction elements. These elements are crucial in establishing the biosensors' detection limit. The signal transduction element converts the biometric event into a quantifiable signal that can be measured using electrical, magnetic, optical, thermal, or piezoelectric properties, whereas the biometric element converts data from the test object into a chemical and physical output signal with high sensitivity and specificity. In biosensors, biorecognition, signal transduction, and signal measurement usually occur on a single surface at the sensor-solution interface. For example, in surface plasmon biosensors, both refractive index and resonant frequency changes occur on the same surface that stores the biometric element [69]. Furthermore, with solution-based homogeneous biosensors, biorecognition, signal transduction, and signal measurement do not occur on the same surface. For instance, biorecognition processes like DNA hybridization take place in solutions or on the surface of dispersed beads in certain biosensors used in the field of DNA nanotechnology. Then, through consistent signaling events, the biomolecular interactions are translated into observable changes in physical signals.

In comparison to bulk sensors, the biosensor's signal-to-noise ratio improves as its shape reduces toward the nanoscale and its signal transduction rate rises. As soon as the target analyte is gathered on the sensor surface, this happens. However, to gain insight into the impact of nanoscale geometry on biosensor performance, especially on response time, we can consider a set of rules of thumb proposed by Squires et al. [70]. When the analyte is transported to the sensor surface faster than using surface receptors, the sensor operates in a "reflection-limited" state, which allows us to account for the surface bound to the target through first-order Langmuir dynamics concentration

$$\frac{b(t)}{b_m} = \frac{\frac{c_0}{K_D}}{1+\frac{c_0}{K_D}}(1 - e^{-(k_{on}c_0 + k_{off})t}) \tag{1}$$

In Eq. (1), The binding target's surface concentration is denoted by b(t), the receptor's surface concentration is b_m, the bulk analyte concentration is c_0, the binding reaction's kinetic rate constants are k_on and k_off, and the equilibrium dissociation constant is $K_D = \frac{k_{off}}{k_{on}}$. In the event that the system reaches a steady state, the binding target's equilibrium concentration can be expressed as

$$\frac{b(t)}{b_m} = \frac{\frac{c_0}{K_D}}{1+\frac{c_0}{K_D}} \tag{2}$$

With a diluted analyte concentration ($\frac{c_0}{K_D} \ll 1$), the total number of targets bound on the sensor of area A is

$$N = b_m A \frac{c_0}{K_D} \tag{3}$$

The critical concentration for a target molecule to bind to the sensor at equilibrium (N = 1) is

$$c^* = \frac{K_D}{b_m A} \tag{4}$$

Eq. (4) shows that the critical concentration and the sensor area are inversely correlated, meaning that a decrease in the sensor area will result in a rise in the critical concentration. A single-molecule detection or sensor patch is needed if the concentration of the target analyte in the detection solution is less than the system's critical concentration.

In addition to this, when the response time is dominated by the reaction kinetics, it can be expressed as

$$\tau_R = (k_{off} + k_{on}c_0)^{-1} = {k_{off}}^{-1}(1+\frac{c_0}{k_D})^{-1} \tag{5}$$

Eq. (5) shows that the reaction time is inversely related to the target binding dissociation rate at low analyte concentrations. In case mass transfer plays a major role in determining the sensor's response time, it is imperative to meticulously design the sensor's size and form to ensure that it meets the necessary detection limits within a reasonable reaction time.

3.2. Nonspecific binding

In the first subsection, we consider the balance between detection limit and response time. Biosensors are not a simple system, and sometimes interfering substances bind non-specifically, so we need to distinguish the target analyte from the rest of the impurities in the sample. We name this result due to the nonspecific binding as the "basic biological noise floor", which can lead to a significant increase in the detection limit of the sensor. Regions where the nonspecific binding may occur include functionalized, passivated, and untreated regions of the device, and so it could be important to limit measurement sensitivity. Von Muhlen et al. [71] highlighted that nonspecific binding, not the system's intrinsic sensitivity, is what primarily determines the detection limit. Nevertheless, the resulting detection limits deviate significantly from the expected values when we solely take the device's mass resolution into account. Especially in nanodevices or functional arrays of nanodevices, the constraints imposed by the nonspecific binding are found to be more critical when we consider the situation where non-reactive regions dominate the functionalized surface. As such, understanding and controlling the nonspecific binding through methods such as the use of passivation membranes is key to improving sensitivity.

4. Applications of nanobiosensors

4.1. Detection method

4.1.1. Electrochemical biosensors

Electrochemical biosensors belong to a traditional classification of biosensors, which mainly use solid electrodes as the primary electrode and use the recognition characteristics of biomolecules to attach and fix sensitive biomolecules on the surface of the electrode. Subsequently, the target molecules are recognized specifically by biological molecules on the electrode surface. In order to accomplish the quantitative or qualitative analysis of the target analytes, the concentration signal is finally transformed by the primary electrode into electrical signals that can be measured as potential, current, resistance, or capacitance as response signals [73]. The working diagram of this sensor is shown in Fig. 6. Currently, electrochemical mechanisms are the basis for the development of the majority of biosensors. High sensitivity, high selectivity, easy miniaturization, ease of use, and acceptable cost are among the benefits of electrochemical biosensors, which have been used in environmental monitoring, healthcare, food, industry, and agriculture [74–76]. Concurrently, electrochemical biosensors are among the most widely used techniques for identifying a wide range of illnesses and hold considerable promise for point-of-care (POC) testing uses [77–79].

Electrochemical sensors usually have three main measurement categories: current, potential, and impedance. The most widely used technology in biosensors is the measurement of current. The first is voltammetry and amperometry. One of the electrochemical biosensors used in analytical detection the most frequently is the voltammetry/amperometric biosensor. Their technological aspects include detecting the current that comes from electrolysis at the working electrode through electrochemical reduction or oxidation and applying an electric potential to the working electrode in respect to the reference electrode. In contrast to voltammetry, amperometry measures current by stepping the potential straight to the required value without the need for a scanning potential. Numerous techniques, including as square wave, differential pulse, cyclic, and linear scanning voltammetry, have been devised for the development of voltammetry biosensors.

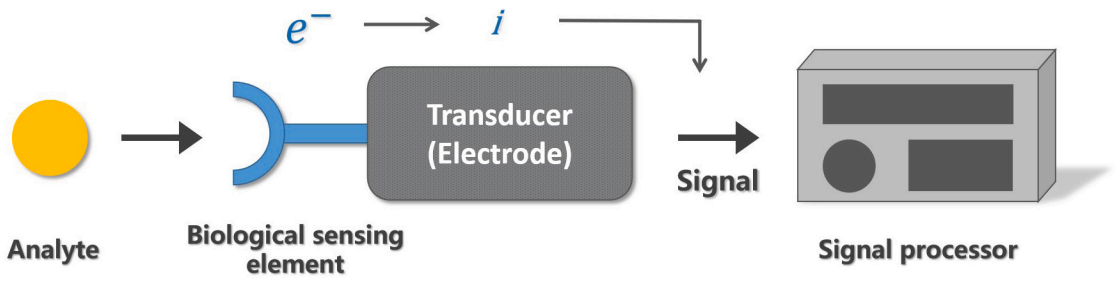

Fig. 6. A schematic of a biosensor with electrochemical transducer [72].

Potential sensors exist as well; these rely on determining an electrochemical cell's potential. Using an electrochemical cell with two reference electrodes, the detectors track the electrical potential across a membrane that interacts with charged ions selectively. These sensors can be made into biosensors by coating the membrane with biological molecules. Penicillinase, for example, catalyzes the creation of H^{3+} from penicillin; this enzyme can be used to coat a pH electrode for the purpose of using penicillin sensors. Penicillin can be tested indirectly by detecting changes in the pH value on the surface of the pH electrode. Prospective biosensors show promise for point-of-care (POC) diagnostic applications due to their small size, independence from sample volume, fast reaction, low cost, and ease of use [80]. By using conductance detection to measure the sample solution's and other media's change in conductivity, biosensing can also be achieved. For instance, the charged products produced by enzymes alter the ionic strength and hence increase electrical conductivity. As a biosensor detection modality, the conductance approach has been applied to clinical analysis and environmental monitoring. In addition to conductance approaches being used for drug detection, conductance immunosensors have been created to detect foodborne infections.

Another popular electrochemical biosensor is the impedance biosensor, which has the benefits of being unlabeled and having a modest amplitude perturbation. To accomplish target analysis, it makes use of electrochemical impedance spectroscopy (EIS) [81]. EIS can identify the circuit's resistance and capacitance components using a frequency-shifted, small-amplitude sinusoidal AC excitation pulse. High frequencies limit the pace at which oxidation–reduction materials can migrate to the electrode surface; this migration might be impeded by an item in the way, causing a frequency-dependent phase lag between the AC voltage and current. Both Faradaic and non-Faradaic modes of operation are available for the EIS. Among these, Faradaic EIS necessitates the insertion of redox pairs since it includes charge transfer between electrodes. Conversely, non-Faradaic detection [82] produces capacitive behavior without the requirement for additional reagents by means of charge separation at the electrode-electrolyte interface. Additionally, electrochemical biosensors known as field effect transistor (FET)-based biosensors may detect changes in conductivity caused by charged particles on the sensor surface [83]. The attractive qualities of FET-based biosensors, such as label-free operation, compactness, ease of mass fabrication, high flexibility, and low cost, make them highly promising for POC diagnostics.

With nanotechnology continuing to advance over the past few decades, we now have a deeper understanding of carbon materials. Numerous fields have employed carbon nanostructures in their various allotropes, ranging from zero to three dimensions. There have also been applications for the various carbon nanomaterials discussed in Section 2 in the realm of electrochemical biosensors. Furthermore, carbon nanomaterials have progressively moved from being electrode materials to becoming building blocks in electrochemical sensors. Different carbon nanomaterials have other outstanding characteristics, including electrochemical activity, conductivity, large surface area, biocompatibility, and ease of functionalization. Because of these characteristics, carbon nanomaterials can be used as nanoprobes, nanocarriers, or to improve the analytical performance in the electroanalysis.

