Research Insights on the Development of Biosensors

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Abbreviations

CE	Counter electrode
EIS	Electrolyte-insulator-semiconductor
E_{pa}	Potential of the anodic peak current
E_{pc}	Potential of the cathodic peak current
IHP	Inner Helmholtz plane
I_{pa}	Anodic peak current
I_{pc}	Cathodic peak current

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LAPS	Light-addressable potentiometric sensor
OHP	Outer Helmholtz plane
R_B	Bulk resistance
R_C	Contact resistance
RE	Reference electrode
R_I	Interface resistance
R_S	Surface resistance
WE	Working electrode

1 Introduction

Biosensors are applicable in such fields as the medical realm, food industries, agriculture, the treatment of industrial wastes, and armed defence (Kara 2012; Thévenot et al. 2001). Biosensors are devices that convert biological or biochemical signals to electrical responses (Mohanty and Kougianos 2006; Turner 2013). It is an advanced technology compared to traditional sensors. The multifunctional sensing system has been developed by combining many sensors. Various transducer types such as acoustical, optical, electronic, and mechanical have been developed by utilizing biosensors. The biologically active materials have more influence on the functions of biosensors. Factors to be considered when choosing biological materials include environmental conditions, storage, and operations. Annually, 60% of research work has been carried out with biosensors in the medical field (Malhotra 2017). Clark developed an enzyme electrode at the beginning of biosensor research (Pandey and Malhotra 2019). Thereafter, researchers from such fields as physics, materials, and medical worked together to develop multipurpose, higher-sensitivity biosensor devices (Hinze 1994; Malhotra et al. 2005; Vadgama and Crump 1992). Biosensors are utilized not only for commercial purposes but also in the field of defence during biowars (Song et al. 2006). Biosensors are defined based on the field of application and the purpose. In general, a biosensor is a device that has a biological sensing element for converting complex biochemical signals to electrical signals with sophisticated, understandable measurable formats.

The following factors or conditions are required when fabricating biosensors (Grieshaber et al. 2008; Turner 2013):

- The required sensing device should be stable under environmental conditions.
- The device should be accurate, precise, and have a higher degree of sensitivity.
- The sensor must be small in size and biocompatible so it can be used in medical settings.
- It should be easy to fabricate, portable, low in cost, and usable by less skilled laborers (Perumal and Hashim 2014).

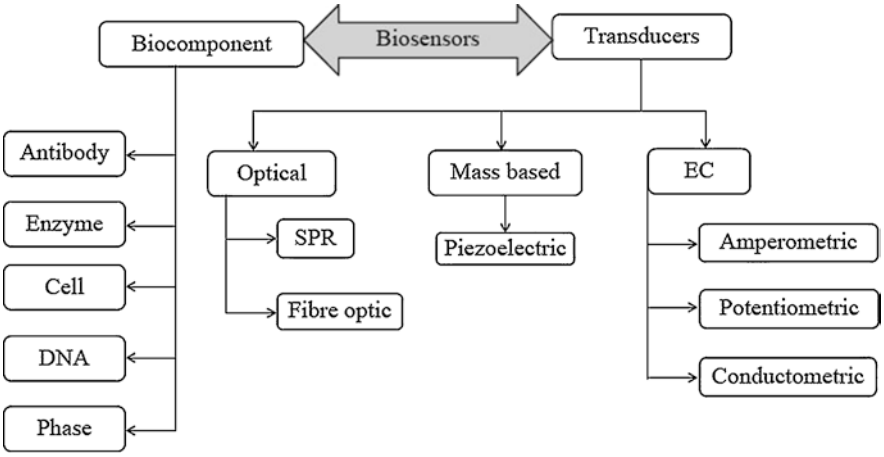

Fig. 1 Classification of biosensors

The most important part of the biosensor is the transducer, which functions to convert complex measurable biochemical data to understandable electrical signals Biosensors are classified into two types: biocomponents and transducers (Fig. 1).

Biosensors are classified as optical, thermal, electrochemical, and piezoelectric according to the transducer element.

2 Electrochemical Biosensors

Electrochemical sensors are widely used in various fields because they allow biomolecules with high sensitivity (Thévenot et al. 2001). Biosensor response is based on the proximity of the three electrodes required for functioning: working electrode (WE), reference electrode (RE), and counter electrode (CE). The overall performance of biosensors depends on the type of electrode used. The factors that affect the detecting properties of electrodes are electrode material and dimensions (Grieshaber et al. 2008).

