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MINI-REVIEW

Recent advances in the potential applications of luminescence-based, SPR-based, and carbon-based biosensors

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Abstract

The need for biosensors has evolved in the detection of molecules, diseases, and pollution from various sources. This requirement has headed to the development of accurate and powerful equipment for analysis using biological sensing component as a biosensor. Biosensors have the advantage of rapid detection that can beat the conventional methods for the detection of the same molecules. Bio-chemiluminescence-based sensors are very sensitive during use in biological immune assay systems. Optical biosensors are emerging with time as they have the advantage that they act with a change in the refractive index. Carbon nanotube-based sensors are another area that has an important role in the biosensor field. Bioluminescence gives much higher quantum yields than classical chemiluminescence. Electro-generated bioluminescence has the advantage of miniature size and can produce a high signal-to-noise ratio and the controlled emission. Recent advances in biological techniques and instrumentation involving fluorescence tag to nanomaterials have increased the sensitivity limit of biosensors. Integrated approaches provided a better perspective for developing specific and sensitive biosensors with high regenerative potentials. This paper mainly focuses on sensors that are important for the detection of multiple molecules related to clinical and environmental applications.

Key points

- *The review focusses on the applications of luminescence-based, surface plasmon resonance-based, carbon nanotube-based, and graphene-based biosensors*
- *Potential clinical, environmental, agricultural, and food industry applications/uses of biosensors have been critically reviewed*
- *The current limitations in this field are discussed, as well as the prospects for future advancement*

Keywords Biosensors · Bio-chemiluminescence · Carbon nanotubes · Graphene · Diseases · Pollution · Agriculture and food industry · Environmental application

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Introduction

Biosensors have rapidly emerged as a more straightforward, faster, and convenient way for the detection of molecules, diseases, and pollution from various sources. Biosensors have the advantage of rapid detection, specificity, low reaction time, and high output that could beat the conventional methods for the detection of the same molecules (Fig. 1). Humans have exploited the environment for their selfish purposes that lead to many global problems such as global warming, water pollution, and solid waste pollution apart from pollutions; biosensors are developed in various fields that detect various deadly diseases such as cancer. This paper mainly focuses on sensors that are important for the detection of multiple molecules related to clinical and environmental applications. Different types of biosensors are disclosed and characterized. Advances in developed biosensors as well as their future potential applications are discussed. The review summarizes novel developed biosensors and however also highlights notable earlier-developed biosensors. The main purpose of this review is to provide an overview in the rapid developing area of modern detectors and their possible utilization in the future.

Chemiluminescence-based sensors are mainly of three types: (1) bio-chemiluminescence-based, (2)

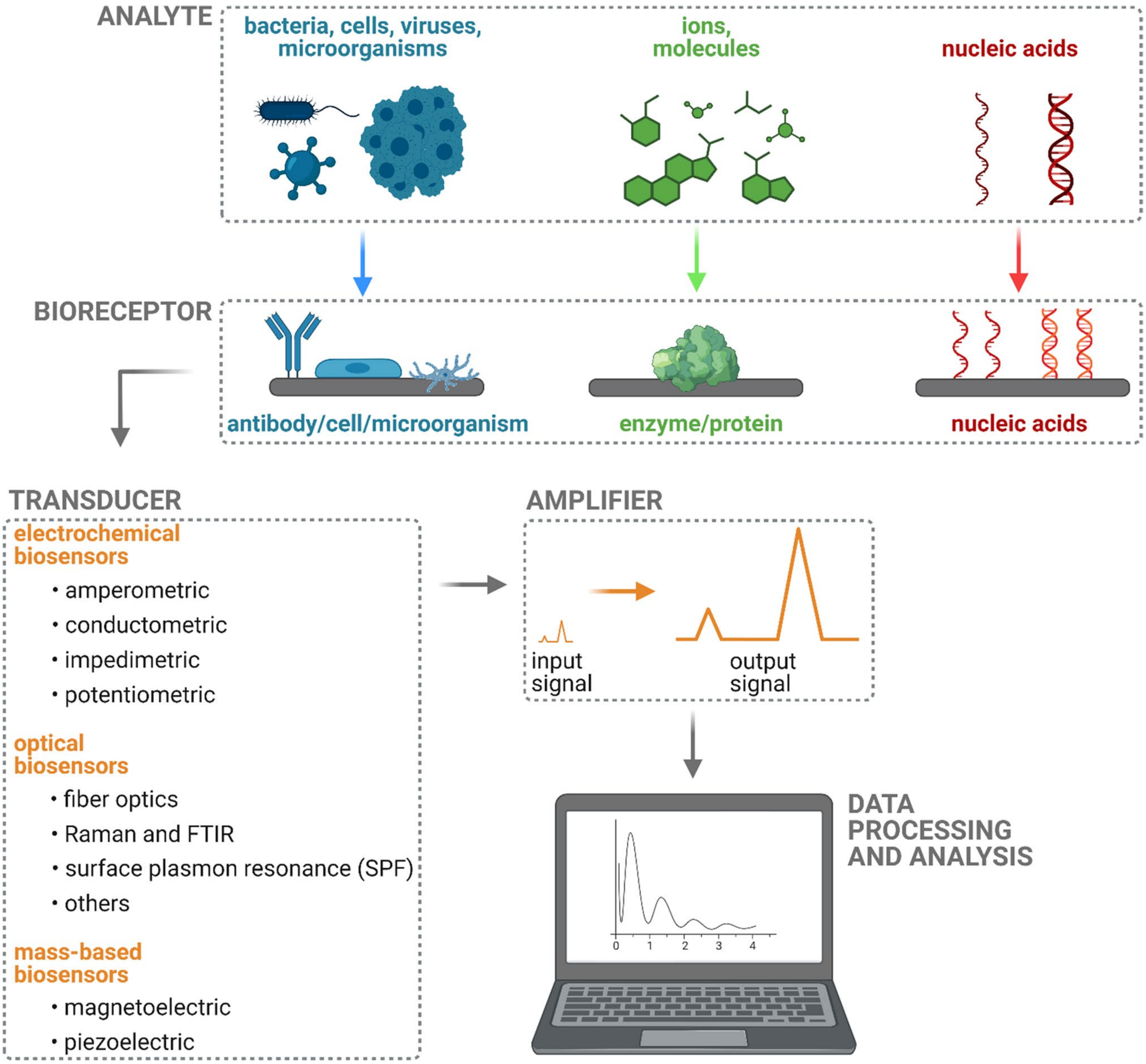


Fig. 1 General scheme and operation principle of biosensors. Figure created with BioRender.com

thermo-chemiluminescence-based, and (3) electrochemiluminescence (Roda and Guardigli 2012). Bio-chemiluminescence-based sensors are very sensitive when they are used in biological immune assay systems; they can detect up to attomole concentrations. Chemiluminescence technology is used widely for biologically important molecules (Roda et al. 2016). Discussing clinical applications, breast cancer is a major issue, and there are so many techniques being used, MRI mammography and some immunological techniques such as enzyme-linked immunosorbent assay (ELISA) and radioimmunoassay (RIA), but these techniques have some drawbacks such as they are time-consuming and sometimes give false-positive results; to avoid this, so many biosensors are being developed which provide a signal when a particular biomarker related to breast cancer is detected in a sample (Mittal et al. 2017). Surface plasmon resonance is a widely used immunological technique based on antibody-based detection of molecules. Gold and other noble metal-based biosensors have come into existence recently; they use the differential properties of gold nanoparticles to enhance the detection, as because of the size and shape, the nanoparticle gives distinct signals so that it can be used for the detection of different clinically important molecules (Cao et al. 2014). Gold nanoparticle-based SPR biosensor has been developed, which can detect hepatitis B infection in very low concentrations in Tris buffer-based systems (Wang et al. 2010).

These are successful technologies; however, there are so many chemiluminescence-based sensors that have not been developed for the detection of molecules but are not available commercially in the market (Park and Kricka 2014). Biosensor research aims to produce low-cost semi-quantitative and fast biosensors, which can work virtually in all kinds of environments and are relatively easy, not consisting of many economic steps (Marquette and Blum 2010). The development in chemiluminescence and bioluminescence is getting fused, and it must be to develop small-sized sensing devices and new molecules that can help in the development of the sensors for personalized diagnostics (Roda and Guardigli 2012).

Optical biosensors are emerging with time as they have the advantage that they act with a change in the refractive index. These biosensors have an additional benefit as they do not get interference from magnetic fields. These sensors are useful for a wide range of applications, from diagnostics to the battlefield. There are mainly two kinds of strategy: first is to label the target molecule with the fluorescent tag so that upon binding it will release signal and it has very high sensitivity only with a disadvantage that the labelling cannot be controlled properly. The second is direct sensing in which binding of the molecule with the target will lead to a change in the refractive index that is very sensitive in comparison to fluorescent-based labelling. There are some differences between the direct detection systems and fluorescent-based systems; however, both technologies are being used for sensing for a wide area of applications as they provide good sensitivity and can determine analyte concentration very efficiently (Fan et al. 2008).

Carbon nanotube-based sensors are another area that has an important role in the biosensor field. Carbon nanotubes are being used vastly in biosensing because they have some unique properties. Carbon nanotubes may be single-walled or multi-walled and mostly composed of rolled graphene sheets. Carbon nanotubes can act as semiconductors or superconductors according to needs and modifications. Carbon nanotubes have been successfully used in enzyme-linked sensing mostly, and they can be used for sensing with redox reaction coupled enzymes as well as for the detection of glucose using redox mechanisms. Apart from the enzymes, it can also be coupled with antibodies or DNA molecules for selective binding applications (Wang 2005).

Chemiluminescence fluorescence technologies require the detection of photons emitted by the system for that various technologies are being used for detection starting from photomultiplier tubes to cell-phone-based detection of the emitted light in recent days. Photomultiplier tubes have some disadvantage as the detection is between 360 and 670 nm. Apart from the detection range, it consumes high electricity. However, recent flat photomultiplier tube has removed disadvantages and has been proven to be good for the detection of the emitted wavelength. Advanced detectors include charge-coupled devices (CCD), complementary metal-oxide semiconductors (CMOS), and silicon and organic photodiodes. These have very good sensitivity and have the advantage of small size, and they are also able to detect multiple spots at a time (Lengger et al. 2014; Zhou et al. 2014b; Zangheri et al. 2015). Recent back-illuminated CMOS have attracted great attention because of their low power consumption and high sensitivity.