Because graphene nanomaterials have almost all the high-quality characteristics of the above carbon nanomaterials, they are very suitable for electrochemical biosensors. We take them as an example to illustrate the benefits of nanomaterials for electrochemical biosensors. Graphene materials provide improved features over standard electrodes, including quick heterogeneous electron transport, high surface area, and outstanding two-dimensional conductivity. Bovine serum albumin (BSA) was used by Ingber et al. [84] to create a graphene-based multi-channel electrochemical affinity biosensing platform for three distinct procalcitonin (PCT), C-reactive protein (CRP), and pathogen associated molecular patterns (PAMPs). This sensor coats the electrode surface with graphene containing BSA, which addresses the issue of biological pollution induced by electrochemical sensing components. It retains the conductivity while preventing biological contamination. Drug detection has also made use of electrochemical sensors based on graphene. A simple ratiometric electrochemical biosensor for the sensitive detection of 4-acetaminophenol (4-AP) was proposed by Guo et al. [85]. Graphene oxide (GO) can self-assemble with ferrocene (Fc) attached, generating GO-Fc complexes with electrostatic interactions. In the meantime, a specific amount of nafion is added to the complex to render it immobile. To create a GO-Fc-Nafion/GCE sensing platform, the GO-Fc-Nafion complex was dropwise deposited onto the surface of a glassy carbon electrode (GCE). The sensor platform exhibits outstanding LDR and LOD, according to experimental data. Although the original graphene materials have some unique properties, they still have some defects that limit their application in electrochemical biosensors, such as low flux, small size, and hydrophobicity. On the other hand, graphene oxide (GO) makes graphene materials more hydrophilic, making them better suited for sensor selection. By removing graphene oxide's oxygen-containing group, reduction of graphene oxide (RGO) can be achieved. In the use of electrochemical analyses, it may produce strong electrochemical activity, outstanding conductivity, and a special combination that is simple to functionalize and offers additional benefits. Tablets made of graphene and graphene oxide have been developed as medicine delivery and biomolecule detection nanocarriers. Graphene-related nanomaterials can be used as electrochemical nanoprobes in two manners. One is to obtain signals from oxygen-containing groups by electrochemical reduction of GO. Luo et al. fixed the thrombin aptamer (THR-APT-15) on the electrode surface through physical adsorption, then combined with thrombin and GO in turn, and finally realized the measurement of thrombin by detecting the electrochemical signal of GO reduction. In the presence of thrombin, the thrombin aptamer binds explicitly to it, and due to the conformational change, the immobilized thrombin aptamer is partially removed from the electrode surface. Moreover, due to the solid p-p interaction, graphene oxide is adsorbed on the remaining immobilized aptamers. Graphene oxide is adsorbed on the fixed thrombin aptamer when there is no thrombin. The other way is to improve the electrocatalytic activity of graphene by doping external particles into graphene and modifying it with foreign atoms, which can essentially change the properties of the leading materials, such as potassium, nitrogen, sulfur, etc.[86]. There have already been reports of this method's application in the literature [87,88]. First, Li et al. [87] suggested a straightforward

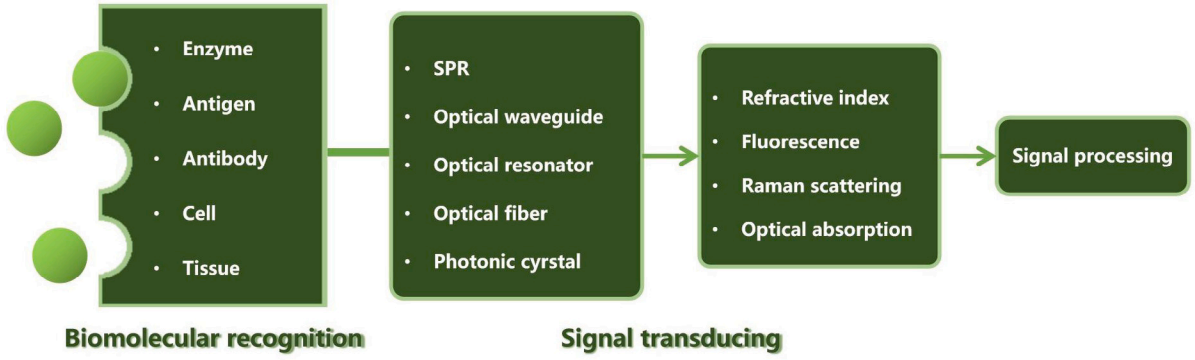

Fig. 7. An optical biosensor's component parts are shown graphically. Among its parts are signal transducing and processing units, as well as a sensor unit [89].

and gentle method of modifying graphene with K in a greenhouse. Compared to the original graphene, the created K-modified graphene is more effective at promoting charge transfer and acting as a medium for electron transport. In addition to the electrochemical performance, we can use graphene materials as nanocarriers by taking advantage of other properties of graphene. In this way, redox probes, target molecules, or components to be identified can be well assembled into electrochemical biosensors, thus improving the analytical performance.

In addition, carbon nanomaterials, including carbon nanotubes, carbon nanoparticles, diamond nanoparticles, etc., can also be used in electrochemical biosensors. From the materials perspective, the applicable sensors require uniformity and repeatability. Therefore, we should use more carbon-related nanomaterials, improve their classification and purification methods, and, at the same time, study and utilize their characteristics in developing biosensor diversity.

4.1.2. Optical biosensors

Compared to other physical signals, optical signals have the benefits of high sensitivity, low noise, superior stability, and resistance to external interference. Consequently, optical biosensors have demonstrated strong performance in identifying biological systems and have advanced significantly in drug development, environmental monitoring, clinical diagnosis, and food process control [90,91]. The interaction between biometric components and the light field is essential to the optical biosensor's operation. It consists of a little device with an optical transducer and a biological detector incorporated. As seen in Fig. 7, an optical biosensor consists of a sensing unit, a signal conversion unit, and a processing unit. Label-free and label-based methods are the two general types of optical biosensor recognition technologies. In label-based approaches, light signals must be produced via colorimetry, fluorescence, or luminescence; in label-free methods, the interaction between the material to be studied and the transducer can directly provide the detection signal. Nevertheless, labeling will alter the binding properties when detecting some simple compounds, resulting in systematic mistakes in biosensor analysis. Based on their transduction methods, several types of optical biosensors can be categorized, such as surface plasmon resonance (SPR), evanescent wave fluorescence, optical waveguide interferometry, surface enhanced Raman scattering (SERS), and bioluminescent optical fibers.

Currently, the most popular method is surface plasmon resonance (SPR), which detects changes in refractive index brought on by molecule interactions on metal surfaces using surface plasmon waves (SP). The primary functions of an SPR biosensor are the detection of tiny molecules, biological macromolecules, and hazardous metal ions [92]. The concept of its operation is depicted in Fig. 8(a). This SPR-based biosensor system is very promising for point-of-care (POC) HIV infection detection since it is faster, simpler, less expensive, more useful, and more stable than other sensing strategies and older approaches [93]. Based on traditional surface plasmon resonance (SPR), modern biosensor researchers have developed upgraded technologies such as local surface plasmon resonance (LSPR), long-range surface plasmon (LRSP), and surface plasmon resonance imaging (SPRi) [94–97]. In addition, the combination with nanoparticles has made SPR biosensors good development in application. The nanoparticles here generally include nanowires (NW), nanotubes (NT), nanospheres (NS), etc. One of its main working mechanisms is the plasma band displacement induced by local plasma resonance coupling through the aggregation of nanoparticles. The shift of the peak position is visually displayed as a colorimetric response. Colorimetric biosensors are inexpensive and easy to use. Utilizing tailored gold or silver nanoparticles (Ag NPs), numerous groups have created colorimetric biosensors [98–100]. Recently, there has been a lot of interest in the field of research on the integration of SPR sensors and 2D nanomaterials [101–103]. Two-dimensional nanoparticles possess notable electrical and unusual physical features. It has been shown that graphene-filled polymer matrices greatly enhance the mechanical characteristics of composite materials [104], and TMDCs with intrinsic band gaps show promise in optoelectronic and electrical applications. An important development over conventional biosensors is the ability of SPR biosensors to provide comprehensive detection while preserving the viability of biological cells when combined with two-dimensional nanomaterials. Tarik et al. [105] suggested a highly sensitive graphene-based multilayer (BK7/gold/PTSE2/graphene) coated surface plasmon resonance (SPR) biosensor for the rapid detection of novel coronaviruses (COVID-19). This sensor is modeled utilizing Total Internal Reflection (TIR) technology in order to detect ligand analyte immobilization in real time inside the sensing area. The interaction between ligands and analytes at different concentrations causes the sensing region's refractive index (RI) to change, which in turn affects the surface plasmon polariton (SPP) excitation at the interface of multilayer sensors. The sensitivity of this sensor is significantly higher than that of traditional biosensors. In order to increase sensitivity, graphene can be employed as the carrier of AuNPs. The challenge with SPR technique is that it is difficult to detect small molecules since the refractive index shift brought on by the binding event of small biomolecules is too faint. The special structural and optical characteristics of graphene, such as (i) its carbon-based ring structure's great adsorption affinity for biomolecules and (ii) the sensitivity of SPR to changes in refractive index, allow for improvements to the graphene–Au system.

Fluorescent biosensors are widely used in the diagnosis of infectious diseases because of their speedy analysis, high sensitivity, low cost, and ease of use.[106,107]. Fluorescent biosensors are commonly created by means of fluorescence resonance energy transfer (FRET), which is the transfer of energy from donor to acceptor fluorophore. Additionally, some nanomaterials with special chemical, physical, and electron transport properties can also be used to generate fluorescence signals.[108,109]. Nanomaterials are frequently employed as fluorescence signal producers, quenchers, and signal amplification probes in fluorescence biosensors. For instance, the strong quantum confinement effect in semiconductor quantum dots can result in variable optical

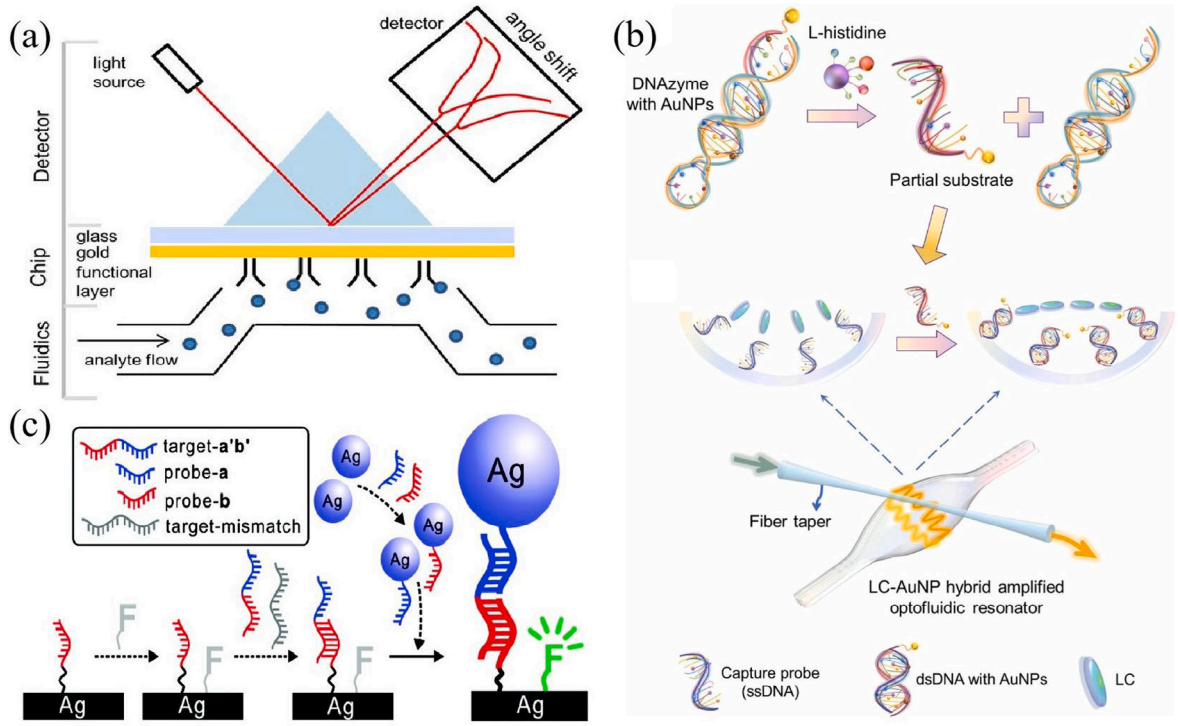

Fig. 8. (**a**) The principle of surface plasmon resonance instrument [116]. (**b**) DNAzyme-based biosensor schematic and principle for L-histidine detection using LC-AuNP hybrid amplification [117]. (**c**) Diagrammatic representation of the SERS method for detecting single-stranded DNA. Ag-AgNP/a'b'/b-AgFilm-F is the SERS-active structure formed by the capture of a target strand (a'b') by probes on AgNP and AgFilm-F. By gathering the surface-bound Raman label's SERS signal, target DNA detection is verified [118].