Figure 2 shows the electrodes present in electrochemical biosensors. Figure 3 is a diagrammatic representation of an electrochemical biosensor. The working electrode (WE) is a transducer element of the electrochemical biosensor, which is present in the biochemical reaction taking place. The counter electrode (CE) functions as a connection between the electrolytic solution and working electrode. To obtain the necessary stable potential, the reference electrode (RE) is kept at a distance from the reaction area. The materials silver and silver chloride have been used for the reference electrode. Electrons move from the analyte (the electroactive element) to the working electrode or from the working electrode to the analyte while the oxidation-reduction (redox) reaction is taking place. The direction of electron flow depends on the characteristics or properties of the analyte and the electric potential

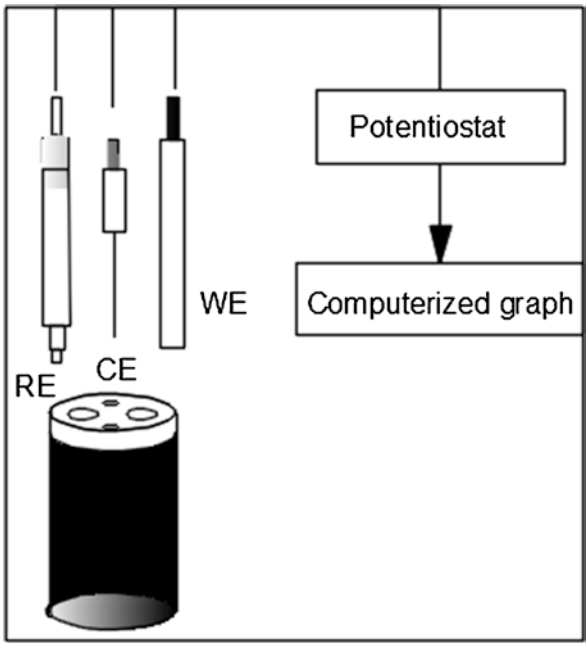

Fig. 2 Electrodes present in an electrochemical biosensor

of the working electrode. The working electrode is stimulated as a positive potential when the oxidation reaction takes place. The potential difference that occurs depends on the concentration of the electroactive element dispersed on the surface of the working electrode (Grieshaber et al. 2008). The reduction reaction takes place when the working electrode is stimulated as a negative potential. The counter electrode is used to measure the potential difference when the working electrode and counter electrode are acting as anode and cathode, respectively. Such materials as gold, platinum, and carbon are used to fabricate auxiliary sensors.

Electrochemical biosensors have been used to measure current flow during oxidation and reduction reactions. Three electrodes are connected to the potentiostat: the working electrode, reference electrode, and conductive or auxiliary electrode. When a reaction takes place, a potential is applied on the working electrode, and the resulting current is displayed in the form of a graph with respect to time. A redox couple forms in solution from the equilibrium concentration of the oxidation and reduction reactions. The Nernst equation [Eq. (1)] shows the link between potential and redox couple:

$$E = E_0 + \frac{RT}{nF} \ln \frac{C_{\text{oxi}}}{C_{\text{red}}} \tag{1}$$

where

E = potential

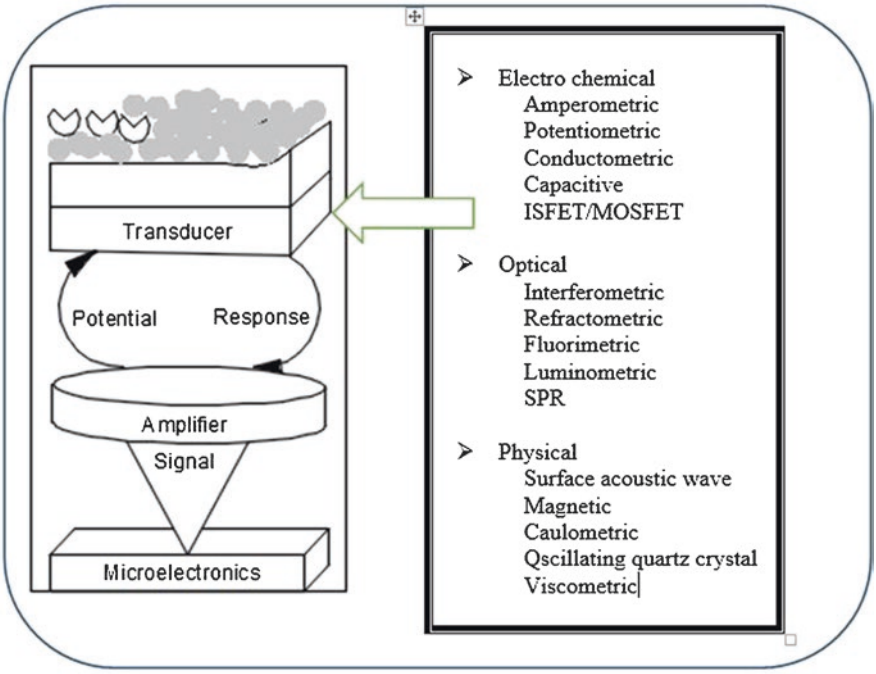

Fig. 3 Diagrammatic representation of an electrochemical biosensor (*ISFET* ion-selective field-effective transistor, *MOSFET* metal oxide semiconductor field-effect transistor)

E_0 = standard half-cell potential
F = Faraday constant.
C_{oxi} = oxidation concentration
C_{red} = reduction concentration
T = absolute temperature.

The advantages of the electrochemical sensor are fast response, ease of use, and high sensitivity: it is economical and a comparatively simple device (Ronkainen et al. 2010; Sin et al. 2014). Electrochemical biosensors are classified into four types: amperometric, potentiometric, impedance, and conductometric (Aizawa 1991).

2.1 Amperometric Sensors

Amperometric sensors are electrochemical biosensors that are used to measure current variations resulting from redox of electroactive materials when the same intensity of potential is applied. The amount of the variation of current corresponds to the concentration of the electroactive materials in solution. In amperometric sensors three types of electrodes are used: working electrode, reference electrode, and coun-

ter electrode. Carbon, platinum, and gold are used for the working electrodes and silver or silver chloride is employed as a reference electrode. The potential of the working electrode is controlled by a fixed electrode, the reference electrode. The counter electrode or auxiliary electrode with the reference electrode is employed for the measurement of current flow. During redox reactions, electrons are moving from the analyte to the working electrode. The flow of electrons is controlled by the analyte characteristics. If the working electrode stimulates a positive potential, the results show an oxidation reaction has taken place (Dzyadevych et al. 2008). In other words, a reduction reaction takes place when the working electrode stimulates negative potential. Various analytes can be combined with the amperometric sensor for medical applications (Hasan et al. 2014). One of the major disadvantages of the amperometric sensor is showing false current readings; this limitation can be rectified by coating the electrode with conducting polymers and altering the type of analyte (Reinhardt et al. 2002). Figure 4 shows an amperometric biosensor.

2.2 Cyclic Voltammogram

Figure 5 depicts a cyclic voltammogram of a bare gold electrode in phosphate-buffered saline. In cyclic voltammogram graphs, current (μA) and potential (V) are drawn on the *x*- and *y*-axes, respectively. The sweep is gradual and denotes the potential of the cathodic peak current and anodic peak current as positive and negative on the *y*-axis, respectively; the potential of the working electrode decreases at a definite rate when the resulting electron flow is noted with respect to time. In general, the resulting current is inverted at a certain potential. The graph trajectory rate is constant, and the origin and potential are known; then, the time can be effortlessly