CMOS offers advantages like a high-resolution and high signal-to-noise ratio, and pixel size is significantly reduced, which provides proper resolution even in low light conditions. Recently, large area CMOS was used for the successful detection of multiple chemiluminescence spots simultaneously (Bolton et al. 2002; Sandeau et al. 2015). Cooled CCDs are proven to give the best resolutions. Coloured CCDs are being developed which can be used with the combination of cell phones and tablets, which can detect luminescence with the device camera; they are proven good, but cooled CCDs are still gold standard (Roda et al. 2014b, 2014a). Thin-film photodiodes are another relatively inexpensive thing that can be used for the detection of amorphous silicon thin-film photodiodes, organic photodiodes, and carbon nanotubes coated with photovoltaic polymers (Shim and Ahn 2012; Caputo et al. 2013).

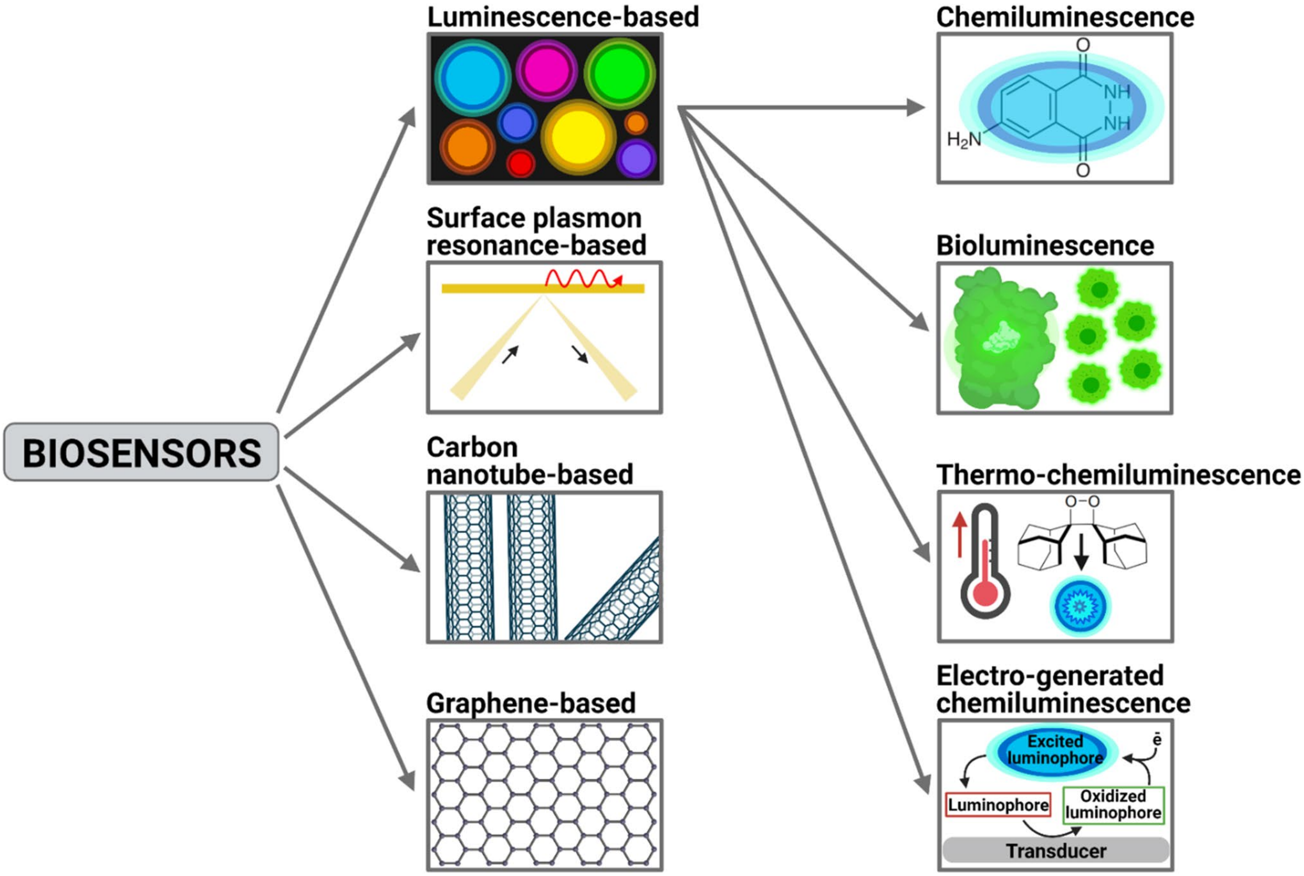


Fig. 2 Diagram shows different types of biosensors discussed in the following subsections. Figure created with BioRender.com

Types of biosensors

Several types of biosensors have been discussed, few are luminescence-based, some are surface plasmon resonance-based, some are optical, and some are carbon nanotube-based sensors. The present section will discuss some essential advances in biosensors. Figure 2 shows the types of biosensors that will be discussed in the following subsections.

Luminescence-based biosensors

There are different types of biosensor in which the luminescence is achieved by different principles; in this section, we will discuss a few of the luminescence-based biosensors.

Chemiluminescence

Chemiluminescent assays generally use direct labelling with the isoluminol and acridinium esters. The sensitivity can be up to nano-molar level, and signal-to-noise ratio is very high. Acridinium salts give very high chemiluminescence value in aqueous solutions with respect to isoluminol; however, the phenomenon is slow because acridinium salts react slowly with hydrogen peroxide because they are in a bound state with bases (Osman et al. 2000). Enzyme labelling is preferred over direct labelling as the enzyme increases the signal in comparison to direct labelling. Horseradish peroxidase (HRP) is generally used for the labelling; it converts luminol, which decays photon in the presence of hydrogen peroxide (Créton and Jaffe 2001). To enhance the sensitivity of these assays, electron transfer mediators such as indophenols, substituted phenols, *N*-alkyl phenothiazines, and substituted boronic acids apart from these 4-dialkylaminopyridine which is a nucleophilic acylation catalyst were also found to increase the intensity of the assay (Marzocchi et al. 2008; Zomer 2010). Apart from mentioned compounds, acridinium compounds can also be used with the horseradish peroxidase for the illumination assay (Osman et al. 2000). Recently, new hybrid molecules are being designed, which may replace the enzyme-based labels. Recently, DNAzymes are being synthesized, which can be designed to have HRP like activity, and the advantage of DNAzymes is that they have higher thermostability in comparison to classical enzyme-based labels. In addition to these molecules, nanoparticle-based systems have also been designed to enhance signal amplification (Huang et al. 2014a; Li et al. 2014; Park et al. 2015; Yu and He 2015).

Bioluminescence

Bioluminescence is a phenomenon that involves biological systems such as proteins and organisms. The advantage of bioluminescence is that it gives much higher quantum yields than classical chemiluminescence. Bioluminescence uses mostly the luciferase enzyme; in the presence of ATP, it gives the luminescence (Niwa et al. 2010; Thouand and Marks 2014). Recently, dihydrofolate reductase-based sensor has been developed for the detection of methotrexate. The protein is the receptor for the methotrexate, so it is used for sensing so that overdose of methotrexate can be prevented (Yu et al. 2017). Bioluminescence by luciferase requires ATP. This property has been exploited for decades to date for the development of various bioluminescence assays (Chappelle and Levin 1968; Borghei and Hall 2014). As the ATP concentration is proportional with the luminescence, luciferase-based bioassays are being used for the measurement of cell concentration, and ultrasensitive assays have been able to detect the ATP up to attomole level (Satoh et al. 2004). So many portable devices and kits are available in the market such as Milliflex® Rapid Testing (Merck-Millipore) and Clean-Trace™ (3 M™). The modification of luciferin and mutation in the luciferase can lead to tuneable biosensor such as mutation, and proper substrate modifications have led to the shift of emission towards red colour. Caged luciferins were used for the detection of small active biomolecules and live imagining studies (Hosseinkhani 2011; Li et al. 2013; Mofford et al. 2014).

Thermo-chemiluminescence

Thermo-chemiluminescence emits photons as a result of the thermolysis of a suitable molecule; it is usually a 1,2-dioxetane derivative, which leads to an exciting product. Adamantylideneadamantane 1,2-dioxetane derivatives were first used in 1980s as labels in immune-assays (Hummelen et al. 1986, 1988). A disadvantage with the thermo-chemiluminescence is that they require high temperature around 200–250 °C for detection; however, fluorescent additives were used to enhance the sensitivity, but the technique was not so useful. The advantage of the technique is that it doesn't require the addition of any chemicals; recently, researchers tried to redevelop this technique; they used acridine-based systems to produce thermo-chemiluminescence around 80–100 °C (Roda and Guardigli 2012; Di Fusco et al. 2015).

Electro-generated chemiluminescence

Electro-generated bioluminescence is generated by the transfer of electrons at the electrode that leads to the emission of electro-generated photon chemiluminescence which can be controlled by the potential which is applied at the electrode; hence, the time and location of the photon emission can be controlled. This technique has the advantage of miniature size and can produce a high signal-to-noise ratio and the controlled emission. Newly developed sensors use inorganic metal complexes, and ruthenium-based sensors that have tiny size have been developed (Pyati and Richter 2007; Zhou et al. 2014a).

Surface plasmon resonance-based biosensors

Surface plasmon resonance (SPR) is a quite sensitive technique that provides a high signal-to-noise ratio with high specificity, and it doesn't require labelling of any kind. Liedberg et al., in the 1980s, started the use of surface plasmon resonance for biosensing since then, and this has been used as one of the most sensitive techniques (Liedberg et al. 1983). Figure 3 shows the broad principle of SPR-based sensing. Surface plasmon wave (SPW) is generated by two different surfaces that have opposite dielectric signs: one is metal such as gold, and silver another one is dielectric. According to the excitation mechanism, there are several types of SPR-based sensing technologies prism coupling (Matsubara et al. 1988), grating coupling (Yu et al. 2004; Alleyne et al. 2007), waveguide coupling (Liedberg et al. 1993), and optical fibre coupling (Sharma et al. 2007).

In prism-based coupling, the incident light is reflected at the metal surface, and that has a resonant wavelength; however, the disadvantage with this method is the prism is quite bulky, and it is difficult to integrate; however, commercial instruments are available on this principle. Wave guide-based coupling works the same as prism-based, but the advantage is that waveguide is light and can be easily integrated with other electric components. In waveguide-based coupling, the light passes through the metal interphase and produces the SPW, which ultimately leads to detection. In the fibre optic-based coupling, the optical fibre is modified in various ways that allow the integration of surface with the fibre, and it provides excellent SPW. Grating-based technologies are very cheap, and they can be produced in bulk and provides the same results (Fan et al. 2008). Recently, aptamer-based SPR and bacterial detection sensors have been developed, which can detect targets in great sensitivity and complexity (Zhu et al. 2015; Vaisocherová-Lísalová et al. 2016).