characteristics, wide absorption spectra, and limited emission, making them widely used fluorescent labels. The necessary optical qualities, which can be used in sensors, are easily obtained by modifying the characteristic values. Wei et al. [110] described a straightforward fluorescent biosensor for acrylamide detection in food that uses carbon quantum dots (CQD) and single-stranded DNA (ssDNA). In this sensing platform, the analyte's presence attenuates the drop in fluorescence intensity caused by the attachment of ssDNA to CQDs at 445 nm. Moreover, carbon-based nanomaterials and metal nanoparticles can be employed as fluorescence quenchers. Because they combine well with powerful fluorescence emitters and may absorb the visible area of electromagnetic spectra, metal nanoparticles are effective nano quenchers. On the other hand, organic dyes and quantum dots' fluorescence can be effectively quenched by carbon nanomaterials. SERS-based biosensors offer unique benefits over fluorescent biosensors, such as label-free detection, high sensitivity, dependable multiplexing, and outstanding reproducibility [111,112]. More significantly, coinagemetal nanostructures enable single molecule detection for SERS-based biosensors [113]. The SERS biosensor's sensing mechanism is depicted in Fig. 8(c). Assuming the detection of single-strand DNA as an example, the probes on AgNP and AgFilm-F ensnare the target chain (a'b'), establishing a SERS active structure in the form of a-AgNP/a'b'/b-AgFilm-F, and subsequently producing SERS signals with surface Raman labeling. SERS is a potent analytical method that is heavily dependent on the substrate material. The location, intensity, and dispersion of the surface plasma peak are strongly dependent on the material's composition, size, form, and surface roughness. Traditional precious metals have been replaced in the creation of substrate materials by semiconductor nanostructures or novel nanocomposites [114]. SERS-based signal detection and molecule recognition can be very helpful for research in biological sciences, biomedicine, analytical chemistry, and other fields [115].

The evanescent field directly penetrates the environmental medium through which the guiding mode propagates in the waveguide. A shift in the mode phase might be caused by the adsorption phenomenon on the biological layer or a change in the volume refractive index. This is the fundamental idea of the biosensor based on optical waveguide interference. To determine the analyte concentration to be measured, an interference signal is produced at the sensor output by combining the mode phase shift and the reference mode. The Mach Zendel interferometer (MZI), Hartmann interferometer, and Young's interferometer are the three major interferometers employed in this biosensor design. A novel sensor utilizing silicon nanowire ridge waveguide (SNRW) was presented by Gamal et al. [119]. This sensor satisfies the needs of high-density integration for chip laboratory applications and has the qualities of high sensitivity and minimal space occupied area. The waveguide is made out of silicon nanowire arrays with a ridge waveguide shell on an insulating substrate.

Moreover, the optical resonator-based biosensor makes use of the optical cavity's many qualities, such as its high speed, versatility, affordability, ability to detect many analytes, and compatibility with other optical components. Microcavity can be used as an optical signal sensor. The geometric shape or material of the optical cavity changes due to external factors and finally changes into light intensity. This kind of optical biosensor uses four different types of optical cavities: asymmetric, PC, echo wall mode (WGM) resonator, and Fabry Perot (FP) microcavity. Among these, the materials needed to make WGM resonators are becoming more and more common due to the ongoing advancements in nanotechnology, and the geometric shape of the cavity has a variety of designs [120]. Applying WGM resonators in biomedicine and clinical diagnoses has become more popular. Wang et al. [121,122] studied the application of liquid crystal (LC) and WGM resonators in biosensors. They created a hybrid amplification from LCs and Au nanoparticles (AuNPs) to create a DNAzyme biosensor that is ultra-sensitive, label-free, and fast-responding [117]. Fig. 8(b) illustrates the biosensor's detecting principle. L-histidine molecules were employed in the experiment as the analyte in order to reach the sub-molecular ultra-low detection limit. Furthermore, by combining LC-AuNP hybrid amplification with this suggested optofluidic scheme, DNAzyme-based biosensors can be used to detect a wider range of chemicals.

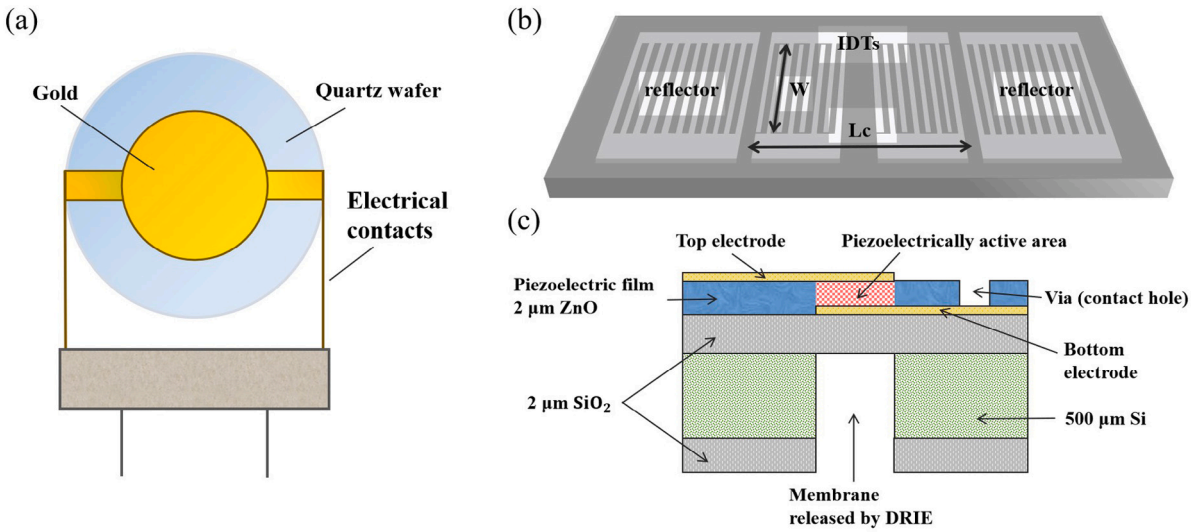

Fig. 9. (**a**) Schematic of a typical piezoelectric crystal [129]. (**b**) The 2-port SAW resonator diagram was obtained on a quartz substrate using two IDTs positioned synchronously between reflecting gratings, where Lc represents the cavity length and w represents the finger overlap [130]. (**c**) A schematic cross-sectional view of a designed FBAR [131].

Researchers have been adopting fiber optic biosensors in recent years due to their features such as high sensitivity, good stability, strong specificity, and low analytical costs. When developing in-situ label-free technologies, the use of fiber optic devices as biological/chemical sensing components presents substantial advantages in terms of cost, size, and convenience when compared to electrochemical techniques. Consequently, fiber-based biosensors become more popular and present a novel method for the widespread identification of biological analytes [123,124]. Among these, photonic crystal fiber (PCF) biosensor applications have grown in popularity [125,126]. PCF's geometric design gives it special qualities and capabilities. Pores (AH) in PCF serve as fluid conduits for biological sample injection. By integrating a gas or liquid into AH and scattering photons in the substrate, samples in PCF are detected. Photonic crystal (PhC) biosensors find extensive uses in medicines, healthcare, biomedical exploration, and other domains. These biomedical sensors aim to detect several biomedical illnesses in things like blood, proteins, glucose, and DNA. When these sensors are combined with nanomaterials, their sensitivity will rise [127]. Various nanomaterials have distinct mechanisms of application. SPR-based fiber optic biosensors, for instance, can be made using two-dimensional metal films and three-dimensional (3D) nanoarrays, which are helpful in enhancing the local electric field of fiber optic structures. Furthermore, new nanomaterials such metal oxides, non-metallic oxides, MoS, and MXene are being progressively added to the field of fiber optic biosensors. The outstanding optical properties and biocompatibility of these materials greatly improve the biosensing performance. Lv et al. [128] suggested a dual-channel PCF multifunctional biosensor based on LSPR, and they used the finite element method to simulate and determine sensor features. The coupling amount is greatly increased by filling optical fibers with silicon and connecting Au nanowires to them. By deepening the penetration, silicon coating improves connection and raises sensitivity. In the medical field, this kind of biosensor may be a viable option for organic analyte detection. Optical fiber biosensors based on nanomaterials may prove to be the next big thing in quick and affordable biomarker detection.

4.1.3. Piezoelectric biosensors

A piezoelectric sensor is a type of sensor that measures physical qualities like strain, stress, pressure, or acceleration by converting them into electrical impulses via the piezoelectric effect. The traditional piezoelectric biosensor is based on the interaction between the analyte and the sensitive layer applied to the sensor's surface. Using an electronic oscillator to measure variations in the sound wave's velocity, attenuation, delay time, and resonance frequency, one can identify changes in mass or viscosity caused by the interaction between the analyte and the sensor layer [2]. However, depending on the piezoelectric material employed and additional factors like electrical contact or crystal structure, oscillations can appear in a variety of ways. For instance, oscillations in adiabatic waves typically propagate across the entire mass in a manner similar to sound waves. Both bulk sound waves that arise in deep matter and surface sound waves that propagate on the material can occur in an oscillating crystal. By monitoring oscillation frequencies, typical analytical applications can help determine analytes by analyzing interactions with individual crystals or with electrical impulses directed by electrodes on the surface of crystals. According to the Sauerbrey equation, the frequency shift of ordinary quartz crystals is proportional to the bound mass on the crystal surface, which is as follows:

$$\Delta f = \frac{-2f_0^2 \Delta m}{A\sqrt{\rho_q \mu_q}} = -2.3 \times 10^6 f_0^2 \frac{\Delta m}{A} \tag{6}$$

where f_0 is the fundamental mode of crystal oscillation (Hz), A is the piezoelectric effective area (cm), ρ_q is the density of quartz (2.648 g/cm^3), and η_q is the shear modulus (2.947×10^{11} g/cm × s^2). Although the Sauerbrey equation has accurately described the interaction with mass, it does not take into account the effect of other properties such as the viscosity of the ambient solution on the frequency shift. This allows us to consider using another quartz crystal equation described by Kanazawa [132]:

$$\Delta f = f_0^{3/2} \sqrt{\frac{\Delta(\rho_l \eta_l)}{\pi \rho_q \eta_q}} \tag{7}$$

where the meaning of the symbols in the formula is the same as that in Sauerbrey equation, where the symbol "l" represents the ambient liquid and "q" represents the quartz crystal. This equation shows that the frequency shift is proportional to the increase in ambient viscosity "η", and the fact that viscosity affects the frequency shift needs to be taken into account in any measurement process.

The quartz crystal microbalance (QCM), which is inexpensive and easy to acquire, is currently the most used experimental platform for the piezoelectric effect in biosensing. QCM is usually composed of tiny AT-cut quartz discs (a few hundred microns in size) with metal electrodes (usually Au) on both sides, as Fig. 9(a) illustrates. Its fundamental frequency spans from one to tens of megahertz, and it operates in the thickness-shear mode. Moreover, SAW delay lines, thin-film bulk

acoustic resonators, and surface acoustic resonators (SAW) can be included into microfluidic devices and utilized in biosensing applications. The sensing outcomes of SAW and FBAR devices are more sensitive than those of QCM because they operate at higher frequencies. A new piezoelectric aptasensor was devised by Tian et al. [133] to detect Okada acid (OA). QCM devices are employed as sensors for response signal detection, and adapters that are particularly coupled to OA are used as sensing elements. AuNPs are involved in sensor detection signal amplification. This biosensing technology offers a label-free, extremely sensitive, highly specific, economical, and easy way to detect OA. QCM has drawbacks, including increased vulnerability and manufacturing constraints, despite being able to achieve frequencies of hundreds of megahertz and improve sensitivity [134].