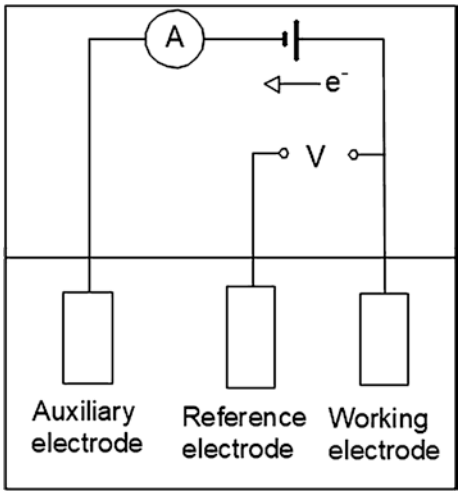

Fig. 4 Amperometric biosensor

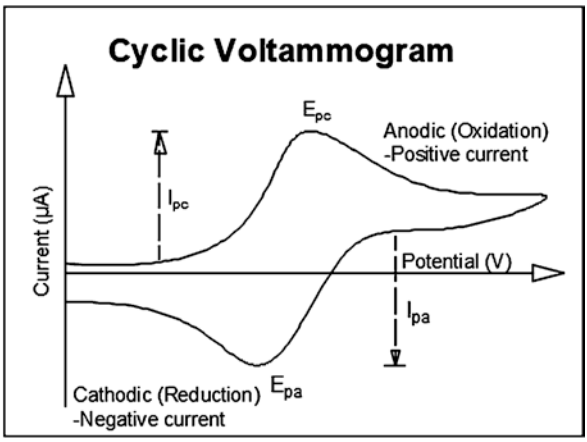

Fig. 5 Cyclic voltammogram of a bare gold electrode in phosphate buffer saline (E_{pa}, potential of the anodic peak current; $E_{pc,}$ potential of the cathodic peak current; I_{pa}, anodic peak current; I_{pc}, cathodic peak current)

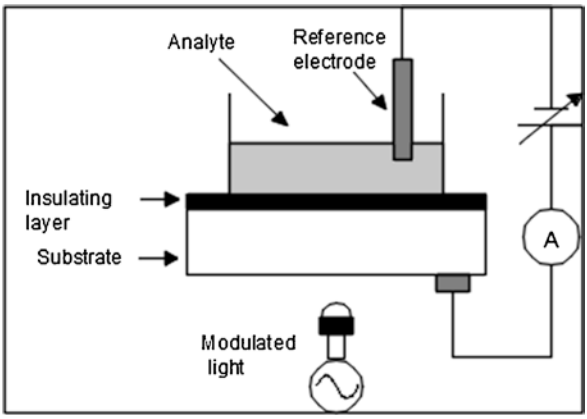

Fig. 6 Light-addressable potentiometric sensor (LAPS)

converted into potential and the current versus potential graph is drawn easily. The current is noted at the working electrode through a potential test against a constant reference electrode potential.

The cyclic voltammogram is a multipurpose device used to analyse reversibility of the electrochemical reactions and its dispersion-controlled properties. Beyond the sensing application, it can be using to identify the processes carried out at the electrode (Mabbott 1983).

2.3 Light-Addressable Potentiometric Sensor (LAPS)

Figure 6 shows a schematic diagram of the light-addressable potentiometric sensor (LAPS) (Hafeman et al. 1988; Owicki et al. 1994). It is a kind of chemical sensor with a semiconductor device that is used to envision the three-dimensional

distribution of ion concentrations in the solution. The sensor consists of an electrolyte-insulator-semiconductor (EIS) as shown in figure. A direct current bias voltage has passed over the EIS and the exhaust layer has formed between the insulator and semiconductor. The thickness of the exhaust layer depends on the concentration of ion and applied potential differences. The ion concentration-quantifying principle is the same as that of EIS capacitance sensors (Poghossian et al. 2001a, b). In LAPS, a photocurrent is induced by illuminating the semiconductor surface with modulated light. Unlike the EIS capacitance sensor, the LAPS sensor gives the mean value of the entire sensing surface, the quantifying area of the sensor defined by the illuminating surface. In a LAPS, the measured photocurrent value has been obtained by a laser beam focused on the sensing surface. The LAPS is also applicable as integrated multisensors, in which more than one measuring probe is used to the sensing surface by a light beam (Ermolenko et al. 2003; Schöning et al. 2005; Shimizu et al. 1994; Yoshinobu et al. 2005). The three-dimensional resolution is a significant factor in both electrochemical and multisensory applications. Three-dimensional resolution defines the smallest size of particles or elements that can be envisioned by the chemical sensor, and it restricts the concentration of the measuring point on the multisensor layer (George et al. 2000; Nakao et al. 1994; Sartore et al. 1992). The beam size and adjacent dispersion of photocarriers on the semiconductor surface have more influence on the three-dimensional resolution. The beam size is minimized by a one micrometer (1-μm) scale or is equivalent to the light wavelength with suitable focusing optics (Yoshinobu et al. 2004). The effect of light absorption coefficient and dispersion length is greater in lateral diffusion. More effort has been made by researchers to reduce the thickness of the silicon substrate for developing three-dimensional resolution of a chemical imaging and potentiometric sensor. Instead of minimizing the thickness of the sensor element, thickening of the semiconductor has been achieved by increasing the deposition rate and time from the vapor phase.

2.4 Conductometric Sensors

Conductometric sensors are generally bipolar instruments. A sample arranged with a selective layer in an adjacent surface is shown in Fig. 7.