Carbon nanotube-based biosensors

Carbon nanotubes (CNT) have been a great field of study since the time of their discovery. CNTs have great applications in the field of biosensing because they have properties like a high surface to volume ratio and they are ultrasensitive to the binding of the biological molecules and they can respond to the oxidation–reduction occurring on the surface coated molecules. CNTs can be used for the immobilization of enzymes because of the large surface area. They are

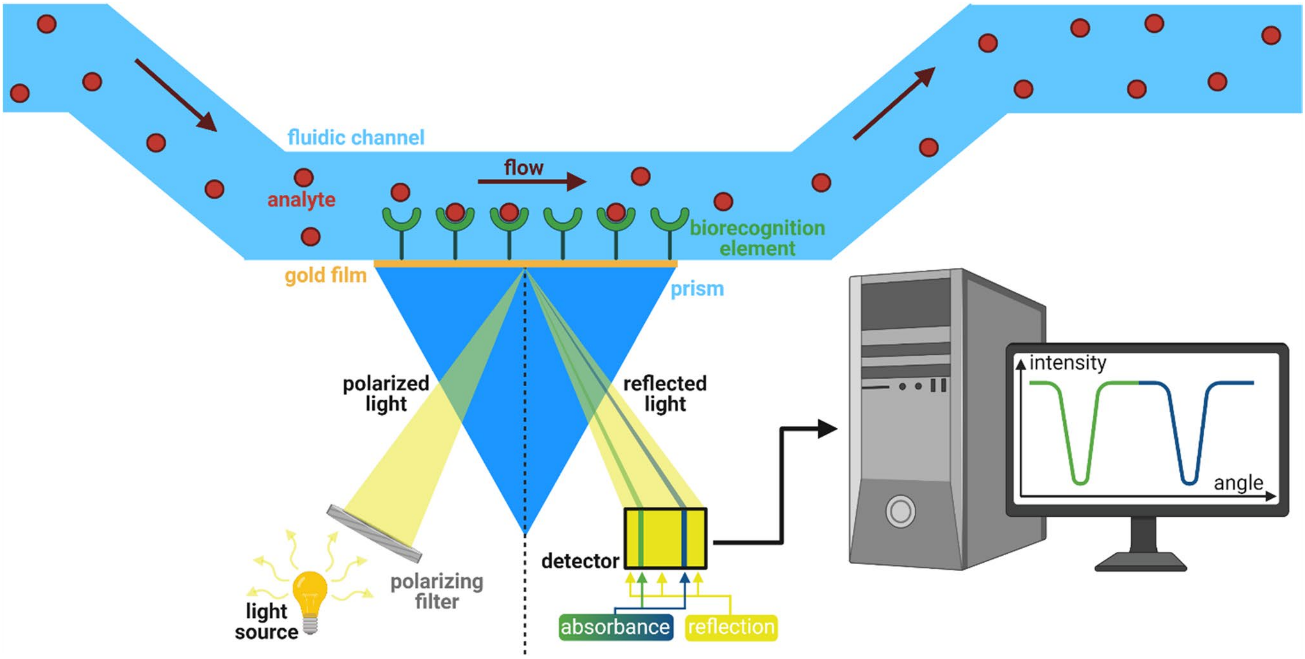


Fig. 3 The general principle of surface plasmon resonance. Polarize light is coupled by a glass prism on the biosensor chip. Thin-film of gold coating the chip is integrated with a flow channel for continuous flow of buffer. At a defined incidence angle, the surface plasmon resonance results in the decrease of the reflected light intensity, characteristic of the specific reflection angle. The shift of the reflection angle reveals a change in the composition of the medium near the thin gold layer as a result of the analyte binding to the biorecognition element (green and blue reflection intensity curve on the screen) (Brogioni and Berti 2014). Figure created with BioRender.com

commercially and economically feasible for large-scale productions as well. CNTs can be synthesized using several ways such as arc discharge laser ablation (Yang et al. 2015). Various biosensors have been developed based on CNTs; here, we will discuss a few. Enzyme-linked CNT-based biosensors are being developed for a wide range of applications. Glucose detection biosensors based on glucose oxidase have been developed as the detection of glucose is very important for diabetic individuals. Chitosan gel and CTNs based glucose biosensor have also been developed by researchers. Chitosan-based glucose biosensor was very robust and did not show interference with other substances like ascorbic acid in normal physiological conditions, and it had very high sensitivity (Fatoni et al. 2013; Pourasl et al. 2014). Apart from enzyme-based biosensors, a non-enzymatic glucose biosensor was also developed, which uses copper and nickel nanoparticles and electrode-based detection of the glucose. It is highly sensitive and low interference (Lin et al. 2013). Enzyme-linked CNT-based biosensors are mainly developed using four strategies, (1) covalent bonding, (2) crosslinking, (3) adsorption, and (4) embedding; using these techniques, so many sensors have been developed such as glucose oxidase, laccase, tyrosinase, and horseradish peroxidase (Yang et al. 2015). DNA-based CNTs biosensors have also been developed, which use DNA as the sensing molecule, and CNT acts as the base. Most of the CNT-based DNA sensors use single-stranded DNA rather than double-stranded DNA as it absorbs more rapidly on the surface of CNTs. Apart from this completely electronic CNT-based DNA sensors which have also been developed, CNT-based DNA sensors have also been developed for methylation regulation studies (Bachilo et al. 2002; Tang et al. 2006; Huang et al. 2014b). Figure 4 shows CNT functionalization mediated by covalent and noncovalent interactions.

Graphene-based biosensors

Pristine graphene, polycrystalline graphene, graphene oxide (GO), reduced graphene oxide (rGO), and graphene quantum dots (GQDs) are the different forms that are being used in the biosensor (Fig. 5). Pristine graphene is a flawless lattice of honeycomb-like structures of graphene with sp^2 hybridization. Polycrystalline graphene is made with grain-like graphene crystal with defined boundaries. GQDs are tiny nanoparticle of graphene; generally, they have a diameter of 20 nm. Graphene oxide is also an sp^2 hybridized lattice of carbon molecules that are disrupted by sp^3 hybridized carbon molecules (Morales-Narváez et al. 2017). Heterogeneous electron transfer (HET) in reduced graphene oxide is because of their functional groups, the number of functional groups depends on the reduction method by which reduced graphene oxide is synthesized

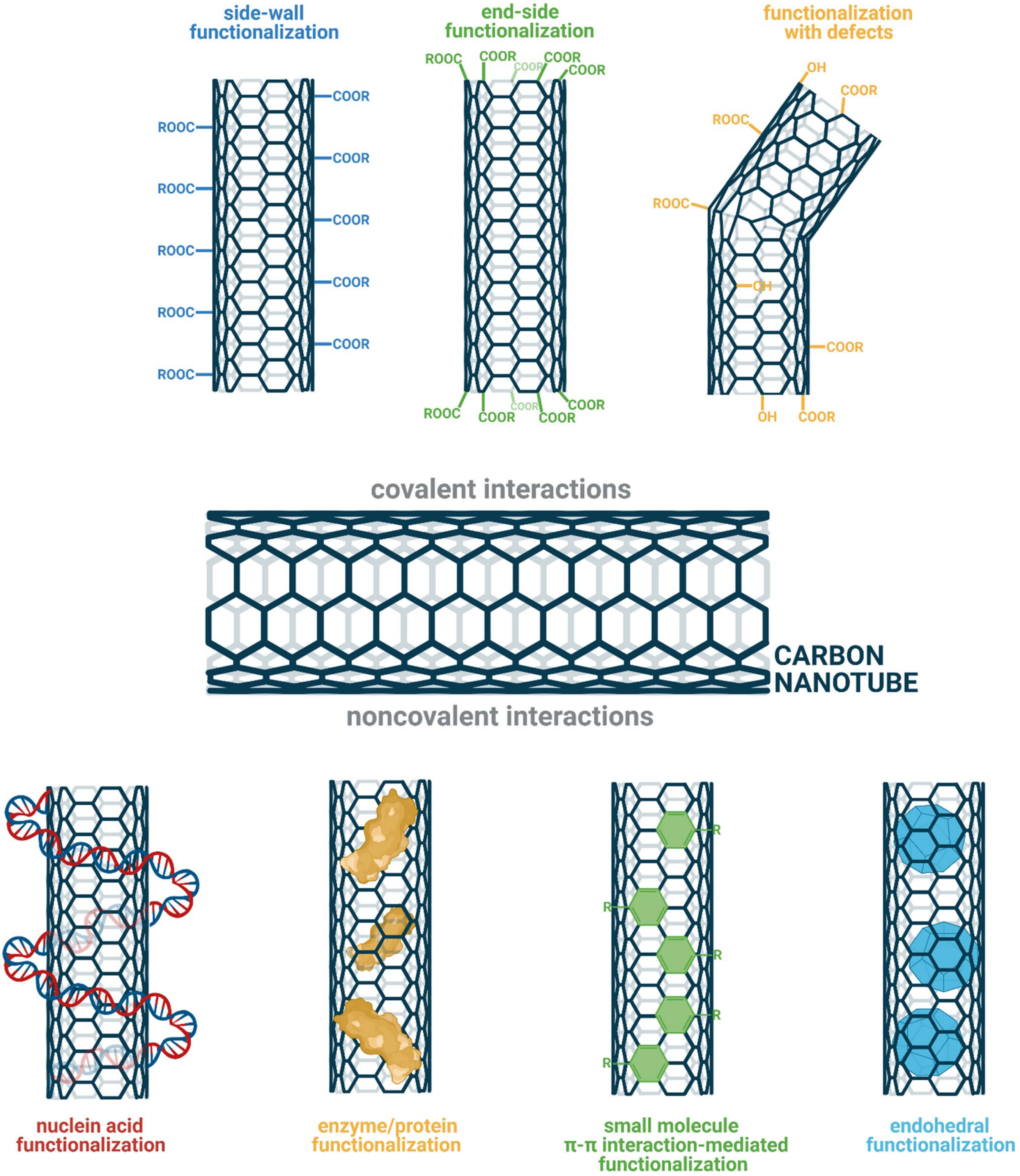
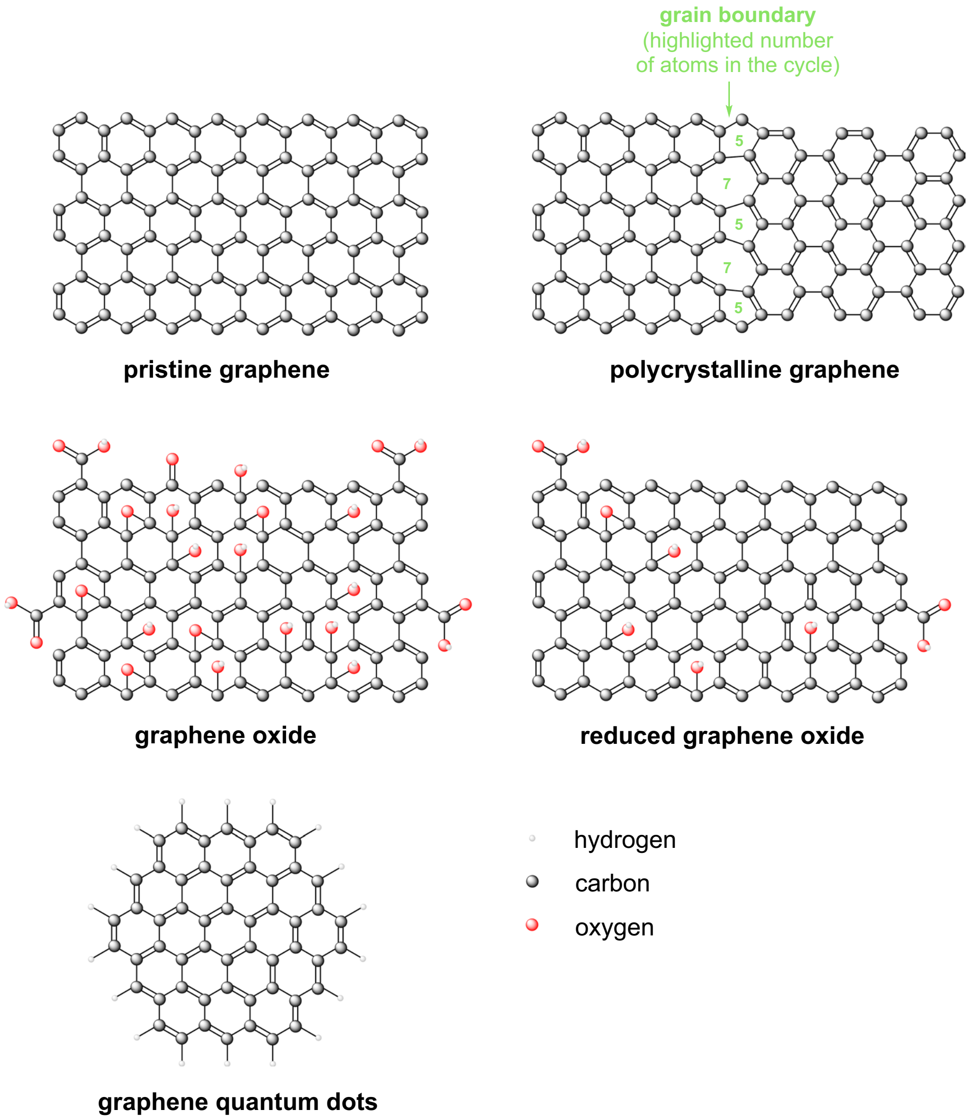