Piezoelectric materials should have strong biocompatibility and high electromechanical coupling to meet the key criteria of biomedical applications. High mechanical flexibility and strength, as well as sensitivity to inputs and physiological responses, may also be required [135,136]. Compared with bulk materials, bio-piezoelectric nanomaterials have unique advantages in biomedicine, mainly in the following aspects. Firstly, bio-piezoelectric nanomaterials are able to effectively pass through a variety of physiological barriers due to their incredibly tiny size. Secondly, based on the application of piezoelectric catalysis, the smaller size provides the piezoelectric nano-catalyst with a higher electron transfer rate and more vital interaction with the substrate. Piezoelectric nanoparticles can also be utilized as multipurpose drug nanocarriers for medication administration and illness treatment due to their larger surface area. Because of their piezoelectric qualities and nanoscale features, bio-piezoelectric nanomaterials offer enormous potential in a variety of biomedical domains. Biological piezoelectric nanomaterials are categorized into three types based on size: 0D, 1D, and 2D. Nanoparticles, nanoclusters, and quantum dots are examples of 0D bio-piezoelectric nanomaterials. They are distinguished by their enormous surface area, superior piezoelectric qualities, and single domain nature [137,138]. Furthermore, several 0D bio-piezoelectric nanomaterials exhibit rapid metabolism and good biocompatibility, satisfying the demands of the biomedical industry [139,140]. Nanowires, tubes, rods, fibers, and other nanomaterials are examples of 1D bio-piezoelectric nanomaterials. They are able to overcome the agglomeration disadvantage of 0D bio-piezoelectric nanomaterials in addition to demonstrating greater charge transfer efficiency [141]. Wang et al. [142] developed a self-powered biosensor to identify creatinine in perspiration. Because the device uses the piezoelectric effect of ZnO NWs modified with creatinase/creatinase/creatine oxidase and the coupling effect of enzymatic activities, the biosensor can actively output electrical signals and interpret them as biological signals. Moreover, a significant association has been seen between the creatinine concentration and the piezoelectric output voltage, which serves as an indicator of creatinine concentration. Real-time human creatinine level measurement is possible with this sensor since it does not require external power sources. It offers a tremendous deal of potential for sickness prediction and may offer information about general body health. Among the typical 2D biological piezoelectric nanomaterials are carbon nitride [143], boron nitride [144], and black scale [145]. They have various planar structures and forms, have photosensitivity, thermal sensitivity, good REDOX activity, and excellent biocompatibility, and have been extensively studied in biomedicine [146].

4.2. Detection targets

4.2.1. Detection of DNA

Deoxyribonucleic acid, or DNA, is a type of nucleic acid that is vital to an organism's growth and healthy operation since it contains the genetic information needed to synthesize RNA and proteins. Infectious illness diagnostics, medical bioengineering, and gene discovery have all made extensive use of DNA hybridization. Molecular hybridization is one of the many biological methods for detecting DNA. It uses fluorescence-labeled DNA to identify alterations in the target DNA as a result of the hybridization process between the probe and the target DNA. Moreover, methods utilizing DNA binding proteins and polymerase chain reaction (PCR) technology exist. Although these techniques are commonly used in clinical and analytical laboratories, their field and point-of-care applications are still in their early stages of development. The main challenges these traditional methods face are the requirement for complex and expensive equipment in addition to the absence of an easily comprehensible transduction mechanism for the generated detection signal. As nanomaterials in the field of DNA sensing continue to progress, effective sensors with superior signal processing and microfabrication capabilities are being developed. Nanomaterials are highly popular in the development of biosensors because of their appealing features. Additionally, because of the enormous surface area to volume ratio of nanomaterials, biological receptors on their surface have a higher loading capacity, which raises the sensitivity levels. Many biosensors have been developed in the field of DNA sensing, making use of the unique electrochemical or optical properties of various nanomaterials, such as metal nanoparticles, carbon nanotubes (CNTs), quantum dots (QDs), graphene and its derivatives, and other carbon-based materials. Because NPs are more stable than enzymes, they are frequently employed as electrochemical markers in electrochemical sensors. Certain carbon-based nanomaterials can be used to alter the electrode surface and facilitate the detection of various targets by increasing the electrode's effective surface area and electron transfer rate. Because of their ability to quench fluorescence, several nanomaterials like graphene oxide, gold nanoparticles, and carbon nanotubes are used in fluorescence biosensors. Regarding colorimetric biosensors, its primary application is the color shift brought about by the aggregation action of gold nanoparticles. The target DNA can be identified by coupling the probe ssDNA with gold nanoparticles and observing color changes that result from hybridization with complementary DNA. Typical SERS techniques involve the direct coupling of nanomaterials to certain biological receptors and Raman reporter molecules to generate SERS tags, which provide strong Raman signals for target DNA detection. Nanomaterials-based DNA biosensors are employed as important tools in genetics, pathology, criminology, pharmacogenetics, and the medical/food industry. Because of their large surface area, similar size to biochemical molecules, and strong biological compatibility, nanomaterials are also crucial for DNA analysis and detection.

In recent times, gold nanoparticles have found extensive application in the field of biosensing due to their unique optical, electrical, and catalytic properties [154]. When combined with various other materials, gold nanoparticles can play a role in different biosensing scenarios. The deadly disease dengue hemorrhagic fever (DHF) affects people severely. This disease can be contracted from one of four serologically separate but closely related dengue viruses (DENVs). Serotype identification is just as crucial as viral detection since the fatality rate rises sharply when a secondary infection is caused by a different virus serotype than the original infection. Response surface methodology (RSM) was applied by Jahwarhar et al. [147], who also enhanced the functionality of a DNA hybrid biosensor for dengue virus (DENV) detection (see Fig. 10(a)). This biosensor uses methylene blue (MB) as a redox indicator and is based on silicon nanowires coated with gold nanoparticles (SiNW/AuNP). In previous studies, it was found that SiNWs/AuNPs nanocomposites can distinguish electrochemical signals of dengue virus genes from those without them [155–157]. Therefore, this composite material is very suitable for use as a sensing material. The primary goal of this work is to optimize the circumstances for DNA hybridization, including pH, ion strength, temperature, time, and hybridization time. Researchers can find combinations of parameters that can maximize the sensitivity, specificity, and stability of biosensors and improve their performance by using RSM for statistical modeling design. This sensing technique combines electrochemical detection with sample pretreatment. It is faster, more accurate, more sensitive, easier to use in labs and hospitals, and more standardized

Table 1
Applications of nanomaterial-based biosensors for detection of DNA.

Type of nanomaterial	Target	Detection principle	Limit of detection	Ref.
SiNWs/AuNPs nanocomposite	DENV	Differential pulse voltammetry (DPV)	2.8 ng mL^{-1}	[147]
AgNWs	respiratory bacterial DNA	SERS coupled with PCR	3.12 pg/μL	[148]
AuNPs	L-histidine	Optofluidic scheme with LC-AuNP hybrid amplification	5×10^{-16}	[117]
MoS_2 NSs	CHIGV DNA	Methylene blue to interact differentially with the guanine bases of the single and double-standed DNA	3.4 nM	[149]
3D DNA walker	Zika virus	Amplify fluorescene signals through 3D DNA walker and LCHA cascade amplification	20 pM	[150]
TGA-CdS QDs/TiO_2	Chloramphenicol	Photocurrent intensity changed due to specific recognition between aptamer and chloramphenicol	0.23 pM	[151]
DNA tetrahedron nanostructures	HPV-16	Electrochemiluminescence (ECL)	8.86 fM	[152]

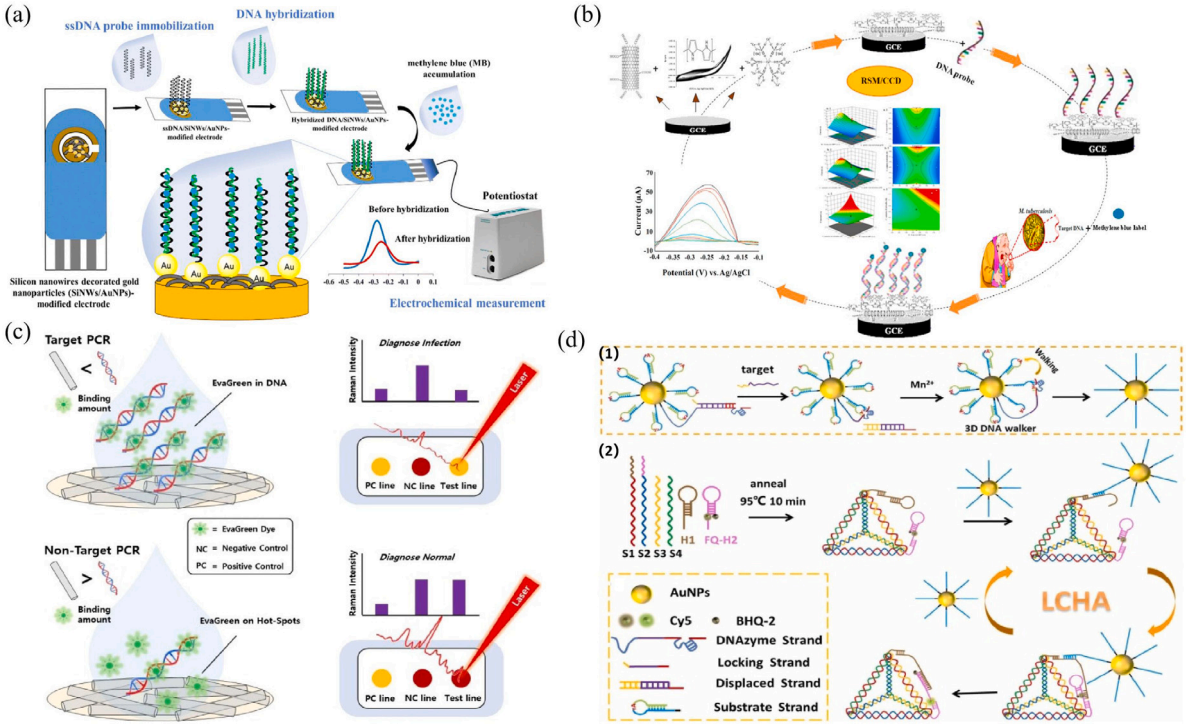

Fig. 10. (**a**) Systematic of the fabrication and mechanism detection of the developed biosensor [147]. (**b**) Schematic representation of the electrochemical DNA biosensor [153]. (**c**) Diagrammatic representations of the respiratory bacterial DNA testing procedure utilizing a paper-based SERS substrate. When there is a target, EvaGreen dye intercalation predominates in the DNA structure; however, when there is no target or non-target, most EvaGreen adheres to the AgNW hotspots. A comparison of the Raman intensities of the test and control lines can be used to make the diagnosis [148]. (**d**) The principle of the fluorescence biosensor for ZIKV detection. (1) the 3D DNA walker portion and (2) the LCHA portion [150].

than more conventional techniques like gel electrophoresis visualization and ELISA detection. Nevertheless, liquid crystal (LC) materials can also be used in conjunction with biosensors that rely on the utilization of AuNPs. High directivity, dielectric characteristics, and optical anisotropy characterize LC as a unique material. Chemical and biomolecular binding events influence the arrangement of LC molecules; these characteristics, along with their optical anisotropy, make LC molecules ideal for biosensing applications. An ultra-sensitive, label-free, and fast-responding DNAzyme biosensor was created by Wang et al. [117] using a hybrid amplification of LCs and AuNPs in conjunction with a WGM optofluidic resonator. The sensing procedure in this work may be broken down into three simple steps: first, the analyte (in this case, L-histidine) splits the substrate chain containing the recognition site into two pieces, which are then hybridized with the capture probe. The orientation of LC molecules will then change from their original vertical orientation to a horizontal orientation due to the hybridization of DNA strands. In the end, the direction shift of the LC molecules causes a shift in the spectrum. AuNPs, which have a diameter of around 10 nm, are larger than a lot of L-histidine and DNA strands. This allows them to drastically change the surface topology, which in turn promotes the orientation transition of LC molecules. As a result, AuNPs can enhance the signal in this process, resulting in lower detection limits and higher sensitivity. For analyte analysis, this sensing platform offers label-free, fast-responding, and ultra-sensitive detection options. Moreover, additional biomolecules can be detected using this LC-AuNP hybrid-amplified optofluidic transduction technology.

