Environment Remediation Tools: Chemosensors and Biosensors

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J. Brindha, Milind Shrinivas Dangate, and M. M. Balamurali

Abstract

Pollution is one of the major problems persisting in our environment causing an increase in the morbidity and mortality, which ultimately affects the economic growth of a nation. Therefore, environment quality sensing tools have become inevitable in everyday life. Though several tools are reported in the scientific literature and much more are available in the market, this field of research on environment sensors has always been on its priority. Simplicity, cost-effectiveness, reliability, and stability are the challenges that decide the performance of sensors. This chapter will discuss achievements made toward various chemosensors and biosensors that can pave the way toward environment remediation.

Research on environment sensors is one of the evergreen areas with contributions from transdisciplinary researchers round the world. Though technological advancements and industrial developments are happening at a daunting rate, on one hand, the hazards posed by them on the environment are increasing at a much faster rate. Therefore, it becomes necessary to develop such a tool to meet the challenges ahead in food, healthcare, and environmental sectors. With the emergence of highly infectious and/or antibiotic-resistant pathogens, advancements in biosensors are made with the need for quicker detection/treatment and ease of use in diagnostics. This chapter deals with various kinds of sensors available for the detection of pathogens and toxic chemicals, with their classifications based on the type of transducer used, along with the recent findings in each type.

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R. Prasad (ed.), *Environmental Pollution and Remediation*, Environmental and Microbial Biotechnology, https://doi.org/10.1007/978-981-15-5499-5_10

Keywords

Chemosensor · Biosensor · Pathogen detection · Piezoelectric

10.1 Introduction

In this modern era, sensors have become an inevitable device. With the explosion in technological advancements and industrial developments, the morbidity and mortality rates are also steeply rising. Therefore, it is mandatory to monitor our environment and to sustain a healthy life. Sensing involves recognition of a particular entity such as matter, energy using a specialized device termed sensor. A sensor is built with a selective sensing element coupled to a transducer which helps in converting the changes observed into a readable output signal such as electrical, magnetic, or optical, with its magnitude directly proportional to quantity sensed. Sensors are applied in human lives in various ways including medicine/health in drug/pathogen detection and also in industries like automobiles, electronics, and waste management. It is thus significant to develop sensors, and to date, several endeavors are made to move further in this area of research.

There are a number of transducers with different operating principles such as fluorescence (Li et al. 2015), surface plasmon resonance (Liu et al. 2016a; Rifat et al. 2015), colorimetric (Taneja and Tyagi 2007), cantilever (Fritz 2008)/piezoelectric crystal/quartz crystalline microbalance (Farka et al. 2013; Fawcett et al. 1988), and electrochemical mode comprising of amperometric, voltammetric and impedimetric (Chen and Shah 2013; Wan et al. 2011), and the immuno−/biochemical sensors (Menti et al. 2016; Sign and Sumana 2016). Detection of lower concentrations of target analytes such as nucleic acids or other analytes in the sample mixture has been a daunting task which is addressed by means of concentrating the sample using various methods including polymerase chain reaction and use of magnetic beads, suitable nanoparticles, or other labels. In general, a typical sensor solely relies on the selectivity of recognition element/receptor, specific recognition of an analyte, sensitivity and specificity of the detection process, enrichment of response signals, and transmission of output readable signals using the transducer.

The development in science and technology yielding incredible findings has led to increased vulnerability of all life forms to numerous toxins and infectious pathogens, which compelled the researchers to broaden the range of sensors to safeguard human lives by developing simple sensors, in particular chemosensors and biosensors targeted toward hazardous chemicals/pesticides, clinical diagnosis (Yanase et al. 2014), food industry (Scognamiglio et al. 2014), and water and environmental quality measures/monitoring (Teo and Wong 2014; Bereza-Malcolm et al. 2014; Singh et al. 2020). Since the period of the 1980s, there is an extensive growth and development of the various chemosensors, initiated by de Silva and Czarnik, known to be fathers of modern chemosensors. Chemosensors are essential for the detection of environmentally hazardous/toxic chemicals, cations, anions, neutral molecules, and physiologically important molecules/ions which are in

continuous development along with new advancements in technologies for microscopic imaging. Among biosensors, the classical techniques like cell culture, cell counting, and plating can detect the presence of specific pathogens (Monis and Giglio 2006; Gracias and McKillip 2004), yet in a longer time period for completion of the detection process. It is thus certainly necessary to expand the biosensor tools with easier, sensitive, and rapid detection. In this chapter, we will be focusing on two major sensors in demand, namely, chemosensors and biosensors, along with their classifications, advantages, limitations, and interesting recent findings.

10.2 Chemosensors

There is a substantial increase in the design and development of chemosensors in the last few years. Exposure to various toxic substances, hazardous chemicals, food additives/adulterants, pesticides, industrial effluents, etc. has imposed the need for expansion of chemosensors. Parallel advancements in the field of fluorescence/colorimetric chemosensing have induced the progress of chemosensor research. Chemosensor design and development has been interdisciplinary including synthesis of organic/inorganic molecules combined with different analytical techniques. These are designed to have a high sensitivity and specificity that allow them to interact selectively with a specific target analyte present in different complex environments and are used in clinical diagnostics and detection of agricultural, industrial, or environmental pollutants, making them significant for health and safety of all life forms.

Chemosensors, like any other sensors, require the generation of a signal on binding for detection. Selection of a suitable signal transduction method is vital to achieving success in the sensing process. Commonly employed strategies in chemosensors include fluorescence, electrochemical, colorimetric, and surface plasmon resonance (SPR). Every method has its own advantages and disadvantages based on the requirements to be met, as given below with significant findings.

10.2.1 Fluorescence-Based Chemosensors

Fluorescence is one of the most frequently used signal transduction methods with promising sensing applications, as it serves as a highly sensitive technique, solely due to the emission wavelength which is usually longer compared to the excitation wavelength and the need for low analyte concentrations ($>10^{-6}$ M) for signaling. A fluorescent sensor is more like a molecular machine with the ability to signal the presence of analytes like ions/molecules. The two main parts required for designing of fluorescent sensors includes a signaling moiety or the fluorophore and a receptor that serves as a recognition molecule. The signaling molecule serves as a signal transducer, which converts the data obtained (recognition event) into an optical signal response. The recognition moiety is accountable for attachment to an analyte specifically and selectively in an efficient manner. This binding relies on the ligand

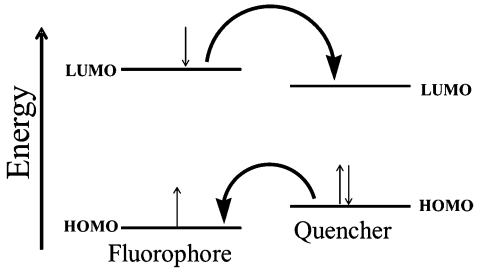

Fig. 10.1 Mechanism of energy transfer by an electron exchange process

structure, characteristics of the target analyte such as a cation or anion, or organic molecules' structure such as drug candidates. Apart from this, it is also essential to consider the nature of the solvent including polarity, pH, and ionic strength, which can affect the capability of the receptor to detect and bind the target analyte.