Fig. 4 Surface functionalization examples of carbon nanotubes. Figure created with BioRender.com

(El-Kady and Kaner 2013). Paper-based reduced graphene oxide biosensors have been developed for the detection of cancer (Wu et al. 2013). Graphene derivatives are responsive both in terms of fluorescence and quenching; however, these properties highly depend upon the layers of the graphene (Chen et al. 2010). Graphene-coupled single-stranded DNA-based sensors have been developed, which is quenched in the absence of analyte, and in the

Fig. 5 Different graphene forms used in biosensors



presence, it will start to fluoresce. *Escherichia coli* detection is also made possible up to 10 colony-forming units/mL in the sample using graphene-based fluorescent biosensors (Morales-Narváez et al. 2015).

Advances and potential applications of biosensors

Biosensors in agriculture and food industry

Various techniques are being used in agriculture for the determination of health status in crops including polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA), immunofluorescence (IF), gas chromatography-mass spectrometry (GC–MS), and flow cytometry (FCM). These methods allow us to recognize several diseases, nutrient deficiency, sensitivity to weather conditions, and stress conditions in plants. Presently, the stress condition in plants is being detected through changes in chemical indicator levels. However, the existing methods to analyse health condition in crops are time-consuming and laborious and developed for laboratory conditions. Advancements in biosensors seem to be crucial in a deeper understanding of agricultural processes (Kundu et al. 2019). In 2015, Larrieu et al. reported that a fluorescence-based biosensor to analyse the jasmonate signaling in plants has been developed. The biosensor provides information about hormone distribution in plant under abiotic and biotic stresses (Larrieu et al. 2015). Chong et al. also developed a fluorescence-based biosensor to detect early signs of water stress in plants before the permanent wilting point is reached (Chong et al. 2007).

Harvested fruits before shipment or distribution to consumers are in general stored and allowed to ripen for a certain period. During storing and ripening of the fruit, there are changes in the balance of chemical composition that are important to monitor. Simple monitoring systems ensure the required quality of the fruit for final consumers. A needle-type biosensor for the determination of sugars in fruits has been developed and applied for the analysis of glucose and sucrose concentrations in banana, orange, and kiwifruit. The biosensor combined three conventional electrodes (working, reference, and counter electrode), and side effects of citric and malic acids on both sucrose and glucose needle-type biosensors were evaluated to be small (Heineman et al. 2016). Dudchenko et al. developed a silicate/glucose oxidase-based biosensor for the determination of glucose in juices and nectars. A series of fruit juices and nectars were analysed using the biosensor, and the obtained results showed a good correlation ($R = 0.99$) with the data of high-performance liquid chromatography (HPLC). Even the biosensor sensitivity reached four- to fivefold higher levels compared to glucose oxidase-based biosensor (Dudchenko et al. 2016). An amperometric glutamate biosensor was developed and reported by Soldatkina et al. in 2017. The biosensor for glutamate detection uses a typical method of glutamate oxidase immobilization via adsorption on silicate particles. As an amperometric sensor, the disc platinum electrode is used. The linear range of glutamate detection was from 2.5 to 450 μM, and the limit of detection was 1 μM. The authors suggest the utilization of the developed biosensor in real samples with potential application in the food industry, fundamental and clinical medicine, neurophysiology, and neuropathology and in analytical biochemistry and biotechnology (Soldatkina et al. 2017). An electrochemical biosensor for detection of naringin, a flavonoid compound present in different citrus fruits, was reported by Ensafi et al. in 2016. The biosensor utilizes a modified pencil graphite electrode with a limit of detection of 10 ng/mL. Biosensing methodology is based on the interaction of naringin with DNA. Change in the oxidation signals of adenine and guanine was used as probes for the biosensor evaluation, using differential pulse voltammetry. The authors highlighted advantages of the proposed biosensor which include a wide linear dynamic range, low detection limit, ease of application, high speed, selectivity, and cost-effectiveness (Ensafi et al. 2016).

Further possible applications of biosensors in the agriculture and food industry result from requirements on food quality. Global agriculture nowadays unambiguously depends on the application of various chemicals, such as fertilizers, herbicides, and pesticides. Despite their positive effects on crops in the pre-harvest stage, the presence of chemicals in the post-harvest stage of crops is not required. The residues of agricultural chemicals represent a potential risk for consumers, causing several health problems, allergies, and anaphylaxis even death. Therefore, to avoid unintentional poisoning from agricultural chemicals, it is necessary to determine their levels in crops. Although many techniques involving HPLC, gas chromatography (GC), nuclear magnetic resonance (NMR), ultraviolet–visible spectroscopy (UV–Vis), and Fourier-transform infrared spectroscopy (FTIR) are advantageous and beneficial, demand for novel, fast, cheap, and universal detection systems remains a challenge (Kundu et al. 2019). The most frequently used pesticides to crop protection, due to their great efficiency, were organophosphorus pesticides (OPs). However, these compounds may cause environmental pollution and may threaten the health of humans. Therefore, a rapid and reliable sensor for OP detection is required. Amperometric acetylcholinesterase (AChE) biosensors have been shown as a suitable tool for OP detection due to their fast response, simplicity, convenience, and low-cost analysis. The crucial aspects to improve the performance of AChE biosensors are enhancement of conductivity and biocompatibility of modified electrode materials. Ma et al. developed an AChE biosensor with Pt nanoparticle-anchored zirconium-based metal–organic framework nanocomposites for the detection of OPs in the environment (Ma et al. 2019). Earlier, Pohanka et al. used an electrochemical sensor to provide information about cholinesterase activity in blood of rats intoxicated with paraoxon. Paraoxon, an organophosphate inhibiting AChE and butyrylcholinesterase (BuChE), is the active metabolite of the insecticide parathion. The blood cholinseterase activity represents an important marker of organophosphate intoxication. The authors declared that the electrochemical-based sensor provided a precise evaluation of cholinesterase activity (Pohanka et al. 2009).

Besides artificial pesticides, various chemicals are present in food that are important to detect including toxins, heavy metals, additives, antibiotics, and organic and inorganic contaminants. These compounds also decrease food quality and represent a potential risk for consumers. However, an advance in biosensor food monitoring is a promising approach to improve the quality of food. Kaur et al. reported a simple colorimetric and potentiometric biosensor construction based on urease inhibition by Pb^{2+} ions in milk samples. The lower detection limit for lead in colorimetric approach was 38.6 μM in water and milk samples. The lower limit of detection in the potentiometric approach was 9.66 μM, and the sensor detected leads specifically in the milk without any pretreatment (Kaur et al. 2014). Ramachandra et al. in 2016 reported that a biosensor for the detection of CaC_2, an artificial ripening agent in mangoes that causes serious health issues (neurological disorders, ulcers, hypoxia, memory loss, etc.), has been developed. The biosensor comprises of CeO_2-modified Pt electrode for the determination of CaC_2 based on AChE enzyme inhibition. The developed biosensor showed good conductivity, biocompatibility, and enhanced electron transfer rate with the limit of detection of 0.6 nM and linear range of 1–20 nM and response time less than 4 s. The authors also suggested its potential application for the detection of CaC_2 in other artificially ripened fruits (Ramachandra et al. 2016). Formaldehyde is considered a toxic compound since it has been classified as group 1 carcinogen to human. Despite this, it has been proved the use of formaldehyde in fish preservation, particularly in Asian countries. Ease, fast, and low-cost formaldehyde detection can be useful to protect consumers from poisoning. Therefore, Aini et al. turn their attention to the development of formaldehyde biosensor for the determination of formalin in fish samples. The biosensor is based on gold nanoparticles, ionic liquid, chitosan (nanocomposite membrane), and glassy carbon electrode. As a biorecognition receptor in the system, an enzyme formaldehyde dehydrogenase was used to ensure selectivity towards the substrate, formaldehyde. Under optimal conditions, a wider linear range of formaldehyde concentrations from 0.01 to 10 ppm within 5 s was detected using the differential pulse voltammetry, with the limit of detection of 0.1 ppm. The biosensor was successfully applied for the detection of formaldehyde presence in fish samples, *Lutjanus malabaricus* and *Thunnus Tonggol*. The developed method is highly accurate, rapid, and simple, compared to the existing technique (Noor Aini et al. 2016). Dervisevic et al. utilized an electrochemical biosensor based on a hybrid bionanocomposite platform in the evaluation of meat freshness assay. The authors in the study focused on the detection of xanthine, a product of adenosine-3-phosphate degradation, using a xanthine biosensor based on chitosan-polypyrrole-gold nanoparticles. Electrochemical studies were performed by the modified electrode with immobilized xanthine oxidase. The biosensor was tested on real samples of fish, beef, and chicken. Xanthine biosensor overall exhibited a very good linear range of 1–200 µM and low limit of detection of 0.25 µM with an average response time of 8 s. Study further revealed that the xanthine biosensor was not prone to significant interference from ascorbic acid, uric acid, glucose, and sodium benzoate (Dervisevic et al. 2017). An inadequate stocking food may also represent a potential risk for consumers. A wet and humid climate can be profitable for different types of moulds such as *Aspergillus flavus* or *Aspergillus parasiticus* producing aflatoxins. Aflatoxins represent secondary metabolites, products of a polyketide pathway. These toxins are considered as one of the most carcinogenic natural compounds causing hepatocellular carcinoma. Pohanka et al. developed a method for the detection of aflatoxin B1 in capsicum spice. The assay utilized an electrochemical immunosensor with immobilized aflatoxin B1-bovine serum albumin conjugate. The authors declared that the whole device and assay are very practical for application in real conditions (Pohanka et al. 2008).