Mycoplasma pneumonia, Haemophilus influenza, Chlamydophila pneumonia, and Streptococcus pneumonia are human pathogenic bacteria that cause pneumonia. The most common cause of death for kids under five is pneumonia. The symptoms of respiratory diseases are similar, thus a rapid and accurate point-of-care test (POCT) technique is needed to diagnose infections in order to avoid overusing antibiotics.

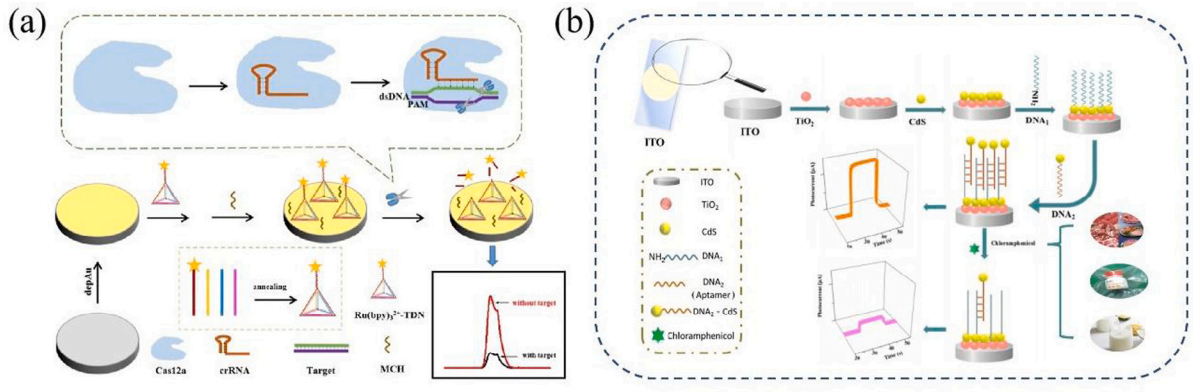

Fig. 11. (**a**) Diagrammatic Representation of the Trans-Cleavage Activity of the CRISPR/Cas12a-Mediated ECL Biosensor and the DNA Tetrahedron Nanostructure [152]. (**b**) A schematic representation of the CdS-DNA_2/DNA_1/CdS/TiO_2/ITO PEC biosensor's construction and signal multiple amplification technique. When chloramphenicol is added, DNA_2 recognizes it and then competes with the CdS-labeled DNA_2 for its presence, which lowers photocurrent [151].

Lee et al. [148] developed a PCR-coupled SERS technique for the rapid and precise detection of respiratory bacterial DNA (see Fig. 10(c)). The detection method uses a surface-enhanced Raman scattering (SERS) substrate made of silver nanowires (AgNWs) on paper along with polymerase chain reaction (PCR). As a DNA embedding molecule, it adds EvaGreen dye to the lowest heat cycle PCR result. Using Raman spectroscopy, the variation in dye intercalation in the DNA structure was evaluated to verify the presence of a target gene. The plasmonic nanostructure on the paper substrate served as both a nano filter for DNA and a SERS material, giving AgNWs an advantage over other nanomaterials. With Mycoplasma pneumoniae (M. Pne) as the model organism, the experiment's detection was conducted under various gene concentrations and amplification cycles, yielding a detection limit as low as 3.12 pg/μL. According to these experimental findings, PCR-coupled SERS sensors are very sensitive and fast, making them useful for a wide range of molecular diagnostics, particularly those involving infectious disorders. In order to increase diagnostic precision and detection resolution, it is also anticipated that this detection technique will be coupled with several POC molecular diagnostic systems.

Furthermore, electrochemical biosensors can be fully integrated with nanoelectronics and are a perfect fit for miniaturization. The issue of efficiently fixing DNA probes and achieving quick hybridization must be resolved in order to create high-performance electrochemical biosensors for DNA detection. Numerous nanomaterials have been used in DNA biosensors, despite the fact that they might offer a high surface area to volume ratio for DNA fixation [158]. The deadly and highly contagious Zika virus is transmitted by mosquitoes. In recent times, ZIKV infection has grown increasingly likely due to global warming, posing a severe danger to global health [159]. Currently, the standard diagnostic method for ZIKV is reverse transcriptase polymerase chain reaction (RT PCR) detection. This method necessitates expensive equipment, difficult operation, and sophisticated processing, and it may result in false positive or false negative findings. Therefore, accurate, timely, and reasonably priced diagnosis is essential for the worldwide control of viral infections. Liang et al. [150] reported a low-cost, simple, and sensitive fluorescence biosensor that combines an LCHA with a DNAzyme-driven 3D DNA walker for extremely sensitive and enzyme-free ZIKV detection (see Fig. 10(d)). Among them, the 3D DNA walker is a remarkable dynamic DNA nanomachine that can travel freely on the intended nanoscale orbit and generate cascaded amplification signals [160]. The 3D DNA walker employed in this sensing device was built onto AuNPs using a base hairpin probe and a locked walking strand. The LCHA was created by confining hairpin DNA 1 (H1) and fluorophore-quencher-labeled hairpin DNA 2 (FQ-H2) inside a DNA tetrahedron. When ZIKV is present, the initially locked walking strands will start to travel independently along the hairpin routes. Ultimately, the track strands parted ways. The DNA pieces affixed to the AuNPs function as catalysts for the LCHA reaction during centrifugation, potentially restoring fluorescence. This approach uses the signal amplification effect of a 3D DNA walker in concert with LCHA to obtain a lower detection limit than earlier ZIKV detection techniques. Furthermore, the biosensor has great feasibility and reliability and can be utilized directly to serum samples in less than two hours, saving time and effort on the laborious sample processing procedure.

DNA biosensors, sometimes referred to as gene sensors, have seen a sharp increase in development in recent years. These sensors work by allowing complementary probes and DNA targets to hybridize. In a place where tuberculosis is widely prevalent and access to reference labs is limited, they might be able to identify infections immediately [161]. A serious global public health concern, TB is one of the top 10 causes of death worldwide. The prognosis of tuberculosis (TB) is largely dependent on how quickly appropriate antibiotic therapy is initiated after a proper diagnosis. As a result, we require a quick and efficient detection technique. Rizi et al. [153] developed a fast, low-cost, PCR-free DNA biosensor based on multi-walled carbon nanotubes (MWCNTs), polypyrrole (PPy), and hydroxyapatite nanoparticles (HAP-NPs) for the very sensitive and specific identification of Mycobacterium tuberculosis (see Fig. 10(b)). Mycobacterium tuberculosis, a member of the Mycobacterium tuberculosis complex species, is the causal agent of tuberculosis (TB). In this configuration, the M.tb ssDNA probe is covalently bonded to the surface of HANPs, PPy, MWCNTs, and GCE. It then hybridizes with complementary target sequences to form a duplex DNA. The electroactive Methylene blue (MB) oxidation signal on the modified GCE surface provides the foundation for identifying the M.tb target through the use of the differential pulse voltammetry (DPV) technique. Because MWCNTs have a high surface area, volume ratio, and excellent conductivity, we use them. As an essential biomaterial, HAPNPs have good biological activity and biocompatibility, are non-toxic, and have specific multiple adsorption sites, making them the correct choice as fixed substrates for biomolecules. Additionally, the biocompatibility, conductivity, chemical stability, and toxicity of biosensors can all be decreased by employing organic polymers like PPY in their production. This biosensor, which has a limit of detection (LOD) of 0.141nM, has potential applications in clinical diagnostics and as a real-time screening tool for Mycobacterium tuberculosis detection.

Electrochemical sensors are a multifaceted detecting system that include light, sensors, and electrochemistry. Photoelectrochemical (PEC) sensors are a technology that originated from electrochemical sensors. Following the addition of bioactive units to the sensor, the analyte's chemical interactions with the bioactive units will alter the charge migration, changing the photocurrent response and enabling target selection. An further source of alternating photocurrents is the little charge transfer that occurs between electrodes and optoelectronic materials. In order to detect trace chloramphenicol, Yao et al. [151] created a

Table 2
Applications of nanomaterial-based biosensors for detection of enzyme.

Type of nanomaterial	Target	Detection method	Limit of detection	Ref.
AuNPs@gelatin /AuNCs	MMP-9	Fluorescence and colorimetric strategy	2 ng mL^{-1}/0.25 ng ml^{-1}	[162]
BSA-Au NCs, Au NBPs	Trypsin	Colorimetric strategy	0.45 μg mL^{-1}	[163]
AuNPs	Trypsin	RGB recognition/photothermal sensing	1.2 μg mL^{-1}/6 μg mL^{-1}	[164]
AuNPs	SARS-CoV-2 Mpro	Colorimetric strategy/Electrochemical impedance spectroscopy	10 pM/0.1 pM	[165]
AuNP-peptide-DNA combined nanoprobe	papain-like cysteine protease	Square wave voltammetry (SWV)	1 pg mL^{-1}	[166]
CNP	ALP	Fluorescence and colorimetric two-channel strategy	0.05 mU mL^{-1}	[167]

novel PEC biosensor utilizing TGA-CdS QDs/TiO_2 as a photosensitive material. This was achieved by combining a multiple amplification technique with DNA specific recognition (see Fig. 11(b)). Prior to placing particular DNA sequences tagged with TGA-CdS QD on the electrode, the scientists synthesized rutile type TiO_2 nanosheets and mercaptoacetic acid modified CdS quantum dots (TGA CdS QD). The light capture and carrier migration capabilities of this heterojunction structure can be improved, increasing the sensitivity of PEC biosensors. The photocurrent intensity changes significantly when the target chloramphenicol is present in the solution as a result of the aptamer's particular recognition and competitive binding with the chloramphenicol. This allows for an accurate determination of chloramphenicol. The PEC biosensor shows good stability and repeatability toward chloramphenicol while operating in ideal conditions. Furthermore, the biosensor exhibits outstanding anti-interference capabilities in real-world applications because of its unique capacity to recognize base pairs. This outstanding performance highlights the biosensor's extensive potential for antibiotic detection. A sensitive and amplification-free electrochemiluminescence (ECL) biosensor based on CRISPR/Cas12a and DNA tetrahedron nanostructures (TDNs) was developed by Yu et al. [152] (see Fig. 11(a)). A DNA probe tagged with $Ru(bpy)_3^{2+}$ is attached at the tip of TDN as an ECL signal probe in this sensing platform. Target DNA causes $Ru(bpy)_3^{2+}$ to separate from the electrode surface, weakening the ECL signal and converting changes in target DNA concentration into changes in ECL signal, enabling the quantitative detection of HPV-16. This process activates the trans-cleavage activity of the Cas12a-crRNA duplex. The biosensor is very selective since the experiment makes use of CRISPR/Cas12a's particular detection of HPV-16. The cleaving efficiency of CRISPR/Cas12a can be enhanced and cleaving steric resistance can be decreased with the TDN-modified sensing interface. Research findings show that this electrochemiluminescence biosensor not only has a high detection rate but also strong reproducibility because of the reaction system's straightforward design and lack of a cyclic amplification procedure. Furthermore, by only altering the crRNA sequence, it can be utilized to identify other targets and may find utility in sensitive and quick nucleic acid detection (see Table 1).