There are several metal ions that play a significant role in our routine life, including sodium (Na^+), calcium (Ca^{2+}), potassium (K^+), and zinc (Zn^{2+}). However, certain heavy metal ions like lead (Pb^{2+}), cadmium (Cd^{2+}), and mercury (Hg^{2+}) are highly toxic and lead to severe health and environmental issues. It is necessary to develop tools like chemosensors to detect these toxic metals/chemicals. The most typical fluorescent sensor is based on photoinduced electron transfer (PET) developed initially by de Silva et al., for sensing various cations, anions, and neutral molecules (Silva and NimaláGunaratne 1996). This is shown schematically in Fig. 10.1. Recently, a novel pyrene (Pyr1-2)-based fluorescence chemosensor for specific detection of Hg^{2+} was reported (Gao et al. 2018). These fluorescent probes Pyr1 and Pyr2 having a side chain of thioacetal moiety with carboxyl and hydroxyl group, respectively, exhibit fluorescence response specifically toward Hg^{2+}, following intramolecular charge transfer mechanism. In the presence of Hg^{2+}, the thioacetal group of Pyr1-2 probes was observed to convert into aldehyde group. Detection limits for these pyrene probes were found to be lower than 1.80 nM. For sensing or monitoring of trace amounts of Fe^{3+} in real water specimens and also for intracellular imaging, for detecting Fe^{3+} in live human breast cancer cells (MCF-7), two fluorescent chemosensors derived from pyridine and rhodamine B conjugates were developed. These were found to possess lower detection limits and lesser interference of metal cations (Song et al. 2019). A benzoindo-croconine-based colorimetric and fluorescent chemosensor (Wang et al. 2016a) was developed for the detection of metal ions, $Fe^{3+}/Cu^{2+}/Ag^+$ ions. It exhibited sensitivity and high selectivity to Fe^{3+}, Cu^{2+}, and Ag^+ ions in ethanol/water (4:1, v/v). Both color change (from brown to pale yellow) and decrease in fluorescence intensity or quenching of fluorescence were reported with increase in the concentration of Fe^{3+}, with complete quenching at a concentration of 0.4 mM (Fe^{3+}). Same way, the fluorescence of the benzoindo-croconine was quenched upon increase in the concentration of Cu^{2+}/Ag^+ ions. A new fluorescence-based chemosensor was developed for sensing organophosphorus pesticides, based on their interaction with a luminescent europium (Azab and Kamel 2016) complex by electroanalytical and fluorescent studies. These

pesticides were found to have quenching effects on the characteristics emission peak for europium (III) ($\lambda = 614$ nm). Selectivity of this chemosensor was also ensured by studying the possible interferents, and also, the quenching mechanism was of dynamic type for the pesticides chlorfenvinphos, diazinon, and isofenphos, while it is static for azinphos ethyl.

Fluorescence detection in chemosensors is known for its sensitivity and wide usage, though it has limitations as well. The major one is its sensitivity to the surroundings, including the solvents, temperature, and interfering species. It needs designing of one or more fluorophores that respond with a change in fluorescence on binding, and it is important to maintain the photostability of these fluorophores used. In this regard, organic dyes are not so preferred, while the metal complexes and quantum dots possess good stability and fluorescent intensity.

10.2.2 Electrochemical Chemosensors

A commonly exploited method of detection in chemosensors is electrochemical detection. There are different ways to detect species using electrochemical methods that include ion-selective electrodes (ISEs) for sensing toxic pollutants and pH analysis in water test samples and a general research technique of cyclic voltammetry (CV) that helps in the study of thermodynamics and kinetics of electron transfer reactions apart from sensing the presence or concentration of a specific target. These methods change the physicochemical information of a specific analyte like a molecule or ion, into appropriate electrical signal possessing particular potential/current or both that could be displayed as the output according to the chemical information. The electrochemical detection is based on a chemical or physical change induced by the target analyte interacting with the electrode, on its surface, or in particular the interfacial area between the electrode and its electrolyte. These electric signals are monitored as either potential/current change or both, based on which detection is done called *potentiometry*, *amperometry* (also called *coulometry*), and *voltammetry*, respectively. Ion-selective electrodes (ISEs) are classic potentiometric sensors that help in converting the target ion's concentration into a readable output potential signal response. Membrane-based ISEs with ion-selective conducting membrane leading to an electric field generation and hence potential difference are available in market; however, most of them detect only the inorganic ions. Ion-selective membrane can also be constructed by exclusive coating of an electrode surface with an ion-selective agent. These coating-based ISEs are easy to develop and possess high selectivity and rate of response. Another new electrode includes the ion-selective (or sensitive) field-effect transistors (ISFETs), which belong to a broader class of chemically modified field-effect transistors (CHEMFETs) which are beneficial especially in equipment miniaturization and gives more data for enhanced reliability. There have been several research in the past two decades, with the aim to develop electrochemical-based molecular probes or sensors with high specificity for cationic, anionic, or neutrally charged analyte molecules (Beer 1996; Beer et al. 1999a).

Electrochemical detection is mainly used for specific target analytes that are charged, such as ions, which can undergo electron transfer reactions on an electrode. The detection of neutral molecules using electrochemical method has been a hard task. The integrated chemical processes involving a redox-responsive receptor which specifically recognizes and electrochemically detects the signaling molecule are known as electrochemical molecular recognition (Beer et al. 1999b). By means of standardized molecular imprinting procedures, a synthetic polymer receptor film specific for the cancer biomarker, neopterin, was designed and developed as a recognition unit of a potentiometric chemosensor (Sharma et al. 2016). This chemosensor worked by measuring the open circuit potential changes that occurred due to selective binding/sensing of neopterin by the polymer film. It served the purpose of detecting neopterin in serum samples with a detection limit of 22 μM. A n-type chemical doping of conducting polyaniline and the formation of Schottky barrier diode in a chemosensor (Ameen et al. 2016) paved way for electrochemical detection of hydrazine benzene chemical, with high sensitivity and detection limit of 5.11 μM. Chemosensors employing transducers coated with D- or (L-phenylalanine)-templated molecular imprinted polymer films (Iskierko et al. 2017) following extended-gate field-effect transistors were also developed for enantioselective determination of (D- or L-) phenylalanine. These were found to have a detection limit of 13 μM. Differential pulse voltammetry of two ligands made up of the diphenyl derivatives, 3-(2,4-dinitrophenoxy)phenol (L1) and 3-(2-nitrophenoxy)phenol (L2), was found to exhibit complete quenching of anodic peaks at 1.16 V for L1 and 1.34 V for L2 on adding one equivalent fluoride ions (Sharma et al. 2015). Thereby, both these ligands serve as a voltammetric chemosensor for sensing fluoride ions.