Biosensors bear the potential to detect various diseases caused by microorganisms as well as to provide data about microbial viability. The development of ATP bioluminescence biosensors to determine bacterial viability in milk and other animal food have been reported (Eed et al. 2015). In 2012, Gramberg et al. reported the construction of a cell-based biosensor for the detection of plant viruses. The principle of detection was based on the measurement of bacterial membrane potential changes as a result of virus-antibody binding. Biosensor membranes have been engineered using modified *Escherichia coli* bacteria. The biosensor was applied for the detection of *cherry leaf roll virus* (CLRL) and *tobacco mosaic virus* (TMV). Interestingly, the virus detection limit of the biosensor was 1 pg/mL with assay time 60–100 s (Gramberg et al. 2012). Recently, a whole-cell-based biosensor to detect the presence of *Penicillium digitatum* infection in citrus fruit was developed and evaluated. Detection was based on the luminescent responses of bacteria to changes in volatile organic compounds following a pathogenic microorganism-mediated infection. Biosensors allowed to detect pathogen on the third day of infection, before the appearance of visible signs of fungal infection on the surface of the fruit (Chalupowicz et al. 2020). Izadi et al. described the fabrication of a DNA-based pencil graphite electrode modified by Au nanoparticles for the detection of *Bacillus cereus* in milk. Toxins produced by the bacteria cause two types of gastrointestinal illness, the emetic syndrome and diarrheal syndrome. The authors emphasized a rapid detection, low-cost, and high selectivity of the biosensor specially developed to detect target DNA sequence in the bacteria. Further benefits involve high reproducibility and stability of the biosensor (Izadi et al. 2016). Table 1 summarizes recent advances of biosensors in the agriculture and food industry.

Biosensors in pharmaceutical sciences

Biosensors allow us to study numerous compounds of the pharmaceutical interest and to provide real-time analysis of various processes. These helpful detectors may be employed at home (physiological condition control), in hospital (emergency, surgery, dialysis monitoring), in clinical laboratory analyses (DNA analysis, immunoassays), in laboratory research, and others. Ideal biosensor should be minimal size, low-cost, and easy to use, allowing direct and fast analysis without sample pretreatment. Measurement should be non-invasive, automatized, or remote-controlled (Kauffmann 2002).

Pathogens, such as algae, fungi, bacteria, viruses, and other parasites, are causative agents of various diseases; therefore, their rapid detection is crucial for a successful treatment. Detection of pathogens via biosensors brings a modern solution to an old problem. Various biosensors for pathogen detection have been developed by using electrical, electrochemical, mechanical, NMR, and optical sensing methods. Among the developed biosensors, optical, especially colorimetric sensors allow rapid, easy-to-use,

Table 1 Advances and potential application of biosensors in agriculture and the food industry

Commonly used biosensors	Main aim/application	References
Bioelectric bacterial biosensors	Detection of *cherry leaf roll virus* and *tobacco mosaic virus*	Gramberg et al. (2012)
AuNP-based SPR biosensor, immunosensors, and genosensors	Transgenics plants and foods detection	Sousa et al. (2018); Grześkowiak et al. (2019)
Colorimetric biosensor	Identification and detection of genetically modified foods (GMFs)	Jung et al. (2015)
Acetylcholinesterase (AChE) inhibition-based biosensors	Pesticide determination	Pundir and Chauhan (2012)
Needle-type biosensor	Determination of the internal quality parameters (sugar content) in fruits	Heineman et al. (2016)
Electrochemical biosensors	Pathogen detection in food products	Cesewski and Johnson (2020)
Optical fluorescence biosensor	Plant water stress detection	Chong et al. (2007)
Whole-cell-based biosensor	*Penicillium digitatum* infection detection in citrus fruit	Chalupowicz et al. (2020)
Amperometric biosensor	Quantification of indole 3-acetic acid	Subraya et al. (2013)
Microplate differential calorimetric biosensor	Measurement of intrinsic quality attributes of horticultural crops such as ascorbic acid, total phenolic compounds, and L-arginine	Vermeir et al. (2007); Verma et al. (2015)
Acetylcholinesterase (AChE) biosensors	Organophosphorus pesticides (OPs) detection	Ma et al. (2019)
Genetically encoded biosensors	Cytosolic boric acid determination	Fukuda et al. (2018)
Amperometric glutamate biosensor	Excessive usage of glutamate detection	Soldatkina et al. (2017)
Electrochemical biosensor	Detection of artificially ripening agents in food, detection of calcium carbide ripening in mangoes	Ramachandra et al. (2016)
Ultrasensitive electrochemical biosensors	Rapid assessment of nitrite toxicity	Gahlaut et al. (2019)
Electrochemical biosensor	Determination of flavonoid (naringin) content in citrus fruits/juices	Ensafi et al. (2016)
Silicalite/glucose oxidase-based biosensor	Determination of glucose content in fruits/juices and nectar	Dudchenko et al. (2016)
Real-time colorimetric and potentiometric biosensor	Qualitative and qualitative analysis of the toxicity of heavy metals in soil, milk, fruits and vegetables, and ground water	Kaur et al. (2014)
DNA-based biosensor, electrochemical, carbon nanotubes, quartz crystal microbalance, affinity biosensors	Different fungal mycotoxins (aflatoxins, ochratoxins, citrinin, patulin, and fusarium) detection	Evtugyn et al. (2018); Younis et al. (2020)
Electrochemical biosensor	Determination of histamine content in fish	Ye et al. (2016)
Formaldehyde biosensor	Determination of formalin in fish samples	Noor Aini et al. (2016)
Electrochemical xanthine biosensor	Xanthine detection in meat for freshness	Dervisevic et al. (2017)
Electrochemical formaldehyde biosensor	Detection of artificial preservatives	Noor Aini et al. (2016)
Graphene-based biosensors, carbon nanostructures, electrochemical biosensors	Detection of chemical contaminants in food, fast detection of food contaminants (pesticides, veterinary drug residues, additives, inorganic and organic contaminants, pathogens, and toxins)	Rotariu et al. (2016); Zeng et al. (2016); Bobrinetskiy and Knezevic (2018)
Nanomaterial-based biosensors (NBB)	Food safety detection or food contaminant detection, food toxin (pesticides and biotoxin) detection	Arduini et al. (2016); Dominguez et al. (2017); Lv et al. (2018)
Photoelectrochemical (PEC) biosensors	Food analysis, including mycotoxins, heavy metals, antibiotics, and pesticide residues	Mejri Omrani et al. (2016); Ge et al. (2019)
Electrochemical affinity biosensors	Determination of food allergens and adulterants	Campuzano et al. (2020)
Electrochemical biosensor	Monitoring lead ions in milk	Verma et al. (2011)
Parasitoid biosensors	Boar taint detection	Wäckers et al. (2011)
Enzyme-based colorimetric and potentiometric biosensor	Determination of Pb^{2+} ions in milk	Kaur et al. (2014)
Implant temperature sensor, wearable scanners	Monitor dairy cattle's core body temperature in real-time	Chung et al. (2020)

Table 1 (continued)

Commonly used biosensors	Main aim/application	References
Electrochemical DNA-based biosensor	Detection of *Bacillus cereus* in milk and infant formula	Izadi et al. (2016)
Label-free monolithically integrated opto-electronic biosensor	Assessment of various adulterations such as water, cow milk, buffalo milk, and also the chemicals	Angelopoulou et al. (2015)

portable, and cost-effective analysis (Yoo and Lee 2016). However, other biosensor types are also remarkable and advantageous for employment in health protection. Weerathunge et al. developed an ultrasensitive colorimetric detection of murine norovirus (MNV) using NanoZyme aptasensor. The strategy combines the gold nanoparticles enzyme-mimic catalytic activity with high target specificity of MNV aptamer. The present method achieved the most sensitive detection of the virus using a biosensor approach. The authors further demonstrated the robustness of the MNV NanoZyme aptasensor by its application in the presence of other non-target microorganisms. Developed ultrasensitive MNV detection is simple to use and rapid and eliminates the need for expensive instrumentation (Weerathunge et al. 2019). Pang et al. designed a fluorescent aptasensor system for the sensitive detection of recombinant hemagglutinin (rHA) protein of the influenza A subtype H5N1. Guanine-richen anti-rHA aptamers were immobilized on the surface of Ag-SiO_2 nanoparticles which acted as a metal-enhanced fluorescent sensing platform. Thiazole orange was used as a fluorescent tag, which was free with almost no fluorescence emission in the solution without rHA. However, in solutions with rHA, the aptamer strand bound rHA protein to form a G-quadruplex complex that can bind thiazole orange and excite the fluorescence emission. The rHA protein of the influenza A subtype H5N1 was detected with the limit of detection of 2 ng/mL in aqueous buffer and 3.5 ng/mL in human serum. Moreover, the whole experiment process can be finished within 30 min (Pang et al. 2015). The human adenovirus diagnostic system was developed by Jin et al. in 2018. The methodology involves a novel DNA extraction technique based on the integration of a non-chaotropic reagent with a disposable thin-film platform in a single microchannel. To detect extracted viral DNA, isothermal solid-phase DNA amplification/detection optical biosensor was used. The authors validated the clinical utility of the system in human samples and concluded that this system enables a rapid (less than 1 h) and sensitive (100 times higher than qPCR) diagnostic platform for viral DNA analysis (Jin et al. 2018). A selective and sensitive electrochemical immunosensor for *Zika virus* (ZIKV) protein detection was elaborated by Kaushik et al. in 2018. In this approach, the authors utilized a functionalized integrated micro-electrode of gold (IDE-Au) array. Electrochemical immunosensor was fabricated via immobilization of ZIKV envelope protein antibody onto a self-assembled monolayer of dithiobis (succinimidyl propionate) deposited on IDE-Au. The developed biosensor allowed rapid analysis (operation time around 40 min) with a low detection limit of 10 pM and promising clinical application for early-stage diagnostics of the virus (Kaushik et al. 2018). Babamiri et al. fabricated a novel molecularly imprinted polymer electrochemiluminescence sensor for selective detection of HIV-1 gene with high sensitivity. As a signal producing compound, europium sulphide nanocrystals were used. The HIV aptamer as the template and *o*-phenylenediamine as the functional monomer were directly electropolymerized on the surface of the indium tin oxide electrode. The hybridization reaction was mediated between europium sulphide nanocrystal functionalized 5-amino-labelled oligonucleotides as capture probes and detection target (HIV gene) oligonucleotides. The electrochemiluminescence signal significantly increased using $K_2S_2O_8$ as a coreactant. Selective and sensitive detection of the HIV gene was achieved in a linear range of 3.0 fM to 0.3 nM with a limit of detection of 0.3 fM. The authors further reported that the detection of HIV in real human serum samples was obtained with satisfactory results (Babamiri et al. 2018). Verma et al. recently developed an ultrasensitive DNA biosensor for a rapid detection of the *Loa22* gene of *Leptospira interrogans*, a Gram-negative bacterium causing leptospirosis. The biosensor uses a gold nanoparticle–carbon nanofiber composite-based screen-printed electrode. The authors claimed that the DNA-based biosensor provided a rapid detection of the pathogen with a higher selectivity and specificity (Verma et al. 2021).