4.2.2. Detection of enzyme

Enzymes are biocatellites that promote the rapid process of cell metabolism, which allows the chemical reactions in the organism to be carried out efficiently and precisely under extremely mild conditions. In disease diagnosis, clinical treatment, and life production, enzymes have important research significance. Therefore, enzyme detection is also a crucial research content. In recent years, many research groups have made experimental results combining the detection of nanomaterials and enzymes. In the field of electrochemical sensors, combining the recognition and catalytic properties of enzymes with the electronic properties of various nanomaterials, can design a new generation of biosensors with high sensitivity and stability. Among them, the main function of nanomaterials is to increase the loading of biological receptors, act as probes for electrochemical signal generation, or enhance the loading of electrochemically detectable substances. In the new type of fiber optic optofluidic laser biosensor, nanomaterials such as Au nanorods are coated on the inner surface of thin-walled hollow fibers through electrostatic adsorption, which can obtain a lower laser threshold and enhance the sensitivity of the sensor [168].

In addition to being important regulators of vital physiological functions like blood coagulation and food digestion, proteases are also vital biomarkers for numerous illnesses including cancer. The development of robust, selective, and sensitive protease sensors is strongly encouraged by the intimate link between disease and proteases. For homogeneous protease determination, FRET-based detection methods are frequently employed, and new fluorescent nanomaterials are furthering this area of study. Traditional FRET-based protease sensors rely on covalently bonded organic FRET receptors and donors to peptide chains. In biosensors that identify proteases, nanomaterials like gold nanoparticles (AuNPs), graphene oxide (GO), and carbon nanotubes (CNT) have all been employed as efficient FRET receptors. Peptides can also be bioconjugated onto GO or CNT to create a protease sensor based on frets. These carbon nanomaterials may perform the dual roles of the surface, enabling bioconjugation and fluorescence quenching, and they have π stacking solid contacts. Dadmehr et al. [162] created a novel nanocomposites-based colorimetric and fluorescence detection platform for the dual mode detection of MMP-9 enzymes based on AuNP and AuNC (see Fig. 12(b)). In order to create gold nanoclusters (AuNCs), the AuNPs@gelatin/AuNCs nanocomposite structure utilized in this work was first synthesized based on gelatin. AuNPs were then encapsulated with gelatin/AuNCs. The gelatin layer breaks down and efficiently suppresses FRET between AuNPs and AuNCs when the MMP-9 enzyme is present, which causes notable changes in the fluorescence and absorbance of AuNPs@gelatin/AuNCs nanocomposites. In colorimetric mode, induced aggregation of AuNPs is caused by the enzyme activity of MMP-9. This results in color changes in AuNPs. On the other hand, MMP activity fluorescence detection in fluorescence mode is achieved using the FRET process triggered by AuNPs. We can concurrently ascertain the precise activity of the enzyme with the aid of these two modalities. Additionally, MMP-9 enzymes can be easily recovered and detected using this method in the human serum matrix, making it an effective, practical, and handy instrument for the straightforward identification and accurate detection of MMP-9 enzymes.

An essential digestive enzyme that is normally found in the digestive tract is trypsin. It mostly cuts peptides on the C-terminal side of arginine or lysine residues, activating the peptides. Aberrant trypsin activity causes pathogenic changes in the human body, including aberrant pancreatic function. Many methods, such as colorimetric, fluorescence, electrochemical, chemiluminescence, and liquid crystal-based assays, have been developed for the detection of trypsin because of its good

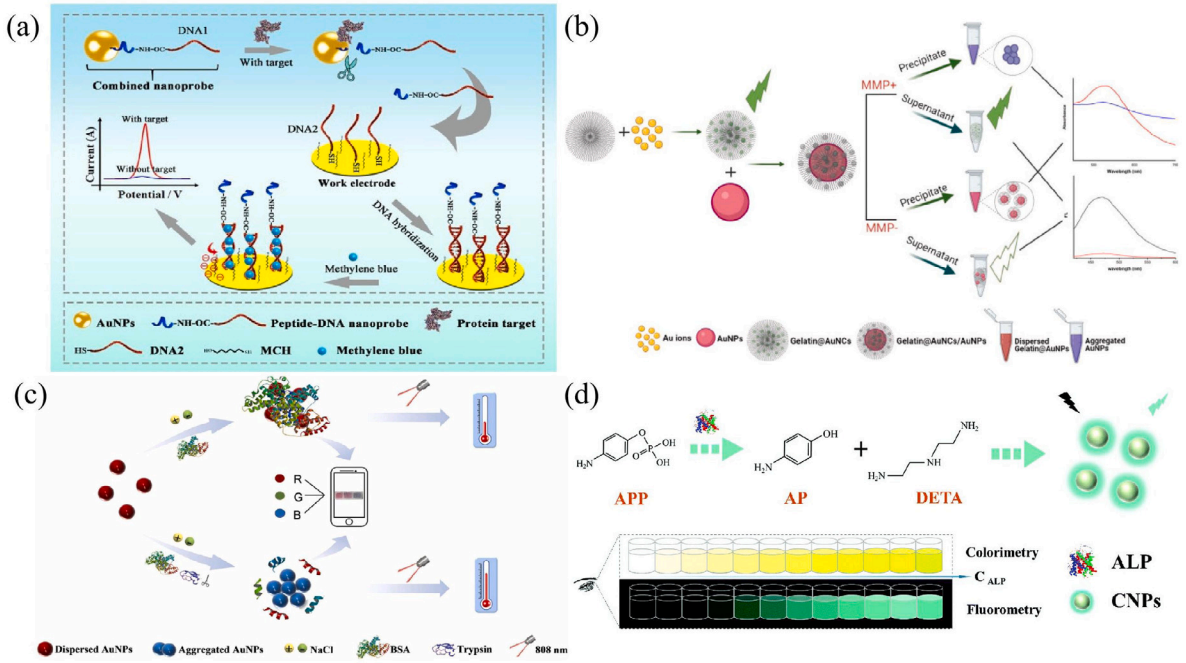

Fig. 12. (**a**) The electrochemical biosensor schematic diagram for detecting SARS-CoV-2 is shown in [166]. (**b**) AuNPs@gelatin/AuNCs nanocomposite platform-based dual mode MMP-9 detection technique [162]. (**c**) Diagram showing the dual way of trypsin detection based on Au NPs aggregated with a smartphone or thermometer [164]. (**d**) ALP-catalyzed colorimetric and fluorometric processes using APP as the substrate [167].

sensitivity and high selectivity [169,170]. In order to achieve point-of-care detection (POCT), researchers have recently concentrated on reducing the size of the device and associated procedures. Among these, POCT's photothermal effect (PT) study area shows great promise. The idea behind it is to transform light energy into thermal energy. Furthermore, temperature is chosen as the signal reading via photothermal sensing, which has the benefits of being inexpensive, easy to use, and having a typical background [171]. A colorimetric double-membrane biosensor device based on photothermal and smartphone for trypsin determination was proposed by Guo et al. [164] (see Fig. 12(c)). The platform's detecting mechanism relies on the gold nanoparticles' local surface Plasmon resonance (LSPR) effect. The protective agent used to keep AuNPs distributed in a salt solution was bovine serum albumin (BSA). BSA is hydrolyzed by trypsin, and when AuNPs congregate in a salt solution, the color changes and the PT rises. The LODs acquired from RGB and PT analysis using a smartphone are 1.2 μg mL^{-1} and 6 μg mL^{-1}, in that order. It has been demonstrated that this technique can diagnose POCT in clinics quickly. Additionally, Luo et al. [163] created a unique multicolor sensor for trypsin detection based on controlling peroxidase activity in gold nanoclusters coated with bovine serum albumin (BSA-Au NCs) and efficiently etching gold nano bipyramids (Au NBPs). Studies have revealed that a high concentration of ligand molecules passivates the surface of Au NC, limiting its accessibility to the reaction substrate. Removing ligands could increase the amount of metal atoms exposed to the reactant [172]. As a result, BSA-Au NCs exhibit increased catalytic activity when trypsin hydrolyzes the BSA ligand on their surface, revealing additional catalytic active sites. Consequently, under acidic conditions, 3,3′,5,5′-tetramethylbenzidine (TMB) is catalyzed to TMB^{+} and oxidized to TMB^{2+}. Au NBPs can be etched with a yellow TMB^{2+} solution to exhibit different hues. This multicolor biosensor effectively overcomes the low detection ability of the human eye for the same color with varying intensities when compared to other classic monochromatic colorimetric biosensors. It increases the sensitivity of detection with the unaided eye. At the same time, displacement values of localized surface resonance peaks of Au NBPs can be used to get precise quantitative trypsin detection. This technique is easy to use, quick, does not require complicated equipment or trained workers, and is widely applicable in places with little resources.

The novel pneumonia produced by the coronavirus has spread around the globe since the beginning of 2020. The new coronavirus was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses, while the World Health Organization (WHO) named pneumonia 2019 coronavirus disease (2019-nCoV). SARS-CoV-2 major protease (Mpro), often referred to as 3C-like protease (3CLpro), is a crucial viral enzyme that cleaves many viral proteins to promote viral growth and illness. As a result, it has been thought that one of the best targets for creating antiviral medications is this protein. An unlabeled peptide AuNP biosensor was created by Feng et al. [165] to measure SARS-CoV-2 Mpro. Through electrostatic interactions, the particular peptide sequence of SARS-CoV-2 Mpro can cause AuNP aggregation in this sensing system. Therefore, when Mpro cleaves, AuNP dissociates, which can be observed through the color change of AuNP suspension. The research team discovered that the sensitivity and anti-interference capability of this approach for identifying Mpro in biological samples were subpar. Conversely, peptide cleavage events at the liquid–solid interface can be sensitively monitored using electrochemical biosensors. This group also proposed that by altering the assembly of peptide-triggered AuNPs on the surface of peptide-covered electrodes, the liquid phase analysis of Mpro might be transformed into an electrochemical analysis. The benefits of surface-bound biosensors and colorimetric analysis are combined in this technique. It is expected to become a universal strategy for designing protease biosensors by matching peptide substrate sequences and using appropriate nanomaterials. Furthermore, Liang et al. [166] presented an electrochemical biosensor that utilizes papain-like cysteine protease (PLpro) to identify SARS-CoV-2 (see Fig. 12(a)). This sensing platform is innovative because it makes use of the particular enzymatic activity of the viral functional protein to facilitate detection. The group created a chimeric peptide DNA (pDNA) nanoprobe that target proteases can recognize and cleave. After cutting, the DNA strand that was initially fixed on the electrode surface combines with the freed DNA strand to generate double-stranded DNA (dsDNA). Subsequently, signal output and electron transport can be accelerated by inserting the

Table 3
Applications of nanomaterial-based biosensors for detection of other micromolecules.