10.2.3 Colorimetric Chemosensors

Colorimetry is different from fluorescence in the working principle that they work with respect to absorption with less sensitivity relative to the emission employed in fluorescence. This method of sensing is not limited by stringent requirements of fluorophore design; instead, there are several dyes available for sensing applications. There are two common signal motifs to be considered: (i) a change in absorbance at a specific wavelength, thereby observing a color appear or fade, or (ii) monitoring the maximum absorption wavelength to change, such as initial color changes into a new second color. Sessler and Miyaji reported (Miyaji and Sessler 2001) several commercially available molecules for use as colorimetric anion sensors, including l-leucine-4-nitroanilide, 1,2-diaminoanthraquinone, 1,8-diaminoanthraquinone, 1-(4-nitrophenyl)-2-thiourea, 4-nitrophenol, 4-nitroaniline, 4-nitro-1,2-phenylenediamine, alizarin, 2,2-bi(3-hydroxy-1,4-naphthoquinone) and Direct Yellow 50.

A recent finding includes a synthesis of a coumarin derivative with benzothiazole Schiff's base structure that detects cyanide anions (CN^-) by nucleophilic addition mechanism (Fig. 10.2) (Wang et al. 2016b). This detection technique involves visible colorimetric changes, where there is a color change from reddish brown to

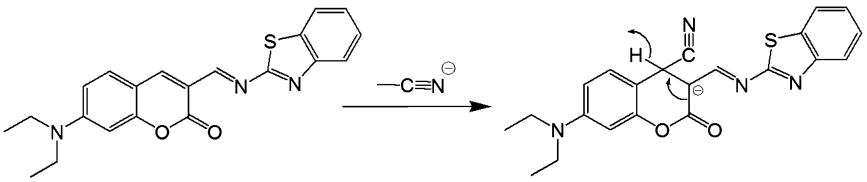

Fig. 10.2 Colorimetric sensing of cyanide ions by intramolecular charge transfer mechanism

white on the addition of cyanide in the test paper. The limit of detection of this compound for the ions, CN^-, was found to be 0.0071 μM. Also, two chemosensors have been developed from the derivatives of N-butyl-3,6-disubstituted carbazole having nitroazobenzene and nitrobenzene in each, for sensing the two strong basic anions (F^- and CN^-) where selectivity is based on polar nature of solvent and acidity and basicity of binding unit and anion, respectively (Tummachote et al. 2019). The sensing was visible in the case of both the sensors, mainly due to the intramolecular charge transfer transition with the removal of protons at the binding site. The sensor with nitrobenzene moiety was proved to have a relatively low detection limit with more stability and selectivity for the targeted anion. A simple dual chemosensor with a highly specific Schiff base derivative, an organic ligand molecule, 5-chloro-2-[(1E,2E)-3-(4-dimethylamino phenyl allylidene amino)]phenol, that acts as a colorimetric as well as surface plasmon resonance-based chemosensor for the sensing of Cu^{2+} ions (Peralta-Domínguez et al. 2016) in spite of various other possibly interfering metal ions including Cd^{2+}, Co^{2+}, Cr^{2+}, Fe^{3+}, Mg^{2+}, Ni^{2+}, Hg^{2+}, Pb^{2+}, Mn^{2+}, and Zn^{2+}. It has a lower limit of detection for copper ions of 1.25×10^{-7} M as well as a lower colorimetric limit of detection of 2×10^{-6} M through naked eyes.

10.2.4 Surface Plasmon Resonance (SPR) Chemosensor

Sensors using the optical property of the surface plasmon resonance (SPR) effect are of main interest due to their ultrahigh sensitivity and nanomolar ranges of detection limits. The mechanism of transduction of response signals based on the variation of the refractive index is an effective method to study the binding between a receptor/ligand immobilized upon a metallic surface and an analyte or the targeted solid substrate introduced into the solution in contact (Patching 2014). These sensors have several other advantages that include being label-free, the compatibility with aqueous media, ability to form miniaturized sensor tools, and integration with other probes such as fiber optics (Tabassum and Gupta 2015), electrochemical setup (Panta et al. 2009), or signal concentration with gold nanoparticles (Chang et al. 2011).

Designing highly sensitive SPR sensors depends on the formation of a gold layer adequately with the attachment of specific stable receptors possessing high affinity and selectivity for the specific analyte. The availability of ubiquitous host–guest or

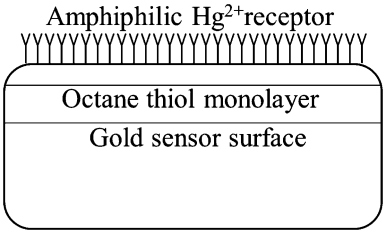

Fig. 10.3 Bilayer sensor surface for the detection of mercuric ions by surface plasmon resonance method

ligand–receptor recognition moieties such as antibody–antigen has been exploited in SPR sensors for monitoring the binding reactions among biological substrates (Couture et al. 2013). Sensing of metal ions in aqueous media is challenging. It is significant to note that SPR sensors are usually designed with a gold surface fixed and a monolayer of polymer fixed with molecular receptors that specifically bind the target (Jung et al. 2013). Similarly, electrodes with gold coatings are in use for the electrochemical detection of mercury (Martín-Yerga et al. 2013). In both cases, the detectors' efficiency is rather limited due to slow diffusion/restricted accessibility of analytes to the recognition sites. Other issues include low chemical stability, film adhesion, and high film resistivity. In this aspect, self-assembled monolayers (SAMs) of specific molecular receptors/biomolecules is emerging as an alternative (Sánchez et al. 2014). The lower chemical stability of self-assembled monolayers (SAMs), for example, thiol group oxidation and the nonspecific binding with impurities of the surface leading to defects/pinholes in the SAMs (Vericat et al. 2010). Apart from SAMs, Langmuir–Blodgett (LB) films containing large or branched amphiphilic chelators are used, which are found to have lower stability as they get leached out from the gold surface during the course of analysis (Prabhakaran et al. 2007). It was demonstrated that the combination of the Langmuir–Blodgett and self-assembled monolayers techniques (Turygin et al. 2006) resulted in sensitive and selective metal-sensing SPR chips with increased stability and homogenous orientation of the binding moieties toward the solution. This SPR bilayer methodology was applied for the direct detection of trace levels of Hg^{2+} cations. An interdigitated bilayer was developed step by step by forming self-assembly of a monolayer of octane thiol on a gold substrate. It was followed by another monolayer containing amphiphilic, highly selective mercury receptor (1,8-diamino-9,10-anthraquinone derivative) (Ermakova et al. 2013) using the Langmuir–Blodgett technique (Fig. 10.3). This resulted in a new approach for sensing metals by SPR chips. The bilayer technology used here serves the purpose of selectively quantifying mercury(II) in aqueous solutions with high sensitivity at the range of sub-nanomolar (0.01 nM) with the significant coordination properties of the amphiphilic chemosensor.