Since early of 2020, a global attention has been focusing on detection of viruses, specially to the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing an ongoing pandemic of coronavirus disease 2019 (COVID-19). Despite hugeous endeavour to reduce the spread of the virus, COVID-19 still remains an international threat. One of the most important factors to overcome the pandemic is an early detection of the virus. Currently, the most effective method for detection of SARS-CoV-2 is reverse transcriptase polymerase chain reaction (RT-PCR). However, an exponential application of RT-PCR as a gold standard in diagnostic of SARS-CoV-2 involves some disadvantages. For example, the method is time-consuming and requires specialized laboratory equipment and qualified personnel. On the other hand, antigen test for detection of

SARS-CoV-2 is fast and easy to handle but has an increased possibility of false results. Therefore, it is not surprising that a continuous demand for the development of novel SARS-CoV-2 diagnostic methods results in development of novel biosensors. Diagnostic of the virus via biosensors is focused on the detection of RNA, antigens, and antibodies (Pradhan et al. 2021; Zare et al. 2021). Oui et al. developed a dual-functional biosensor based on the combination of plasmonic photothermal (PPT) effect and localized surface plasmon resonance (LSPR) sensing transduction. Sensitive detection of SARS-CoV-2 was mediated by using of two-dimensional gold nanoislands (AuNIs) functionalized with complementary DNA receptors. The biosensor allows precise detection of desired target in a multigene mixture with LOD of 0.22 pM for the RNA-dependent RNA polymerase (RdRp) (Qiu et al. 2020). An electrochemiluminescence (ECL) biosensor for a detection of RdRp gene of SARS-CoV-2 was developed by Fan et al. The biosensor utilizes DNA tetrahedron modified on the surface of electrode providing programmable scaffolds upon which target DNA participates. This results in entropy-driven amplified reaction proceeding through $\mathrm{Ru(bpy)_3}^{2+}$ modified S3 linked to the linear single-stranded DNA (ssDNA) at the vertex of the tetrahedron. The biosensor demonstrated considerable specificity and high selectivity towards the detection of the virus with LOD of 2.67 fM. The detection of RdRp of SARS-CoV-2 was achieved in human serum samples supporting its potential application in the clinical bioanalysis (Fan et al. 2021). Moitra et al. reported a selective and visual “naked-eye” detection of SARS-CoV-2 without any sophisticated instrumental techniques. The colorimetric assay is based on gold nanoparticles capped with thiol-modified antisense oligonucleotides specific for the N-gene of SARS-CoV-2. The gold nanoparticles capped with thiol-modified antisense oligonucleotides selectively agglomerate in the presence of the specific RNA sequence of SARS-CoV-2, resulting in a change of its SPR. Moreover, an addition of ribonuclease H yields in a cleavage of RNA strand from the RNA–DNA hybrid, which can be visually detected as a precipitate formed by the additional agglomeration between gold nanoparticles. Diagnostic of the virus can be achieved within 10 min of the isolated RNA samples. The authors selectively detected RNA from SARS-CoV-2 in the presence of RNA from the Middle East respiratory syndrome coronavirus (MERS-CoV) with LOD of 0.18 ng/μL (Moitra et al. 2020). Yakoh et al. developed a paper-based electrochemical biosensor to diagnose COVID-19. The methodology utilizes a sensitive and specific immunosensor detecting immunoglobulin produced against SARS-CoV-2. Sensing is based on the disruption of the redox conversion ($[\mathrm{Fe(CN)_6}]^{3-/4-}$) caused by the presence of SARS-CoV-2 antibodies. The assay can be performed within 30 min with LOD of 1 ng/mL. It was reported that the electrochemical biosensor provided satisfactory results in real clinical sera. Moreover, the methodology for diagnosing COVID-19 can be extended to the detection of antigen (the spike protein of SARS-CoV-2) (Yakoh et al. 2021). Cady et al. reported a detection of antibodies against SARS-CoV-2 using a grating-coupled fluorescent plasmonic (GC-FP) biosensor platform in human blood serum and dried blood spot samples. The GC-FP platform is based on the measurement of antibody–antigen binding interactions. The methodology can be utilized to measure the levels of antibody for multiple antigens in a single sample. The assay is rapid (30 min) and quantitative across a large dynamic range, using serum dilutions in the range 1:25 to 1:1600. The authors concluded that deeper insight into antibody responses across different immunoglobulin classes could be useful for the viral analysis of other bodily fluids (Cady et al. 2021). Seo et al. developed field-effect transistor (FET)-based biosensor for the diagnosis of COVID-19. The FET biosensor is functionalized with a specific antibody against SARS-CoV-2 spike protein conjugated to graphene sheet. Moreover, the biosensor provided no cross-reactivity with MERS-CoV antigen. The determination of the virus in clinical samples was achieved without any pre-processing with a large dynamic range. The biosensor could detect spike protein of SARS-CoV-2 in phosphate-buffered saline at concentration of 1 fg/mL and in clinical transport medium at concentration of 100 fg/mL. In addition, the methodology has a promising potential to detect other emerging viral diseases (Seo et al. 2020). Chen et al. reported the development of lateral flow immunoassay (LFIA) using lanthanide-doped polystyrene nanoparticles (LNPs) for the detection of immunoglobulin G (IgG) antibody against SARS-CoV-2 in human serum. A nitrocellulose membrane functionalized with a recombinant nucleocapsid phosphoprotein of SARS-CoV-2 was utilized to capture the IgG. The methodology provided a simple and rapid detection of the virus. The assay can be also used to monitor the progression of COVID-19 in patient or to evaluate patient’s response to treatment (Chen et al. 2020).

Cancer is the second leading cause of death globally, responsible for about 10 million deaths per year. Most of the deaths from cancer (approximately 70%) occur in low- and middle-income countries (Sung et al. 2021). Early diagnosis of cancer significantly improves the chance for successful treatment. Therefore, several research groups focused their attention on the development of cancer diagnostics biosensors. Pacheco et al. fabricated a gold screen-printed electrode that was modified with a molecularly imprinted polymer to detect the breast cancer biomarker CA 15–3. The biosensors provided a short time analysis (15 min) with a detection limit of 1.5 U/mL that is well below the used cut-off value in clinical practice (25 U/mL). In addition, the simplicity and low-cost of the analysis contribute to the clinical application of the biosensor as a promising tool for the detection of breast cancer and to evaluate the progression/

recurrence of cancer (Pacheco et al. 2018). Salahandish et al. developed a biosensor for the detection of HER2$^+$ breast cancer with a significant signal enhancement by graphene nanostructured polyaniline and silver nanoparticles. In this sandwich-like model of functionalized nitrogen-doped multilayer structure, with a correct arrangement and combination of nanocomposites, excellent conductivity and stability were observed. This approach eliminated the need for any biological enzymes, making the system universal and simple. The biosensor with a dynamic range of 10 to 5×10^6 cells/mL achieved the detection limit of 2 cells/mL (Salahandish et al. 2018).

In recent years, the global popularity of smartphones resulted in the development of a new category of daily-using detectors, termed wearable biosensors. The popularity of wearable biosensors has a growing tendency due to their potential to provide real-time, continuous physiological analysis via measurements of biochemical markers in biofluids, such as sweat, saliva, tears, and interstitial fluid. Present developments are focusing on electrochemical and optical biosensors. Customers prefer multiplexed minimal size biosensors combined with flexible materials to improve wearability and ease of operation. To underpin a future clinical acceptance of wearable biosensors, further studies and development are needed; however, their broad impact on daily life is apparent already to date (Kim et al. 2019). A summary of recent advances and applications of biosensors in pharmaceutical sciences is presented in Table 2.