In a conductometric sensor, the DC current is applied during measurement. The conducting samples sort the resistance from chemiresistors; the field of application may be a gas or a nonconducting liquid. Figure 7 shows chemiresistors and the corresponding circuit. The impedance is measured between the boundaries of conducting samples and selective layers, with AC current owing to the periodically altered exciting signals. The electrochemical sensor consists of complex arrangements of capacitance and resistance. The selective layer contains the primary interface between the conducting samples and the sensors. R_S, R_B, R_I, and R_C represent surface, bulk, interface, and contact resistance, respectively. The points 1 and 2 or 3 and 4 show equivalent resistance by combining all the resistances (Bard et al. 1980).

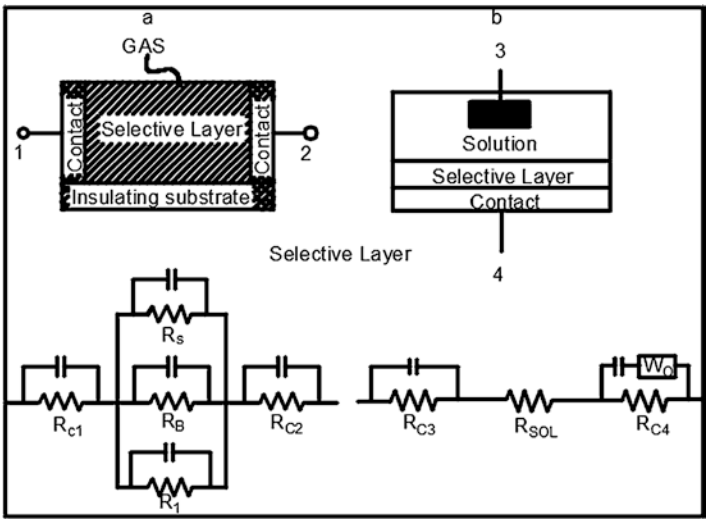

Fig. 7 Common chemiresistors and their corresponding circuits: (**a**) adjacent structure in which any of the five resistances can be controlled by chemical interaction; (**b**) impedimetric chemiresistor in which capacitance C_B is chemically modulated

In recent times, NA hybridisation and immunosensors have been detected by using micro- and nanofield effect sensors. One major advantage is that a reference electrode is not required; the cost is low, and it can be used for miniaturisation or for direct electrical pulses. Although these are specific advantages, sensitivity is less compared to other electrochemical sensors.

2.5 Electrochemical Impedance Spectroscopy

Electrochemical impedance is defined as resistance offered against the flow of electrical current in a circuit. The electrolyte solution, interfaces, and coatings are employed to measure the flow of ions in electrochemical impedance (Ianeselli et al. 2014). The impedance approach is very effective because it can move the test electron at higher frequency and mass movement at lower frequency (Bogomolova et al. 2009). During electrochemical reactions, measurement of impedance is done at an open circuit depending on which current flow occurs in an electrified boundary.

Electrons move from electrodes transversely to the electrified boundary (Fig. 8).

This method has a non-Faradaic component, which is written in the form of Eq. (2):

$$[\mathrm{O}] + n\mathrm{e}^- \rightarrow [\mathrm{R}] \tag{2}$$

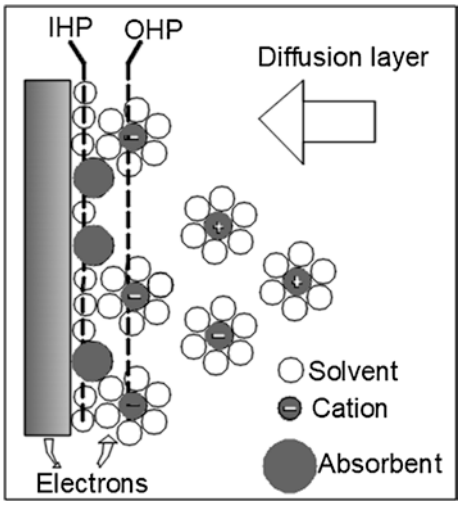

Fig. 8 The electrified boundary at which the electrode is negatively charged; counter cations are arranged in line along the electrified layer. *IHP* inner Helmholtz plane, *OHP* outer Helmholtz plane

where n denotes the number of electrons moved, O denotes oxidant, and R denotes reduction.