10.2.4.1 SPR Integrated Optical Fiber Approach

A novel optical chemosensor for online detection of two chemical markers, dibenzyl disulfide and furfuraldehyde, present in the insulating mineral oil of transformers, was developed (De Maria et al. 2018). It was designed based on surface plasmon

resonance, fixed in a plastic optical fiber that acts as a cost-effective, optical sensing platform along with a molecularly imprinted polymer layer specific for the chemical marker, placed in contact with a thin film of gold. These specific molecular imprint polymers on the gold film form a distinct dielectric medium with optical properties like the refractive index. That would influence the sensing, upon the interaction of the target analyte to the receptor polymers imprinted on the gold film. Dibenzyl disulfide (DBDS) is known to be accountable for the corrosiveness of the mineral insulating oil used for transformer (De Maria et al. 2018). Thus, it is of paramount importance to determine its concentration in mineral oil for diagnostic purposes of the transformer. Also, furfuraldehyde, one among the major byproducts formed during degradation of the insulation paper in a transformer upon overheating. Its presence in the transformer's insulation oil could verify the status of the solid insulation in transformers, which could otherwise become an environmental hazard to many lives.

10.3 Biosensors

Biosensors have significant roles in human health care in the diagnostic procedures to find infections and to prevent epidemics by means of rapid detection techniques (Brindha et al. 2018a; Ellwanger et al. 2017; Du and Zhou 2018; Kaushik et al. 2017). They are analytical devices that work based on the recognition of biological target molecules such as microorganisms, peptide molecules, nucleic acids, proteins, or any biomolecule. The results from an ideal biosensor should be reproducible, sensitive, selective, stabile, and linear (Bhalla et al. 2016). Biosensors possess a biological targeting element that can selectively bind/interact with the target analytes and delivers an output signal depending on the extent of interaction which is then converted to a readable format by a transducer before being transferred to a reader device. The most commonly used biosensors include fluorescent label-based biosensors, surface plasmon resonance biosensors, piezoelectric biosensors, electrochemical biosensors, and biochemical/immuno-biosensors.

10.3.1 Fluorescent Label-Based Biosensor

Fluorescent labeling method (Li et al. 2015) works by energizing a fluorophore at a particular wavelength and observing the photons emitted at another wavelength in a time scale of microsecond. The common fluorophores such as calcein blue, quantum dots (Resch-Genger et al. 2008), carbon dots, and fluorescent diacetate are mostly employed as labels for signal recognition/probe molecules, when the targeted biomolecule under detection is in trace amounts in the sample. Calcein blue is one of the most commonly used blue fluorescent labels that possess the ability to detect and quantify pathogens (Sankaranarayanan et al. 2015). Here, the siderophores released by the bacteria can chelate Fe^{2+} from the iron-bound calcein blue to restore its fluorescence, which is further utilized for detecting the iron chelators quantitatively

and hence the pathogenic bacterial detection in a short period of 7–8 hours. This method has been employed for detecting and quantifying Gram-positive bacteria including *Staphylococcus aureus* (Dale et al. 2004; Zawadzka et al. 2009) and Gram-negative bacteria such as *Proteus* species and *Mycobacterium tuberculosis* (Wells et al. 2013; Himpsl et al. 2010; Adler et al. 2014).

Specific biological recognition elements such as antibodies are used in conjugation fluorescent labels for pathogen detection (Yang and Li 2006). Hu et al. have employed specific antibodies labeled with fluorescein isothiocyanate to detect surface antigens of *Escherichia coli* O157:H7 with (Hu et al. 2016). The sensor surface-bound antibodies capture specific bacterial cells followed by the detachment of fluorescein. This enhances the fluorescence intensity which is then utilized to quantify bacterial cells. The detection limit using this method was found to be 3 cfu/ml. Quantum dots are yet another optical probe that can be tuned for fluorescence emission energy by modifying their sizes and chemical constituents. Simultaneous multiple-pathogen detection, of pathogens like *E. coli* O157:H7 and *Salmonella* detection, is also reported (Yang and Li 2006), using semiconductor quantum dots with multiple wavelengths: 525 nm and 705 nm as labels for their respective specific antibodies attached by means of streptavidin and biotin conjugation. Quantum dots are known to be twentyfold more intense and hundredfold relatively resistant to photobleaching as compared to other fluorescent labels/probes such as organic dyes (Vinayaka and Thakur 2010). It also has its limitations like toxicity, solubility issues, and low quantum yields (Shen et al. 2012). Like quantum dots, carbon-based nanomaterials also possess photoluminescence features (Davis et al. 1998; April et al. 2018) that are exploited for enrichment of pathogens for detection (Deng et al. 2008; Srivastava et al. 2004; Upadhyayula et al. 2009; Elkin et al. 2005). Yang et al. used anti-*S. aureus* antibody conjugated with carbon dots trapped within organosilica nanocapsules for sensitive detection of *S. aureus* (Yang et al. 2018). By using carbon dots, the fluorescence signals were enhanced 2 times as compared with other fluorescence-based immunoassays. This method resulted in the detection of *S. aureus* in the range of 1–200 cfu/ml and can be extended to other pathogens also.

10.3.1.1 Fiber Optic-Based Biosensors

Biosensors equipped with fiber optics are found to work with fluorescence-based labels using an optical transmitter for target detection and transmitting the fluorescent signals to a photodetector where it gets converted into electrical signals. Based on the waveguide patterns (Banica 2012), they can be classified as planar and cylindrical waveguides (Fig. 10.4).