Biosensors in environmental sciences

One of the most promising aspects for the utilization of biosensors in the environment is the detection of pollutants in soil, water, and air. Monitoring in the environment is focused on the determination of heavy metals such as mercury, copper, cadmium, lead, zinc, and arsenic; nitrogen compounds, especially nitrates in the soil, groundwater, and surface water that can harm the health of human and aquatic life; phenolic compounds utilized in industry and manufactures; biochemical oxygen demand, a commonly used parameter for determination of environmental pollution; microorganisms; and other (Singh and Khajuria 2020). Benzene and its derivatives belong to compounds whose exposure poses a significant risk to human health. Ray et al. developed three high selective protein-based biosensors for the detection of benzene and its derivatives with the limit of detection of 0.3 ppm. Moreover, the developed biosensors were able to differentiate between methyl-substituted benzene derivatives (toluene, xylene and mesitylene) (Ray et al. 2018). An enzyme-based fibre optic biosensor for detection of halogenated hydrocarbon pollutants was fabricated by Shahar et al. in 2018. The approach is based on immobilized enzyme-mediated hydrolytic dehalogenation of halogenated aliphatic hydrocarbon to corresponding primary alcohol, halide ion, and proton. The proton concentration changes led to increased protonation of immobilized Nile blue chromoionophore, an optical pH indicator. The resulting optical change is monitored by a fibre optic reflectance spectrophotometer. The biosensor exhibited a dynamic linear response range of 1–30 mg/L with the limit of detection of 0.3 mg/L and rapid response (within 2 min), towards detection of 1,2-dichloroethane (Shahar et al. 2019). Conventional measuring methods of biochemical oxygen demand (BOD), a widely used index for determining the amount of biodegradable organic matter in wastewater, are time-consuming techniques (5 days); therefore, a more rapid method is required. Liang et al. constructed a flame-oxidized stainless steel anode as the probe of a bioelectrochemical system-based biosensor for the measurements of BOD. The evaluation was performed on real wastewater samples to simulate the practical application of the biosensor. As a result, the developed biosensor offered better performance than traditional carbon-cloth anodes in bioelectrochemical biosensors. The authors further proposed various practical utilizations of the biosensor to improve the biomonitoring of wastewater (Liang et al. 2018). The great challenge nowadays is the monitoring of the marine environment. Marine pollutants are hazardous to all forms of aquatic life, such as algae, plankton, crustaceans, fish, and marine mammals. An optical biosensor based on the array of algal biomediators has been developed by Turemis et al. for the measurements of pesticides in marine water. The algae–protozoa algae association between *Chlorella vulgaris* and *Tetrahymena pyriformis* was assessed as a sensitive biomediator for biosensor development. Entrapped symbiotic strain in calcium alginate within novel fluidic flow cells with integrated detectors provided real-time detection mediated by florescence analysis of photosynthetic photosystem II. The biosensor was examined to detect three commonly found pesticides (simazine, atrazine, and diuron), and results were compared with LC–MS analysis. Determined limits of detection were 1.35 µg/L for simazine, 0.44 µg/L for atrazine, 0.25 µg/L for diuron, and 0.13 µg/L for the mixture (Turemis et al. 2018). An optical biosensor for soil contamination assessment utilizing bioluminescent bacterial bioreporters encapsulated in poly-dopamine-coated alginate microbeads was fabricated by Bae et al. in 2020. In their approach, two bioluminescent reporter strains were employed for the detection of toluene as a model soil contaminant in the ambient light-blocking, temperature-controlled biosensor module. Bioluminescence of strain TV1061 (*Escherichia coli*) increased, whereas that of strain GC2 (*Escherichia coli*) decreased in the presence

Table 2 Advances and potential application of biosensors in pharmaceutical sciences

Commonly used biosensors	Main aim/application	References
Förster resonance energy transfer (FRET)-based biosensors	Visualizing cGMP, cAMP, and Ca^{2+} in cells	Thunemann et al. (2014)
Optical biosensors	Detection of pathogenic microorganisms	Yoo and Lee (2016)
Genetically encoded fluorescent biosensors	Live-cell visualization of protein phosphorylation	Oldach and Zhang (2014)
Fluorescent biosensors	Imaging early signaling events in T lymphocytes	Randriamampita and Lellouch (2014)
Electrochemical and optical biosensors	*Campylobacter* and *Listeria* detection	Vizzini et al. (2019)
Microfluidic biosensor	Determination of subclinical ketosis diagnosis	Weng et al. (2015)
Wearable biosensors, motion sensors	Neurological disorder monitoring (multiple sclerosis)	Sasaki et al. (2017); Sparaco et al. (2018)
Mitochondrial biosensors	Monitoring mitochondrial physiology	De Michele et al. (2014)
Electroimmunosensor	Detection of progesterone hormone levels	Zhang et al. (2013)
Peptide-based surface plasmon resonance (SPR) biosensor, aptamer-based biosensors	Bacterial toxin detection, aquatic phycotoxins, and cyanotoxin detection	Dudak and Boyaci (2014); Cunha et al. (2018)
Electrochemical immunosensors, optical biosensors	Small organic molecule detection, antibiotic detection	Piro et al. (2016); Peltomaa et al. (2018); Pollap and Kochana (2019)
Optical immunosensor	*Salmonella typhimurium* detection	Viter et al. (2017)
Electrochemiluminescence biosensor, nanostructured optical photonic crystal biosensor, piezoelectric biosensor	Bacteria and virus detection, HIV-1 gene detection, detection of HIV-1 from biological samples, detecting HIV-1 related protein (Gp41)	Shafiee et al. (2014); Anik et al. (2016); Cheeveewattanagul et al. (2017); Babamiri et al. (2018); Erdem et al. (2019); Saylan et al. (2019)
Optical microchip sensors	Early detection of *foot-and-mouth disease virus*	Bhatta et al. (2012)
Magnetic nanoparticle-based DNA sensor	Detection of HIV and HBV	Hassen et al. (2008)
Surface plasmon resonance biosensor	Hepatitis B surface antigen antibody detection	Tam et al. (2017)
Electrochemical sensor	Detection of *hepatitis B virus* DNA	Li et al. (2015)
Impedimetric nano-biosensor	Detection of DNA from HBV	İstek et al. (2019)
Thermo-sensitive surface-imprinted polymer-based biosensor	Rapid and highly selective in vitro detection of *Hepatitis A virus*	Liu et al. (2017)
Electrochemical DNA biosensor	*Ebola virus* detection	Ilkhani and Farhad (2018)
Optofluidic nanoplasmonic biosensor	Whole live *Ebola viruses* detection from biological media	Yanik et al. (2010)
Optical biosensor	Direct detection and quantification of *Ebola virus* infection (amplification free)	Cai et al. (2015)
Graphene-enabled biosensor	Early detection of *Zika virus* infection detection	Afsahi et al. (2018)
Electrochemical immunosensor	Detection of *Zika virus* protein	Kaushik et al. (2018)
Optical	*Zika virus* detection	Song et al. (2016)
Surface plasmon resonance fluoroimmunosensor	Norovirus virus-like particles detection	Ashiba et al. (2017)
Electrochemical	Norovirus (DNA) detection	Lee et al. (2018)
Colorimetric biosensor	Ultrasensitive and rapid detection of the infective MNV	Weerathunge et al. (2019)
Electrochemical	Isolation and detection of influenza A virus H9N2 subtype	Sayhi et al. (2018)
DNA sensor based on multi-wall carbon nanotubes	Detection of label-free influenza virus (type A)	Tam et al. (2009)
Fluorescent aptasensor	H5N1 influenza virus detection	Pang et al. (2015)
Wearable humidity sensor	Respiration monitoring	Pang et al. (2018)

Table 2 (continued)

Commonly used biosensors	Main aim/application	References
Portable surface plasmon resonance aptasensor	Avian influenza virus H5N1 detection	Bai et al. (2012)
Silicon nanowire biosensor	Dengue serotype 2 detection	Zhang et al. (2010)
Liposome biosensor	Characterization of protein–membrane interaction	Zhang et al. (2016)
Electrochemical peptide sensor	Dengue fever biomarker NS1 detection	Lim et al. (2018)
Impedimetric DNA biosensor	Specific oligonucleotide sequence of *Dengue virus* detection	Deng and Toh (2013)
Surface plasmon resonance biosensor	Detection of anti-dengue virus in human serum samples	Jahanshahi et al. (2014)
Bio-optical sensor	Rapid human adeno virus detection	Jin et al. (2018)
Portable surface plasmon resonance biosensor	Rapid detection and quantification of human enterovirus 71	Prabowo et al. (2017)
SPR biosensor	Diagnosis of Epstein–Barr virus infection in clinical serum samples	Riedel et al. (2014)
Optical	Therapeutic drug monitoring	Garzón et al. (2019)
Piezoelectric, wireless implantable passive strain sensors (WIPSS), electrochemical, immunosensors, label-free electronic sensors	Bone health diagnosis, measure disfigurement of orthopaedic implants, impedimetric detection of bone biomarkers (CTx-I), bone turnover markers detection, bone loss detection, alkaline phosphatase (ALP) as biomarker determination	Ramanathan et al. (2016); Afsarimanesh et al. (2018); Afsarimanesh et al. (2019); Sappia et al. (2019)
Electrochemical	Measurement of antioxidants and reactive oxygen species levels in physiological systems, uric acid detection, hormone measurements	Mello et al. (2013); Erden and Kılıç (2013); Bahadır and Sezgintürk (2015)
Wireless mouth-guard biosensor	Real-time salivary uric acid level detection	Kim et al. (2015)
Surface plasmon resonance	Medical/clinical diagnosis such as haemoglobin detection	Saylan and Denizli (2018)
Label-free biosensors	Laboratory-based diagnostics of infections	Andryukov et al. (2020)
Colorimetric biosensors, fluorescent, biosensors, surface plasmon resonance, biosensors, surface-enhanced Raman scattering biosensors, molecularly imprinted polymer (MIP) based sensors, superwettable electrochemical biosensor	Detecting cancer-derived exosomes biomarker, lung cancer biomarkers detection, cancer biomarkers detection, cancer cell detection	Selvolini and Marrazza (2017); Xu et al. (2018); Yang et al. (2019); Cheng et al. (2019); Khanmohammadi et al. (2020)
Nanoparticle-based electrochemical biosensors	Prostate cancer biomarker detection	Singh et al. (2019)
Nanotechnology-enhanced no-wash biosensors	In vitro diagnostics of cancer	Huang et al. (2017)
Surface-enhanced Raman scattering (SERS) nanoparticles	Direct detection of circulating tumour cells (CTCs) in the blood	Wu et al. (2015)
Molecularly imprinted electrochemical sensor	Point-of-care detection of a breast cancer biomarker (CA 15–3)	Pacheco et al. (2018)
Silicon nanomaterials	Cancer therapy, bioimaging, and biosensing	Peng et al. (2014)
Graphene-based biosensors	Prostate cancer protein biomarkers detection	Xu et al. (2019)
Nano-biosensor	Highly sensitive detection of HER2 positive breast cancer	Salahandish et al. (2018)
Electrochemical and optical biosensors	Diagnosis of early-stage cancer	Balaji and Zhang (2017)
Miniaturized impedimetric immunosensor	Competitive detection of adrenocorticotropic hormone	Li et al. (2017)

Table 3 Advances and potential application of biosensors in environmental sciences