The activation barriers called polarisation resistance and uncompensated resistance are overwhelmed by electron movement across the boundary (Chang and Park 2010; Wolfbeis 2004). The rate of electron movement is defined by the mass movement of the reactant. It also depends on the depletion of the oxidant and the making of reductant close to the electrode surface. The mass movement of the reactants and the products give alternative impedance, which can be used to sense immunological binding measures such as antibody-binding occurrences on the surface of the electrode (Borisov and Wolfbeis 2008; McDonagh et al. 2008). The resulting in-phase and out-phase current reactions can be used for calculating capacitance and resistance in the circuit. Cell toxicology studies, cell movements, and morphology changes are monitored by this technology (Baronas and Kulys 2007).

3 Biosensor Application: Environmental Monitoring Biosensors

The use of biosensors in monitoring the concentrations of different contaminants present in the environment is an emerging field (Rinken 2013). Water, soil, and air are taken as major measurement areas for environmental monitoring. The major analytes identified are pesticides, heavy metals, herbicides, and phenolic compounds (Somerset 2011).

Biosensors for environmental monitoring consist of the analyte used for sensing biomaterials or chemical elements or combinations of these two (Serra 2011). The advantages of biosensors for environmental monitoring compared to other traditional

methods are (1) the data can be transferred easily, and (2) minimal test specimens are sufficient for pollution measurements. The biosensors used for environmental monitoring are generally optical (Akkaya et al. 2016; Baro et al. 2016; Fojta et al. 2016; Giovanardi et al. 2017) or electrochemical biosensors (Dey and Goswami 2011; Fojta et al. 2016; Martins et al. 2013; Xiao et al. 2016).

Table 1 shows the different biosensors for environmental monitoring.

The table displays the different contaminants, the responding elements in the biosensors, the physical transducers, and different applications. Optical biosensors have more advantages compared to other traditional analytical methods (Borisov and Wolfbeis 2008; McDonagh et al. 2008; Wolfbeis 2004). Higher sensitivity, very small size, and low cost are the major advantages of optical biosensors (Rogers 2006). Optical biosensors are classified into two types: label-free and label-based biosensors. In the label-free method, a response signal that has been created by the analyte is exposed to the transducer. In the label-based method, luminescence is employed to generate the optical signal and label. Figures 9 and 10, respectively, depict optical and electrochemical biosensors for environmental monitoring.

3.1 Heavy Metals

Heavy metals are dangerous environmental contaminants. Even though much less contaminating than other pollution sources, heavy metals are also harmful to human beings and the environment. Heavy metals are not eco-friendly. Copper, zinc, mercury, lead, and cadmium are some common heavy metal contaminants. Bacteria have been used as a sensing element for heavy metal detection in the environment. Bioluminescent protein is used as a cell biosensor.

Table 1 Biosensor for environmental applications (from Gieva et al. 2014)

Contamination	Biological responding element	Physical transducer	Applications
Pesticides	Antibody, enzyme, and microbe	Optical sensor, electrode	Water, soil, air
Herbicides	Antibody, enzyme, and microbe	Optical sensor, electrode	Water, soil, air
Dioxins	Microbe and slim mode	Optical sensor, electrode	Water, soil, air
Heavy metals	Enzyme, microbe	Optical sensor, electrode	Water, soil
Nitrogen compounds	Enzyme	Electrode	Water, soil, wastewater
Phenolic compounds	Enzyme, microbe	Optical sensor, electrode	Water, soil