Simultaneous multiple detection of *Listeria monocytogenes*, *E. coli* O157:H7, and *S. enterica* (Ohk and Bhunia 2013) was made possible with a multiplex fiber optic biosensor using waveguides coated with streptavidin and specific antibodies tagged with Alexa Fluor 647. A lower limit of detection of 10^3 cfu/ml was reported for all the above mentioned pathogens displaying negligible cross-reactivity. The detection of cell number differences of *E. coli* present in the sample (Maas et al. 2018) was determined by Maas et al. employing an optical fiber-based biosensor

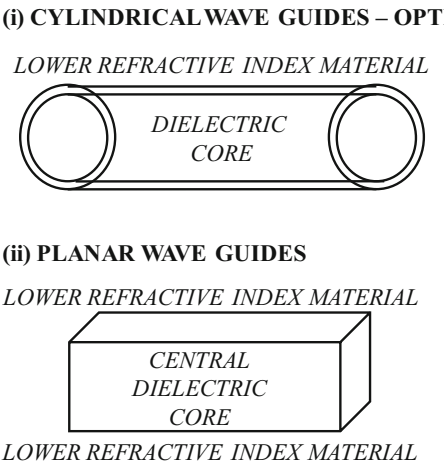

Fig. 10.4 Illustration of two types of optical waveguides based on configuration: (*i*) cylindrical waveguides and (*ii*) planar waveguides

where the polyclonal antibodies specific for *E. coli* are tagged with fluorescent secondary antibodies that are fixed to borosilicate glass fibers priorly treated with silane for the output signal. A photodiode placed at one terminal of the glass fiber monitors the optical changes taking place upon interaction with *E. coli*, the consequent changes in optical emission signals, the refractive index of glass fiber, and eventually total internal reflection. This happens to be a simple and portable biosensor that requires improvement in sensitivity.

10.3.2 Surface Plasmon Resonance Biosensors

The real-time and label-free sensing of bioanalytes was achieved with surface plasmon resonance-based biosensors. The optical phenomenon employed here is accompanied by alteration of surface plasmon wave following the changes on the sensor surface (mostly made of metals such as gold, silver, or copper) upon binding of the target analytes with specificity (Homola 2003).

In this method of sensing, a prism-coupled system is employed as depicted in Fig. 10.5 (Brindha et al. 2018b; Pi et al. 2016). The difference in signal observed in this type of sensing is attributed to the alterations in the interfacial refractive index at the top upon interaction with biomolecules.

Direct detection of *Campylobacter jejuni* was achieved with a sensor surface made of a gold chip which was coated with polyclonal antibodies specific to *C. jejuni.* This type of direct biosensing of *C. jejuni* resulted in a relatively higher limit of detection of 8×10^6 cfu/ml (Masdor et al. 2017). In order to improve the detection limits, the sandwich assay was developed that resulted in detecting as low as 4×10^4cfu/ml. This proved as an efficient and alternate method to replace the traditional enzyme-linked immunosorbent assays with a limit of detection of 10^6–10^7 cfu/ml.

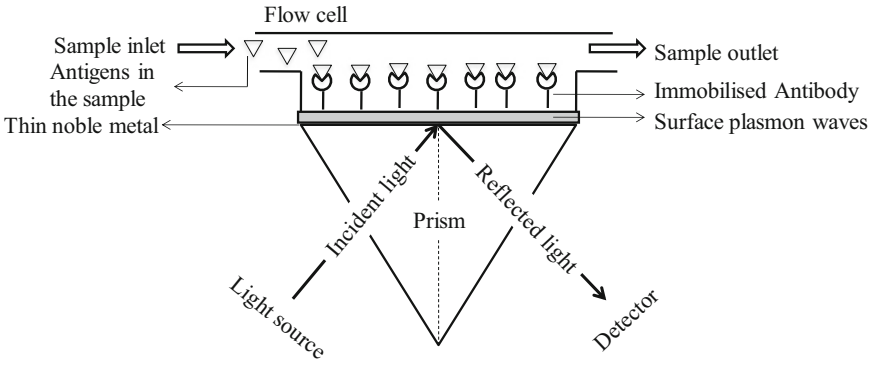

Fig. 10.5 Schematic representation on the construction and working principle of a surface plasmon resonance biosensor

10.3.2.1 Integrated Surface Plasmon Resonance Biosensors

Integration of two techniques has always yielded good results. Likewise, surface plasmon resonance accompanied with other detection techniques or signal enrichment tools including fluorophore labels, immunolabels, magnetic nanoparticles, and polymerase chain reactions are proved to enhance the sensitivity and decrease the detection limit.

Surface plasmon resonance-based biosensors with increased sensitivity were obtained by combining with immunolabels. Such sensors have been developed for detecting *Salmonella* at 10^3cfu/ml in food samples (Farka et al. 2016). It was developed by immobilizing sensor chip surface with capture antibodies with high specificity for *Salmonella* species in the test sample along with secondary antibody conjugation with horseradish peroxidase enzyme. Similarly, the use of sandwich immunoassay in surface plasmon resonance biosensors with sample enrichment using specific antibodies bound to iron oxide nanoparticles followed by magnetic isolation of these pathogenic immunocomplexes exhibited high sensitivity with a lower detection limit of 14 cfu/ml (Fig. 10.6) (Liu et al. 2016a). Here, the chip is immobilized polyclonal antibody for *Salmonella* detection using the specific immunomagnetic nanoparticles as shown in Fig. 10.6. These nanoparticles also amplify the signals by altering the refractive index differences for specific targets. DNA-immobilized surface plasmon resonance biosensors were also established to overcome the issues in the production of specific antibodies (Arya et al. 2011). A gold chip biosensor was developed with carboxylated dextran immobilized on its surface, with a complex of streptavidin/biotinylated oligonucleotide (single-stranded) probes on top (Zhang et al. 2012). The probe hybridizes with a specific and complementary, highly conserved gene of pathogen in the given sample. It had a limit of detection of 10^2 cfu/ml with detection time of 4.5 hours. The regeneration ability of the sensor surface for a minimum of 300 assay cycles makes it a cost-effective pathogen tool.