Commonly used biosensors	Main aim/application	References
Enzyme-based conductometric, colorimetric, and potentiometric biosensor	Detection of heavy metals (copper, cadmium, and lead), ions, and pesticides in water samples	Tekaya et al. (2014)
Amperometric acetylcholinesterase biosensor	Detecting malathion and chlorpyrifos toxicity in water	Chauhan et al. (2016)
Graphene oxide-based optical biosensor, fluorescent bacterial sensor cells	Explosives and buried landmines detection	Zhang et al. (2015); Kabessa et al. (2016)
Piezoelectric biosensors	Organophosphate and carbamate pesticide detection	Marrazza (2014)
Microbial fuel cell-based biosensors	Environmental monitoring	Sun et al. (2015)
Recombinant *Arxula adeninivorans* whole-cell biosensor	Determination of pharmaceuticals in wastewater	Pham et al. (2015)
Aptamer-based optical biosensor, double-layer molecularly imprinted film-based biosensor	Rapid and sensitive detection of 17β-oestradiol (E2) in water samples	Yildirim et al. (2012); Tan and Wei (2015)
Amperometric biosensor	Determination of selected persistent organic pollutants' (POPs) landfill leachates	Nomngongo et al. (2012)
Mixed microbial electrochemical sensor	Detection of biotoxicity of multi-pollutants existing in real wastewater (heavy metal ions, phenol, and pesticides)	Gao et al. (2016)
Aptamer-based biosensors	Detection of low molecular weight pollutants in water sources	Zhang et al. (2018)
Fluorescence-based biosensor	Environmental pollutant monitoring, halogenated pollutant detection	Bidmanova et al. (2016)
Protein-based biosensors	Selective detection of benzene groups of pollutants	Ray et al. (2018)
Enzymatic reflectance biosensor, fibre optic biosensor	Detection of halogenated hydrocarbon pollutants in the water sample	Shahar et al. (2019)
Optical detection module-based biosensor	Assessment of soil toxicity	Bae et al. (2020)
Electrochemical sensor	Detection of precise environmental pollutants	Jin and Maduraiveeran (2017)
Optical biosensor	Marine pollutant monitoring	Turemis et al. (2018)
Electrochemical biosensor	Wastewater acute biotoxicity assessment	Gao et al. (2017)
Electrochemical hydrogen sulphide biosensors	To quantify various environmental polluting gases such as carbon dioxide (CO_2), nitrous oxide (N_2O), methane (CH_4), ammonia (NH_3), hydrogen sulphide (H_2S)	Xu et al. (2016)
Oligonucleotide-based sensor, nanographene-based tyrosinase biosensor, electrochemical biosensor	Detection of endocrine-disrupting compounds (EDCs), rapid detection of bisphenol A, detection of bisphenol A (BPA) in wastewater	Wu et al. (2012); Zehani et al. (2015); Gatel et al. (2019)
SOS-lux-based microbial biosensors	Detection of carcinogenicity and genotoxicity, detection of mutagenic chemicals	Alhadrami and Paton (2013)
Bioelectrochemical system (BES)-based biosensors	Biochemical oxygen demand (BOD) of wastewater monitoring	Liang et al. (2018)
Microbial biosensors, enzyme-based biosensors, nanomaterial-based sensors	Environmental ecotoxicity/pollution assessment and monitoring	Hassan et al. (2016); Sarkar et al. (2019); Brar et al. (2019)
Aptamer-based biosensors	Detection of harmful small toxic molecule contaminants and real-time environmental monitoring	Nguyen et al. (2017)
"EcoStat" potentiostat	Detection and quantification of *E. Coli* in ground, surface, and drinking water	Ettenauer et al. (2015)

Table 4 Summarization of LOD, advances of the abovementioned biosensors, and their comparison with common methods of detection

Biosensor	Detection of	LOD	Common method of detection (LOD of the method)	Advances of developed biosensor	References
Amperometric glutamate biosensor	Glutamate	1 µM	Glutamate Assay Kit; Sigma-Aldrich® (50 µM)	Higher sensitivity	Soldatkina et al. (2017)
Electrochemical biosensor	Naringin	10 ng/mL	Flavonoid assay; Cell Biolabs INC (LOD = 2 µg/mL)	Higher sensitivity, higher selectivity	Ensafi et al. (2016)
Colorimetric and potentiometric biosensor	Pb	38.6 µM (colorimetric approach); 9.66 µM (potentiometric approach)	Most kits for at-home detection of Pb (LOD = 5–20 mg/L)	Direct detection in real samples (water, milk) without any pretreatment	Kaur et al. (2014); Kriss et al. (2021)
Electrochemical biosensor	CaC_2	0.6 nM	-	Rapid, sensitive, biocompatible method	Ramachandra et al. (2016)
Electrochemical biosensor	Formaldehyde	0.1 ppm	Formaldehyde assay kit; QuantiChrom™ (LOD = 0.045 ppm)	Accurate, simple and rapid method	Noor Aini et al. (2016)
Electrochemical biosensor	Xanthine	0.25 µM	Xanthine assay kit; EnzyChrom™ (LOD = 10 µM)	Higher sensitivity, not prone to interference	Dervisevic et al. (2017)
Bioelectric bacterial biosensors	*Cherry leaf roll virus* and *tobacco mosaic virus*	1 pg/mL	Membrane-engineered biosensors for detection of plant viruses (LOD = 1 ng/mL)	Novel method, the detection limit about 1000-fold higher over currently available methods	Gramberg et al. (2012)
Fluorescent aptasensor	H5N1 influenza A (rHA protein)	2 ng/mL (in aqueous buffer); 3.5 ng/mL (in human serum)	Influenza A H5N1 (avian flu) hemagglutinin/HA ELISA Pair Set; antibodies-online GmbH (LOD = 78.125 pg/mL)	Self-contained diagnostic kit, detection can be performed in polyethylene tube within 30 min	Pang et al. (2015)
Electrochemical immunosensor	Zika virus (envelope protein)	10 pM	*Zika virus* (strain Zika SPH2015) envelope protein (ZIKV-E) ELISA Pair Set; Sino Biological Inc. (LOD = 125 pg/mL)	Promising clinical application for early-stage diagnostics of the virus, operation time around 40 min	Kaushik et al. (2018)
Electro-chemiluminescence biosensor	HIV (HIV-1 gene)	0.3 fM	VIDAS®HIV DUO: rapid 4th generation tests, detection of anti-HIV1 p24 antibodies (LOD = 20– > 100 pg/mL)	High selective to HIV-1 gene, satisfactory results in real human serum	Babamiri et al. (2018)
Dual-functional biosensor	SARS-CoV-2 (viral sequence)	0.22 pM	Human SARS-CoV-2 N ELISA Kit; Thermo Fisher Scientific, (LOD = 0.069–50 g/mL)	Selective detection of viral sequence, precise detection in multigene mixture	Qiu et al. (2020)
Electro-chemiluminescence biosensor	SARS-CoV-2 (viral sequence)	2.67 fM	Human SARS-CoV-2 N ELISA Kit; Thermo Fisher Scientific, (LOD = 0.069–50 g/mL)	Novel route for simultaneous assay of RdRp-COVID sequence with high selectivity and sensitivity in human serum samples	Fan et al. (2021)

Table 4 (continued)

Biosensor	Detection of	LOD	Common method of detection (LOD of the method)	Advances of developed biosensor	References
Colorimetric bioassay	SARS-CoV-2 (viral sequence, N-gene)	0.18 ng/µL	Human SARS-CoV-2 N ELISA Kit; Thermo Fisher Scientific, (LOD = 0.069–50 g/mL)	"Naked-eye" detection of SARS-CoV-2, detection without any sophisticated instrumental techniques	Moitra et al. (2020)
Paper-based electrochemical biosensor	SARS-CoV-2 (antibodies and antigen detection)	1 ng/mL	Human SARS-CoV-2 N ELISA Kit; Thermo Fisher Scientific, (LOD = 0.069–50 g/mL)	Targeting SARS-CoV-2 antibodies without the specific requirement of an antibody, antigen detection	Yakoh et al. (2021)
Field-effect transistor-based biosensor	SARS-CoV-2 (spike protein detection)	1 fg/mL (in phosphate-buffered saline); 100 fg/mL (in clinical transport medium)	Human SARS-CoV-2 N ELISA Kit; Thermo Fisher Scientific, (LOD = 0.069–50 g/mL)	High sensitivity, detection achieved without any pre-processing, potential application to other viruses	Seo et al. (2020)
Molecularly imprinted electrochemical sensor	Breast cancer (biomarker CA 15–3 detection)	1.5 U/mL	Clinical practice (LOD = 25 U/mL)	Higher sensitivity, low-cost detection	Pacheco et al. (2018)
Nano-biosensor	HER2 + breast cancer	2 cells/mL	Fluorescence in situ hybridization (FISH) probes (costly and time-consuming detection)	Universal and simple system, eliminated the need for any biological enzymes	Salahandish et al. (2018)
Protein-based biosensors	Benzene and its derivatives	0.03 ppm	PPB VOC Gas Sensor; ION Science (LOD = 1 ppb)	Selectivity and specificity	Ray et al. (2018)
Enzyme-based fibre optic biosensor	Halogenated hydrocarbon pollutants	0.3 mg/L	11.7 eV VOC Gas Sensor; ION Science (LOD = 100 ppb)	Rapid detection (2 min)	Shahar et al. (2019)
Optical biosensor	Pesticides in marine water	1.35 µg/L (for simazine); 0.44 µg/L (for atrazine); 0.25 µg/L (for diuron); 0.13 µg/L (for the mixture of previous pesticides)	-	Real-time detection	Turemis et al. (2018)

of increasing toluene concentrations. This simple optical biosensor can potentially be utilized for soil contamination monitoring in areas suspected of chemical pollution such as petrol stations or petrochemical industrial zone (Bae et al. 2020). Recent advances and applications of biosensors related to the environment are shown in Table 3.

Conclusions and future directions

Biosensors are a continuously developing field; various kinds of biosensors are available. Biosensors mainly include luminescence-based sensors, optical-based sensors, and carbon nanotube-based sensors. Recently developed sensors provide a high signal-to-noise ratio; they are cheap and can be quickly commercialized (Table 4). Biosensors have been developed for the detection of glucose tyrosine DNA and bacteria from various samples. The last few decades have seen a surge in biosensor research related to sensitivity enhancement and innovative target materials for specificity. Nano-technological advances have increased surface plasmon resonance-based biosensor research. Carbon-based nanomaterials, like graphene and its derivatives, have revolutionized the field of biosensing due to their extraordinary properties, such as large surface area, easy synthesis, tuneable optical properties, and strong compatible adsorption of biomolecules. Carbon nanotube-based materials have been used to act as a plasmonic layer to provide the large surface area and compatibility for immobilizing biomolecules, such as enzymes, DNA, antibodies, and antigens, in the design of the sensing layer. As a result, this field continues to be at the forefront of evolving biosensing technology. Carbon nanotube-based biosensors demonstrate an active growth of research interest in food analysis. The high specific surface area and catalytic activity of graphene are utilized for the extraction of analytes from food samples. Their high conductivity contributes to the performance efficacy of the electrodes. They have been utilized as transducers in biosensing platforms such as electrochemical, optical, chemo-resistive, and field-effect transistor-based biosensors for the detection of various analytes in food. We summarize the recent progress for the detection of chemical contaminants in food and the environment, together with clinical applications, and the principles of operation and discuss the perspectives of developing portable devices for rapid in-field analysis.

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Declarations

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