Type of nanomaterial	Target	Detection principle	Limit of detection	Ref.
CdS QD and MWCNT	Glucose	The oxidation of glucose will generate the photocurrent signal.	15.99 nM	[174]
AuNPs and two-dimensional MXene $Ti_3C_2T_X$ nanosheets	Glucose	Glucose are oxidized and generate hydrogen peroxide and SERS signals.	0.32 μM	[175]
Au microcuboid pattern	COVID-19	The anti-COVID-19 antibodies were used as probes based on CV and SWV techniques	276 fmol pg L^{-1}	[176]
AuNPs	H1V1	Current response caused by the combination of antigen and antibody	0.25 pg	[177]
Ab@GO@GOD	L. monocytogenes	Using the catalytic properties of glucose oxidase to change the concentration signal of glucose	101 CFU pg mL^{-1}	[178]
TiO_2/rGO nano-composites	H_2S gas	Grain boundaries results was significantly changed under H_2S gas environment	2 ppm	[179]
Nanocuprous oxide (Cu_2O)	Cholesterol	Differential pulse voltammetry (DPV)	0.0018 μM	[180]

electroactive molecule MB into dsDNA. This biosensor allows for the sensitive and targeted detection of SARS-CoV-2 PLpro in a variety of challenging real-world settings, such as saliva and blood. Consequently, this study might offer some fresh perspectives and suggestions for identifying illnesses and creating antiviral medications. SARS-CoV-2 can also be found using SPR sensors built on 2D materials. SPR-based biosensing chips could be utilized for portable, quick, and accurate SARS-CoV-2 virus diagnostics [173].

Alkaline phosphatase (ALP) is a representative substance of biochemistry, which is actively involved in almost every aspect of biological processes, from metabolism, signal transduction, and molecular transport to the expression of genetic information. An et al. [167] presented a novel technique based on aminophenol (AP) and diethylenetriamine (DETA) for the synthesis of light blue fluorescent carbon nanoparticles (CNP) (see Fig. 12(d)). The produced CNPs exhibit outstanding water dispersion and a consistent spherical shape. Inspired by the fact that ALP can be transformed into AP and catalyzes the conversion of 4-aminophenyl phosphate (APP), they built an incredibly sensitive two-channel sensor platform that combines colorimetric and fluorescence to track ALP activity. Experimental results show that the fluorescence and colorimetry detection limits are 0.05 mU mL^{-1}. This sensor strategy opens up a new way of detecting ALP activity, screening ALP inhibitors, and diagnosing disease (see Table 2).

4.2.3. Detection of other micromolecules

In addition to the proteins, enzymes, and nucleic acids described above, nanomaterial-based biosensors have also been widely used in detecting other small molecules [181–183]. In this section, we will focus on nano-biosensors for other small molecules.

Glucose is an indispensable substance in metabolism and an essential marker in disease diagnosis and beverage quality monitoring. A wide range of methods, including colorimetry, fluorescence, gas chromatography, and electrochemical sensors, have been employed in recent years to measure the amount of glucose present in food and human serum. A method for measuring salivary glucose non-enzymatically, sensitively, and quickly using analytical equipment (μCAD) based on microfluidic technology and photoelectrochemical detection (PEC) was described by Mao et al. [174] (see Fig. 13(a)(b)). Three cloth-based devices and a PEC reaction chamber are produced by carbon ink screen printing and wax screen printing, respectively, using μCAD. On the surface of the working electrode (WE), multiwalled carbon nanotubes (MWCNT) and cadmium sulfide quantum dots (CdS QD) were subsequently altered. When the excitation source containing glucose is present, CdS QDs continuously oxidize glucose to generate an electrical signal for glucose detection. There is a large oxidizing electron hole produced by this action. After optimization, the detection limit of the method can be reduced to as low as 15.99 nM, and its long-term storage stability is enhanced for comfortable transportation. Furthermore, the technique has shown good biochemical application since it has been utilized to identify glucose in real saliva samples. In addition, Cui et al. [175] created a flexible SERS substrate made of two-dimensional MXene $Ti_3C_2T_X$ nanosheets and AuNPs to identify glucose in diabetic patients' tears (see Fig. 13(c)). Through straightforward self-assembly, SERS substrates for GMXeP (AuNPs with MXene nanosheets on paper) were created in this work. The SERS signal was greatly enhanced by the chemical enhancement caused by the charge transfer between MXene and dye molecules as well as the electromagnetic enhancement provided by AuNP. Leucomalachite green (LMG) is transformed into malachite green (MG) by the hydrogen peroxide created by glucose oxidation caused by glucose oxidase when the AuNPs' peroxidase-like activity causes SERS signals. Good sensitivity, repeatability, and stability were demonstrated by the GMXeP SERS substrate, and a detection limit of 0.32 μM was reached. This technique is anticipated to be a useful clinical detection strategy since it can detect blood glucose levels with high sensitivity and without requiring any invasive procedures.

The pathogen that produces the highly contagious 2019 coronavirus (COVID-19) is SARS coronavirus 2 (SARS-CoV-2). The rapid spread of COVID-19 makes the creation of COVID-19 biosensors quick, simple, accurate, and selective necessary. El Said et al. [176] developed a highly homogeneous Au microcuboid pattern to produce a sensitive and selective COVID-19 electrochemical biosensor (see Fig. 14(a)). The research team used cyclic voltammetry (CV) and square wave voltammetry (SWV) to detect COVID-19 in this sensing system by utilizing anti-COVID-19 antibodies as a probe. PDMS modified with Au micro cuboid was employed as a scaffold and flexible microelectrode to immobilize anti-COVID-19 antibodies. The introduction of microstructure not only reduces the amount of analyte used but also improves the electrochemical conductivity of the biosensor. In the end, the experiment produced a LOD as low as 276 fmol/L^{-1}, demonstrating the good detection efficiency and high sensitivity of SWV technology in COVID-19 positive human samples.

The influenza H1N1 in poultry, a viral subtype is extensively distributed and causes serious damage. Mutant forms of it can infect people, therefore its spread is not just restricted to birds and poultry. The virus has a significant infection-related fatality rate, despite the rarity of human infections. There are currently numerous techniques for identifying influenza viruses, including reverse transcription loop-mediated isothermal amplification test, PCR, ELISA, virus plaque assay, etc. A low-cost, high-performance electrochemical immunosensor for H1N1 virus detection was proposed by Bao et al. [177] (see Fig. 14(c)). Due to its low production costs and straightforward technique, electrochemical immunoassay is frequently utilized in the diagnosis of viruses.

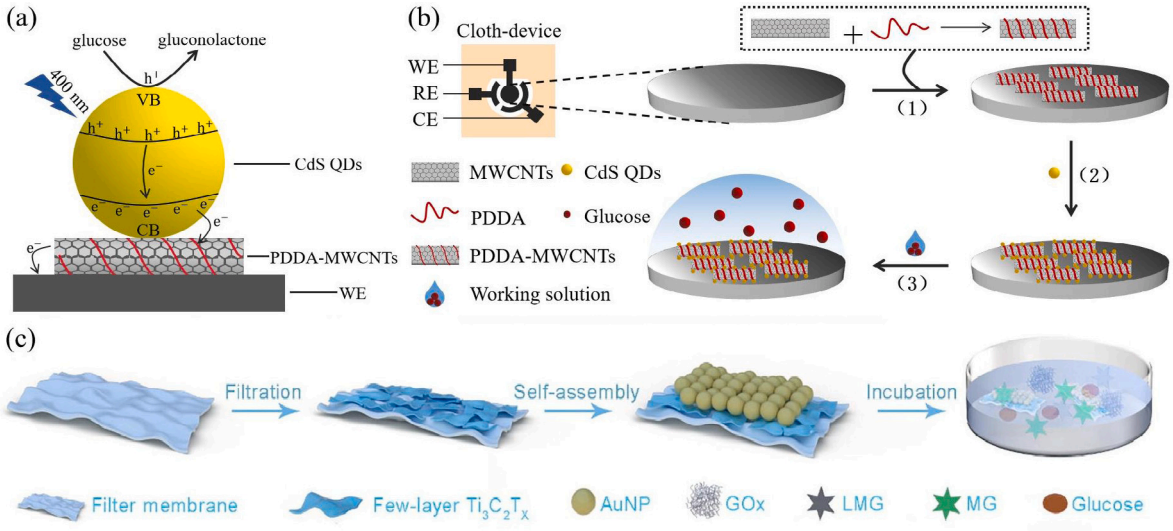

Fig. 13. (**a**) PEC *μCADs* schematic depiction for the nonenzymatic glucose analysis (multiwalled carbon nanotubes, or MWCNTs), VB-valence band, CB-conduction band, and PDDA-poly (dimethyl diadly ammonium chloride) [174]. (**b**) Fabrication of PEC sensing interface and analytical procedure. (1) The PDDA-MWCNTs solution was dropped on the WE surface; (2) the CdS QDs solution was applied onto the surface of PDDA-MWCNTs/WE; (3) the working solution was added into the chamber; and (4) the light source was turned on and the photocurrent was recorded (WE-working electrode, RE-reference electrode, CE-counter electrode, MWCNTs-multiwalled carbon nanotubes, PDDA-poly, and PDDA-MWCNTs-PDDA-functionalized MWCNTs) [174]. (**c**) Diagrammatic representation of glucose detection and GMXeP substrate preparation [175].

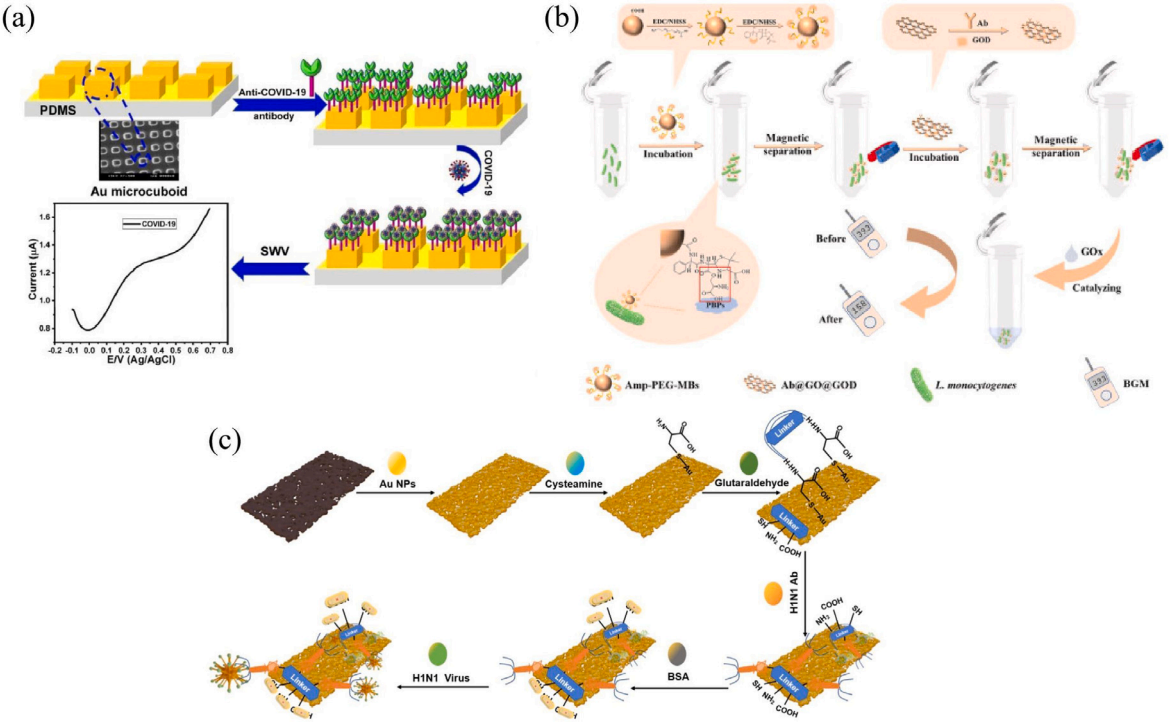

Fig. 14. (**a**) An electrochemical COVID-19 microbiosensor's schematic diagram showing the processes of (i) immobilizing an antiCOVID-19 antibody and (ii) capturing COVID-19 protein [176]. (**b**) The method of Amp-PEG-MBs and Ab@GO@GOD preparation, L. monocytogenes capture, separation, and POCT using MS-Ab@GO@GOD-BGM sensor [178]. (**c**) Fabrication of the BSA/H1N1 Ab/Glu/Cys/Au NP/CP immunosensor [177].