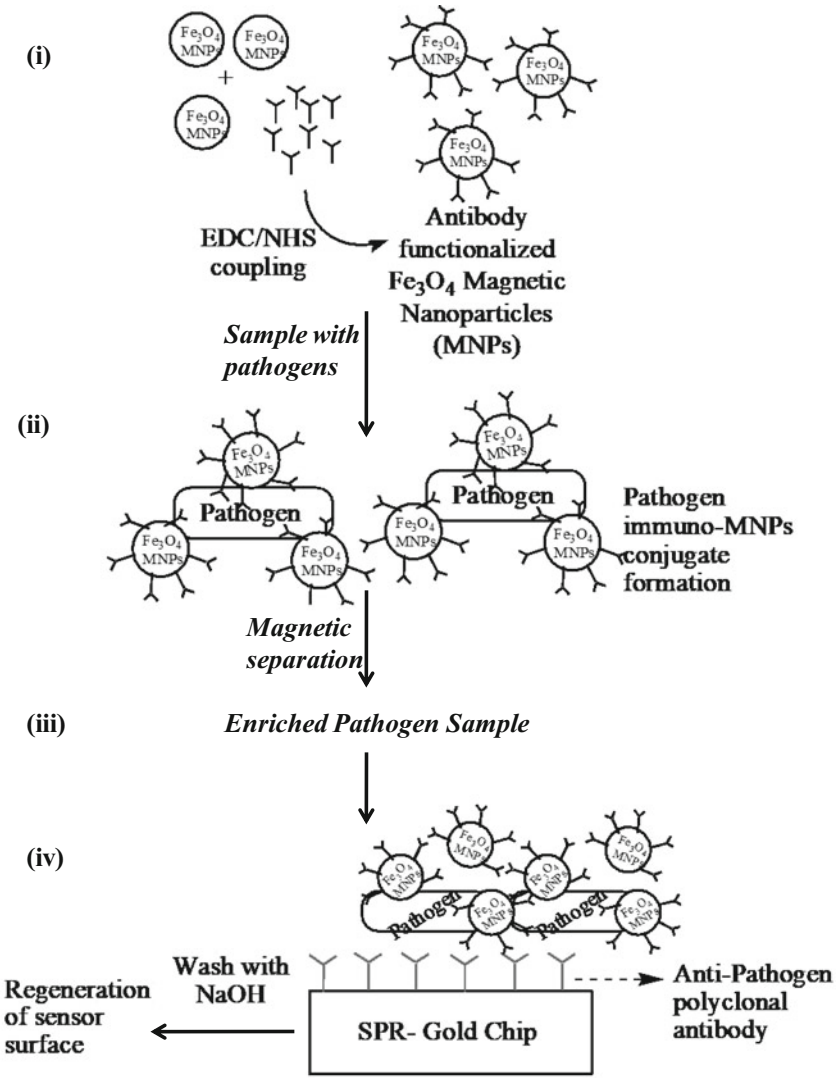

Fig. 10.6 (*i*) Antibody functionalization with magnetic iron oxide nanoparticles by EDC/NHS coupling; (*ii*) target selection by nanoparticle conjugated antibodies; (*iii*) target enrichment by magnetic separation of iron oxide nanoparticle conjugated antibodies from the sample mixture; (*iv*) target detection with an anti-pathogen polyclonal antibody. SPR, surface plasmon resonance; EDC/NHS-1, ethyl-3-(3-dimethylaminopropyl)-carbodiimide/N-hydroxysuccinimide; Fe_3O_4 MNPs, iron oxide magnetic nanoparticles

Other available pathogen-detecting sensors that require very less sample volume is the polymerase chain reaction microchip. Here, the amplified DNA is taken into the optical fiber surface plasmon resonance biosensor (Nguyen et al. 2017). This

proves to be an efficient label-free method with reusability for pathogen detection, as compared to the other abovementioned methods.

10.3.3 Piezoelectric Biosensors

10.3.3.1 Piezoelectric Quartz Crystal Biosensors

Piezoelectric quartz crystal-based biosensors employ the specific attachment of a target biomolecule leading to mass change which can be detected by the equivalent variations in electrical/acoustic properties (Alder and McCallum 1983) of the piezoelectric quartz crystal. It involves a simple methodology without any sample preparation or detection labels (Arlett et al. 2011). Quartz crystal is the mainly used piezoelectric material (Deakin and Buttry 1989), for it has desirable electromechanical and chemical properties. A proportional relation exists between differences in crystal mass and its resonance which is exploited for pathogen detection in these biosensors.

There exists two modes of pathogen detection (Farka et al. 2013) in piezoelectric biosensors, namely, *active mode* or *passive mode*. *Active mode* works by wavering of the piezoelectric crystal with corresponding resonance frequency differences monitored by frequency counter (Arnau 2008), while the *passive mode piezoelectric biosensor* (Zhang et al. 2002) employs an equipment to observe the changes in mass/viscosity as a result of binding of analyte on sensor surface (Itoh and Ichihashi 2008).

A series-piezoelectric quartz crystal biosensor was developed for *S. aureus* detection (Lian et al. 2015), which uses graphene-layered interdigital gold electrodes arranged in series with piezoelectric quartz crystal, upon which aptamers/antibodies specific to the targeted pathogen were fixed as probe molecules for the detection of appropriate pathogens. Here, the targeted pathogenic DNA (i.e., *S. aureus*) hybridizes selectively to the aptamer probes, depleting the binding forces of aptamer with graphene (Shi et al. 2017). This ultimately results in variations of electrical features at the surface of the electrode and appropriate differences in oscillation frequencies yielding a detection limit of pathogen of 41 cfu/ml. Likewise, using an antimicrobial peptide probe, pleurocidin, and a transducer made of a single-walled carbon nanotubes/interdigital electrode, a multichannel series piezoelectric quartz crystal-based biosensor was developed for rapid multiple microbial detection including *S. aureus*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Streptococcus pneumoniae*, *Klebsiella pneumonia*, *Enterobacter cloacae*, *E. coli*, and *Candida albicans* within time period of 15 minutes (Shi et al. 2017). This biosensor finds its significance in clinical diagnosis(Jordana-Lluch et al. 2013) and food safety measures (Farahi et al. 2012). Here, the probe pleurocidin binds with target microbe causing detachment of pleurocidin from the carbon nanotubes, consequently changing the resistance of the electrodes and frequency variation of piezoelectric crystal. It is applicable for all microbes to be detected, considered as the first step for the screening of microbial blood stream infection (Gonsalves and Sakr 2010) and for testing microbial drug susceptibility. It is significant to note that enhanced sensitivity

was reported for early *M. tuberculosis* detection using this piezoelectric quartz crystal-based biosensor than other methods (Zheng et al. 2007; Li et al. 2009).

10.3.3.2 Piezoelectric Cantilever Biosensors

Cantilevers denote the non-flexible structural elements that are fixed at one end of a solid firm support. Piezoelectric biosensors use biological receptors conjugated to the micro-cantilevers, that possess distinct resonance frequencies that respond on binding of target analytes in the sample, with mass increase or mechanical stress on the cantilever (Ahmed et al. 2014). This change in cantilever property is used for many pathogenic bacterial detection such as *E. coli* O157:H7 (Zhang and Hai-Feng 2004; Campbell and Mutharasan 2005a), *S. typhimurium* (Zhu et al. 2007), and *Francisella tularensis* (Ji et al. 2004) (a biowarfare agent). Detection of various bacteria like *E. coli* (Campbell and Mutharasan 2007) and *L. monocytogenes* in milk samples (Sharma and Mutharasan 2013) have been made possible using specific antibody bound to cantilevers excited by piezoelectricity. *E. coli* O157:H7 detection up to a minimum of 700 cells/ml is reported using cantilevers bound to specific monoclonal antibody of pathogen targeted (Campbell and Mutharasan 2005b). Impedance analyzers are employed to monitor the resonance frequency changes and thereby the concentration of targeted pathogen by the selective binding to specific antibody at the cantilever tips. Amplitude ratio and phase angle variations proportional to changes mass/mechanical stress were monitored with the help of an impedance analyzer (Campbell and Mutharasan 2006).