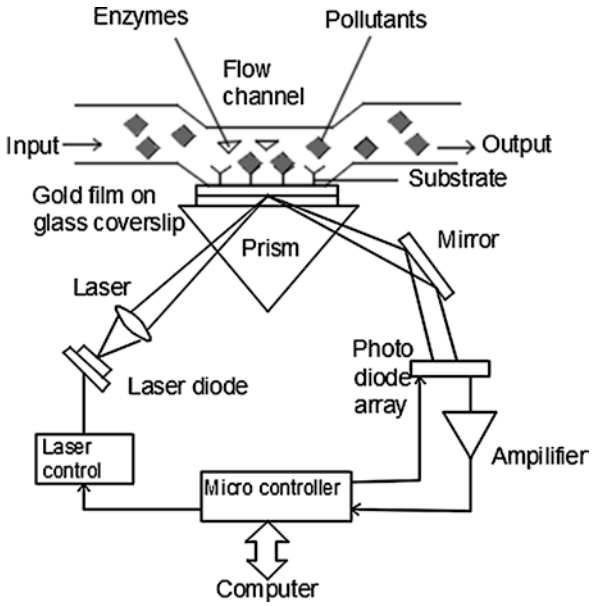

Fig. 9 Optical biosensor for environmental monitoring

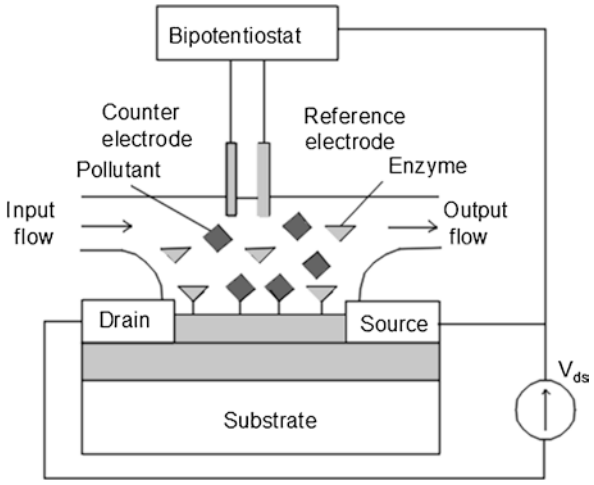

Fig. 10 Electrochemical biosensor for environmental monitoring

The enzyme technique has also been used to find heavy metal ions; in this regard, more enzymes have been employed for the detection of ions. Table 2 contains biosensors for the detection of heavy metals.

3.2 Nitrites

Nitrites are generally utilized to treat plants for protection from insects. However, this method is not suitable for human beings or environments; nitrites are very harmful to the human haemoglobin system. Cytochrome *c* protein is used as the biosensitive element in amperometric biosensors for detecting nitrites. This biosensor is highly sensitive and constant. Table 3 shows the determination of nitrites by two different techniques and sensing elements.

3.3 Herbicides

Herbicides are used to destroy weed plants and thus may damage crops. The toxicity of the herbicides has a wide range. Some herbicides are deleterious to bird populations and some prevent photosynthesis. Phenylureas and triazines are the biosensing elements utilized to detect herbicides in the environment. Two methods, amperometric and bioluminescence, are used to detect these herbicides. Table 4 shows the biosensors used for detection of herbicides.

Table 2 Biosensors for heavy metals detection (from Gieva et al. 2014)

Substances	Sensing biocatalyzer	Technique
Mercury, cadmium	Urease enzyme and microbe	Electrochemical
Cadmium	DNA	Optical, electrochemical
Cadmium, copper, lead	Sol-gel-immobilized urease	Electrochemical
Zinc, copper, cadmium, nickel	Enzyme	Optical
Mercury, lead	DNA	Optical
Copper	Fluorescent protein	Optical

Table 3 Biosensors for nitrite detection (from Gieva et al. 2014)

Substances	Recognition biocatalyzer	Technique
Nitrite	Cytochrome *c*	Amperometric
	Viologen mediator	Electrochemical

Table 4 Biosensors used to detect herbicides (from Gieva et al. 2014)

Analyte	Type of interaction	Recognition biocatalyzer	Technique
Dichlorofenoxiacetic	Immunoanalysis	Acetylcholinesterase	Amperometric
Diuron, Paraquat	Biocatalytic	Cyanobacterial	Bioluminescence

Table 5 Biosensors for dioxin detection (from Gieva et al. 2014)

Analyte	Type of interaction	Recognition biocatalyzer	Technique
Dioxin	Immunoanalysis	Cell	Biomimetic
Dioxin-like polychlorinated biphenyls	Immunoanalysis	Cell	Biomimetic

3.4 Dioxins

Dioxins are organic by-products from different industries. Dioxin contamination is present in water and soil. The waste discharged from industries travels long distances by wind, rivers, and seawater. Dioxins are reduced by various steps, including a recycling process. Table 5 shows biosensors for detection of dioxins.

4 Conclusion

Different types of electrochemical biosensors, namely, amperometric, cyclic voltammogram, potentiometric, conductometric, and electrochemical impedance spectroscopy, have been presented here. Environmental monitoring is presently an emerging trend; hence, the detection of different contaminants in air, soil, and water has been discussed in detail. The detection of different contaminants, such as heavy metals, herbicides, nitrites, and dioxins, is reported. The two methods of biosensors, optical and electrochemical, are discussed with diagrammatic representation.

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