The introduction of nanomaterials has led to better performance of biological immunosensors. Au nanoparticles have several special characteristics with other precious metal nanoparticles, including great chemical and biological stability, good biocompatibility, and a large specific surface area. Based on the idea of specific interaction between antibodies and viral molecules, a sandwich structure BSA/H1N1 Ab/Glu/Cys/Au NP/CP electrode was created for this sensing platform. An active molecule–antibody–adapter structure with strong electrochemical activity and high specificity forms on the electrode surface when it is utilized for sensing. This electrode may be employed in complex sample detection conditions and does away with the laborious sample preparation process.

Since ancient times, food safety has always been a problem worthy of attention. One of the main causes of food safety problems and worldwide health problems is foodborne illnesses [67]. Foodborne pathogens are a major contributor to foodborne illness outbreaks because they can contaminate food and eventually infect humans. Of these, Listeria monocytogenes, often known as L. monocytogenes, is a prevalent pathogen that is found in a wide range of foods. Symptoms of a highly pathogenic L. monocytogenes infection in humans

include diarrhea and vomiting. Furthermore, it has a strong resilience to low temperatures and acidic conditions, which could result in long-term damage. Thus, it is essential to identify L. monocytogenes with sufficient sensitivity [184]. A POCT sensor for L. monocytogenes was developed by Bai et al. [178] using an enzyme-catalyzed magnetic separation (MS) system (see Fig. 14(b)). Firstly, L. monocytogenes can be effectively captured by creating ampicillin-functionalized magnetic beads (Amp-PEG-MBs) utilizing PEG as a mediator. In the meantime, Ab@GO@GOD, a novel combination of graphene oxide (GO), glucose oxidase (GOD), and antibodies (Ab), was created for the purpose of specifically recognizing L. monocytogenes. The glucose can then be catalyzed by the combination of these two to produce the Amp-PEG-MBs@L. monocytogenes-Ab@GO@GOD sandwich structure. Finally, a blood glucose meter (BGM) was used to record the last POCT signal of L. monocytogenes. With this novel sensor, L. monocytogenes can be detected quickly and accurately. Additionally, various pathogens can be detected by modifying particular antibodies, which makes this sensor a promising universal platform for pathogen POCT.

Industrialization has led to an increase in gas emissions in the environment. Detecting these toxic gases to screen is crucial to alter their impact on life and the environment. Of them, the primary sources of H_2S gas are natural and man-made industries such coal mining, oil extraction, sewage water extraction, and refining. An adequate amount of H_2S gas exposure can cause eye irritation, quickly deteriorate the cardiovascular, neurological, and pulmonary systems, and even cause abrupt death and loss of smell. Thus, it is imperative to find a solution to the quick, highly-sensitive, stable, low concentration H_2S gas detection problem in order to safeguard both human health and the environment. Balasubramani et al. [179] proposed a gas sensing platform made of $n-TiO_2$ and $n-TiO_2$/rGO-3 for detecting H_2S gas at room temperature (27 °C). Semiconductor metal oxide sensors are inexpensive, responsive, and portable. One significant semiconductor metal oxide utilized in a variety of sensors is titanium dioxide (TiO_2). However, because of its low conductivity and high operating temperature, TiO_2 has several drawbacks. By covering rGO in between n-TiO_2 and serving as a bridge between neighboring n-TiO_2 particles, this sensing system improves gas adsorption properties and increases electron transport. The grain boundary results in the H_2S gas environment will change significantly, and the target gas can be identified by analyzing equivalent circuit fitting values.

People's consumption of cholesterol rises as a result of modern lifestyle changes and rising living standards, which causes the incidence rate of dyslipidemia to climb quickly. Overweight cholesterol has the ability to pass through blood vessel intima and into the subintima. Due to long-term deposition, it can cause vascular damage and various diseases. With the increase of the incidence rate of cardiovascular and cerebrovascular diseases such as sudden death and coronary heart disease worldwide, measuring cholesterol levels has become critically important. Consequently, it is crucial to develop low-cost, quick, sensitive, easy-to-use, and practical cholesterol detection tools. Using cubic-shaped Cu_2O as the nanomaterial, thionine (TH) as an electron mediator, and chitosan (CS) as a crosslinking agent, Yan et al. [180] created a cholesterol biosensor. The novel P-type oxide semiconductor material nano-Cu_2O possesses the following properties: active electron–hole pairs, large specific surface area, quantum size effect, and volume effect. It is cheap, non-toxic, and simple to make. With its fast electron conductivity and stable electrochemical characteristics, the electron mediator TH may react with redox cofactors in enzymes quickly, increasing the efficiency of electron transfer between electrodes and enzymes. Cholesterol oxidase (ChOx)/thionine/nano-cuprous oxide/glassy carbon electrode (GCE) (ChOx/TH/Cu_2O/GCE) was synthesized, and CS was utilized as a crosslinking agent to immobilize the enzyme. To evaluate the modified electrode's electrochemical performance, differential pulse voltammetry (DPV) was used in PBS solutions with various concentrations of standard cholesterol. The sensing system can be employed for high-sensitivity cholesterol detection in real biological samples because of its strong anti-interference, good repeatability, good stability, and high recovery rate, according to the results (see Table 3).

5. Conclusions and outlook

Due to their tiny size, nanomaterials have different characteristics from conventional materials in terms of conductivity, high reactivity, magnetization, and spectral characteristics. Common nanomaterials include metal nanomaterials, carbon nanomaterials, quantum dots, composite nanomaterials, etc. Different types of nanomaterials play different roles in biosensors. For example, gold nanoparticles can be widely used as probe carriers or signal molecules in electrochemical biosensors because of their stable properties and biocompatibility. At the same time, quantum dots are suitable as fluorescent probes. This paper reviews the characteristics of different nanomaterials and their applications in biosensors with varying detection principles, including electrochemical biosensors, optical biosensors, and piezoelectric biosensors. In addition, the biosensor, after the introduction of nanomaterials, can detect a variety of objects, not only can detect proteins, enzymes, nucleic acids, viruses, and other small molecules but also can explore the interior of atoms or molecules to achieve the real-time single-molecule level detection. Compared with traditional biosensors, nanomaterial-based biosensors can achieve faster, more accurate, and more sensitive biosensing. In addition, further research can be carried out on biosensors based on nanomaterials in multi-function integration, mass production, portable, and one-time research. Biosensing based on nanomaterials has many advantages and can widely meet the needs of various fields, such as medical diagnosis, food detection, drug discovery, and environmental monitoring. It will be an essential monitoring and analysis platform in the future.

Although the research of nano-biosensors has been relatively mature, many areas still can be further explored. For example, in terms of virus detection, we pursue cheaper, more portable, rapid, and accurate detection methods [185]. The resilience and repeatability of biosensors based on nanomaterials is another important factor. In actual use, complexly structured nanomaterials may differ from batch to batch, leading to poor repeatability. Thus, further research is required to comprehend the processes involved in the production and functionalization of nanomaterials. Make that the sensor is accurate and reproducible in clinical settings. To optimize the sensitivity and the specificity based on existing nano-biosensors, to reduce the detection limit, and to enhance the practicability, in-depth research works can be conducted in the following aspects:

(1) Research and development of new nanomaterials, focusing on the integration of emerging nanostructures. Advances in nanostructures are helping develop new biosensors. One way to address the drawbacks of nanomaterials with poorer catalytic activity than real enzymes is to build two-dimensional nanomaterials with large active sites and high surface area. Additionally, by altering nanomaterials and adding new functional groups, biosensor performance can be enhanced to increase the binding sites for target adsorption.

(2) Focus on the use of nanomaterials in combination with other materials, such as optical fiber or metasurface, to address potential challenges related to selectivity and cross-sensitivity based on high sensitivity and low detection limits [186]. For instance, biological samples contain indicators for cardiovascular disease and cancer at quantities well below the present technologies' detection limits. Neurofilament and β Amyloid peptide 42, which are brain-derived biomarkers for many neurodegenerative illnesses, are found in cerebrospinal fluid (CSF) at relatively high concentrations but at very low concentrations in blood [187]. By directly identifying these indicators from blood through minimally intrusive sampling, sensitivity can be increased while also lessening the physiological load on patients.

(3) Attach importance to the miniaturization and automation of biosensors, integrate biosensor arrays with electronic devices, and develop nano-biosensor platforms that are more suitable for practical applications. Specifically, on the one hand, it can reduce the volume of biosensors and increase their convenience and stability of use. On the other hand, the integration and miniaturization of sensors can also be

combined with multiplexing detection to improve the current situation where only one analyte can be detected at a time. Analyzing multiple analytes simultaneously is very important, as multiple detecting tests can obtain more information and improve the detection efficiency.

(4) The application of advanced technologies such as artificial intelligence (AI) in collaboration with the development of biosensors can help promote the commercialization of biosensors and expand their application scenarios. To achieve self-learning, self-assembly, and adaptability of artificial intelligence biosensor systems, researchers should work hard to build flexible electronic materials that incorporate chip technology, the Internet of Things, big data, and artificial intelligence. Flexible bioelectronic materials have extremely flexible mechanical properties, advantages matching the human body and organs, and minimal mechanical damage to tissues. The data collected by sensors will be input into machine learning algorithms, which can monitor vital signs, detect anomalies, and track treatments in the medical field. Moreover, the cross-disciplinary use of artificial intelligence can improve sensing efficiency while reducing usage costs. In the future, with the support of nanotechnology, medical AI biosensors will provide more innovative solutions.

CRediT authorship contribution statement

Yaoxin Fu: Methodology, Resources, Writing – original draft, Writing – review & editing. **Tiegen Liu:** Supervision. **Haonan Wang:** Resources, Writing – review & editing. **Ziyihui Wang:** Writing – review & editing. **Lili Hou:** Supervision. **Junfeng Jiang:** Conceptualization, Supervision. **Tianhua Xu:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work is supported by the National Natural Science Foundation of China (Grant No. 61735011), China Scholarship Council (Grant No. 202006250152) and EU Horizon 2020 Project (Grant No. 101008280) and EU Horizon Europe Project (Grant No. 101131146). All authors have read and agreed to the published version of the manuscript.

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