These piezoelectric cantilever biosensors are also used for specific virulence hemolysin gene, hlyA (DNA/gene)-based detection of pathogen, *L. monocytogenes*, using specific probes bound to a cantilever, detected with a fluorescent indicator and gold nanoparticles bound to secondary single-stranded DNA for hybridization signal amplification (Sankaranarayanan et al. 2015). It proves to be rapid relative to other typical pathogen detection strategies.

10.3.4 Electrochemical Biosensors

Electrochemical biosensors use the changes in electrical properties such as current, voltage, or impedance/resistance at the electrode surface on binding of biological analytes including pathogens/biomolecules in a test sample. On the basis of principle of detection and the electrical properties, they are classified as impedimetric/conductometric and amperometric/voltammetric biosensors.

It also involves another two subtypes including labeled and label-free electrochemical biosensors (Xu et al. 2017) on the basis of usage of labels such as enzymes and nanoparticles (Fei et al. 2015; Xiang et al. 2015) bound to the targeted bioanalyte in the case of labeled biosensors. However, the label-free method operates in the absence of any bound labels, based on interaction of bacterial cells at the electrode surface (Sang et al. 2016), that are discussed side by side along with other biosensor developments.

10.3.4.1 Amperometric/Voltammetric Biosensors

Biosensors detecting pathogens with respect to variations in current or potential (Monzo et al. 2015), due to processes like oxidation or reduction of the targeted biological species, where the electrode is at constant potential or current with respect to a standard reference electrode (Bard and Faulkner 2001). Cyclic sweep voltammetry is a common method to acquire data like oxidation/reduction potentials, reaction kinetics, and mechanisms (Bard and Faulkner 2001; Compton and Banks 2011). Using carbon electrodes infused with magnetic nanoparticles, the specific genomic DNA of pathogens and gold nanoparticles in a sandwich assay like format detection of *Salmonella* and *E. coli* could be performed (Blow 2015). Electroanalysis using differential pulse voltammetry and square wave voltammetry are known for better time resolution and high-frequency operation (Chen and Shah 2013). Labeled antibody-based electrochemical biosensor having an immuno-electrode made up of graphene oxide–silver nanoparticles fixed over anti-*Salmonella typhimurium* antibody, along with the help of cyclic voltammetry was proved to be used for *Salmonella* detection (Sign and Sumana 2016). Likewise, detection of other pathogens can be carried out using specific antibodies.

Amperometric sensors are known to be fast and cost-effective (Barlett 2008; Wei et al. 2009), while they also pose limitations such as poor selectivity due to other interfering constituents in the sample mixture varying the faradaic current (Monzo et al. 2015). Sensitivity in microbial/biomolecule detection enhances using semiconductor devices and field-effect transistors due to enrichment of sensor signals (Grieshaber et al. 2008; Lin et al. 2008). Recently, a DNA chip-based sensor was developed, for *S. pyogenes* detection, which works by hybridization of genomic DNA of pathogens from the sample, with the selective probe bound to the screen-printed electrode resulting in an amperometric change in current recorded using differential pulse voltammetry. It was reported to be a sensitive biosensor with a limit of detection of 130 fg DNA per 6 μl of the sample.

10.3.4.2 Impedimetric/Conductometric Biosensors

Biosensors based on impedance measurements rely on the impedance variations occurring due to voltage signal changes on the binding of targeted biomolecule/pathogen to the electrode (Bard and Faulkner 2001; Barlett 2008). The targeted pathogens interacting with the electrode are evaluated in accordance with variations in the capacitance/impedance at the electrode interface. Impedance spectroscopy offers high sensitivity and selectivity for the detection of biological analytes including pathogens (Felice et al. 1999). A carbon electrode modified with reduced graphene oxide was reported to use impedance spectroscopy (Wang et al. 2011) for the detection of methicillin-resistant *S. aureus*. Similarly, *Salmonella* detection was also successful using a label-free technique employing a combination of polypyrrole-based polymer, poly [pyrrole-co-3-carboxyl-pyrrole] copolymer, and a selective aptamer (Sheikhzadeh et al. 2016). Also, researchers have developed similar biosensors as above with gene−/immune-based (instead of aptamers) synthetically designed specific pathogenic peptides along with a record of impedance variations (Liu et al. 2016b).

More recently development of a microfluidic impedance-based biosensor is shown to be successful for *E. coli* O157:H7 (Yao et al. 2018) detection with a minimum limit of 12 cfu/ml within a period of 2 hours. Here, the impedance was monitored using the microfluidic chip, and normalization of impedance helped in the detection of *E. coli* O157:H7. Another recent patent involves the use of conductometric biosensors along with the use of nanotubes for pathogen detection (April et al. 2018). The conductometric component involving the electrodes measures the resistance variation that is proportional to target analyte concentrations specifically interacting with the recognition elements on the electrodes.

10.3.5 Biochemical Biosensors

Biochemical biosensors help in the detection of specific biochemical reactions occurring between a specific target analyte in the test sample and its specific substrate/receptor molecule on these sensors. These substrates used can be any compatible specific biomolecules such as antibodies/enzymes essential for the immuno/biochemical reactions.

10.3.5.1 Immunosensors

Immunosensors detect a biomolecule/analyte using specific immunochemical or biochemical reactions occurring between bio-recognition elements and specific receptors along with the help of transducers to convert the binding interactions into readable output signals. These immuno/biochemical reactions or the ligand–receptor binding offers high sensitivity and selectivity to the immunosensors. These sensors are equipped with signal amplification in the presence of either magnetic particles or gold nanoparticles (Wang and Alocilja 2015) for high sensitivity of pathogen detection. Developments are made in designing an integrated immunosensor, with specific antibody conjugated to gold nanoparticles employed in enzyme-linked immunosorbent assay along with enrichment of target analytes in the sample mixture, using immunomagnetic separation (Cho and Irudayaraj 2013). It was proven analytically with microtiter assay, for a highly sensitive pathogen detection including *E. coli* O157:H7 and *S. typhimurium* detection up to 3 cells/ml in buffer.

Continuous efforts are made to develop immunosensors with high sensitivity employing signal amplification strategies (Guo et al. 2013). A visible indication strategy is one of those techniques that employ color formation based on nanoparticle aggregation (Priyadarshini and Pradhan 2017). Here, the limitation is the requirement of the presence of a large number of analytes for the generation of visible colorimetric detection signal that lowers the sensitivity of the biosensor (Yoo and Lee 2016). The need for high sensitivity, real-time detection, and lower detection time remains the significant areas under research in the biosensor field, due to existing problems in the current methods. For example, the minimum limit of detection reported to date is 10^2 cfu/ml, and detection time is greater than 6 hours (Prasad and Vidyarthi 2011; Raj et al. 2015). This has encouraged researchers to

develop new strategies for signal amplification such as bifunctional linkers or switchable linkers (Hahn et al. 2017; Lim et al. 2012). A bifunctional linker with biotinylated specific antibacterial antibodies is developed which binds to the specific target and leads to visible color changes due to aggregation of the target with the probe (streptavidin–gold nanoparticles), biotin–streptavidin binding reaction (Weber et al. 1989), and also the localized surface plasmon resonance phenomenon. This strategy was improved by altering the amount of streptavidin–gold nanoparticles, to result in a lower limit of detection (10 cfu/ml) of the pathogens *E. coli* and *Salmonella* (You et al. 2018). This was tested in samples of tap water, lake water, and milk samples, which are unaltered by matrix effects. Thus, it offers a speedy, highly sensitive real-time pathogen detection biosensor. Apart from this, simultaneous detection of multiple analytes is one of the major requirements fulfilled using an immunochemical method for diagnosing various infections in test samples. A unique virulence factor, for example, pyocyanin, secreted only by *P. aeruginosa* (Pastells et al. 2016), was used for its detection. By using antibodies of a specific metabolite of the virulence factor pyocyanin, 1-hydroxyphenazine, the virulence factor and hence the pathogen could be quantified/detected.

Antibiogram is a method of detection of early microbial growth. This method employed the 96-well plate format which was modified by Elavarasan et al., into a handy, polymethylmethacrylate microfluidic chip, wherein resazurin, a blue-colored water-soluble dye, was used. The response was monitored by change of color following the biochemical reactions specific for viable cells (Elavarasan et al. 2013; Kaur et al. 2013).

The reduction of water-soluble resazurin occurs in two steps when in contact with viable cells (Fig. 10.7) (Brindha et al. 2018b). The first step results in an irreversible pink colored, partially oxidized form of pink-colored resorufin. This, upon further oxidation, yields a reversible and colorless hydroresorufin (Sarker et al. 2007). This dye acts as an indicator to test cell viability, growth, and toxicity (Palomino et al. 2002). This immunoassay was carried out on a microfluidic chip not only for detecting the presence of milk pathogens but also for detecting multidrug-resistant pathogens. In this assay, as shown below in Fig. 10.7, the interpretation is based on color developed in the presence of microbial samples. When the microorganisms are susceptible to antibiotics, with no cell growth, the blue color is observed, while when it is resistant, a pink/colorless solution is observed. In the case of moderate to negligible growth of the cells, violet color is seen as a partial/complete reduction of resazurin occurs.

10.4 Conclusion and Future Prospects

All the developments of sensors in the recent past are targeted for specificity, lower detection time, lower detection limits, and enhanced sensitivity for detecting analytes. Integration of multiple labeling techniques with immuno−/enzymatic reagents or fluorophores in association with fiber optics or surface plasmon resonance is in practice, for the enhancement of selectivity/sensitivity of pathogen detection. Recently, biosensor research focuses on target analyte enrichment (Zuo

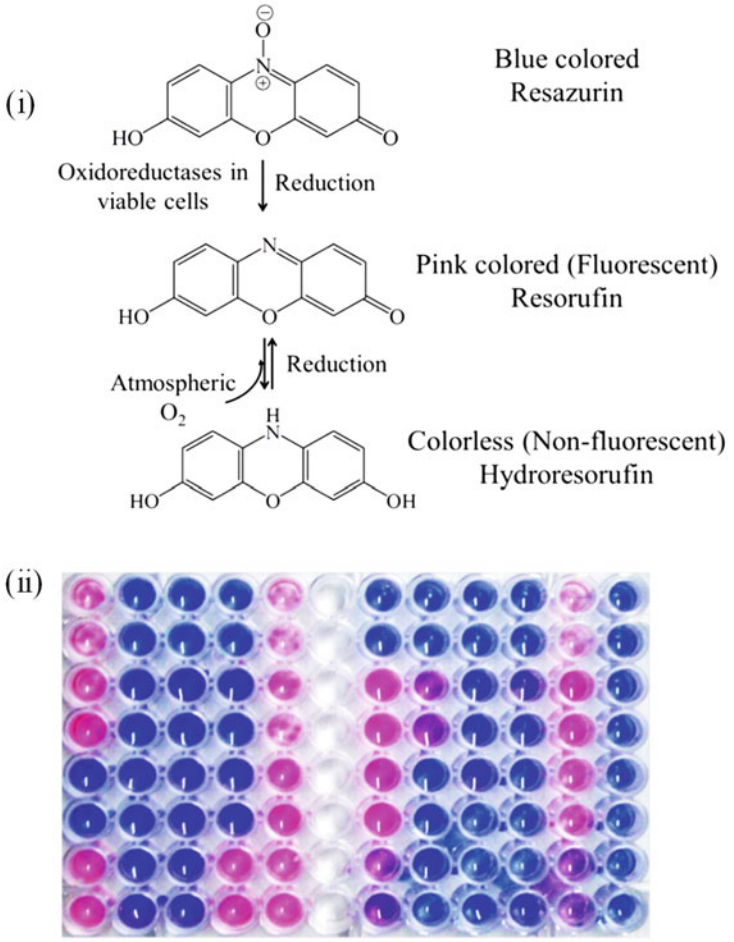

Fig. 10.7 Mechanism of immunoassay following (*i*) the reduction of resazurin to resorufin and further to hydroresorufin in the presence of viable cells, (*ii*) 96-well plate format depicting the antibiogram for a specific pathogen, blue color, blank/antibiotic susceptibility; pink/colorless, antibiotic resistance; violet, intermediate to poor growth of microbes in the sample

et al. 2013; Kim et al. 2014; Hsieh et al. 2015; Altobelli et al. 2016) and amplification of signal responses. New technologies like microfluidics, nanomaterials like nanotubes/nanoparticles, and simpler strategies such as visible indication strategy, and immuno/biochemical reactions in microchips are being developed. Most of the existing chemosensors are fluorescence based. Chemosensor development focuses on new stable fluorophore designing, integration of surface plasmon resonance with fluorophores/optical fibers, and simple miniaturized tools for sensing toxic metal ions/chemicals like pesticides in food/water or other significant environments. Future research endeavors ought to focus on bringing these user-friendly

pathogen/chemical surveillance tools to the market at lower affordable prices as preventive measures against numerous existing infections or other possible epidemics outbreaks.

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