1

Fundamentals of Biomedical Sensors

1.1 Introduction

The use of sensors, education, communication, computers in daily routines, and development of technology over the years has played a significant part in simplifying the human lifestyle [1–3]. Figure 1.1 shows the schematic of a sensor that involve input signal, sensing unit, and output signal. A sensing unit transforms the input signal to an output signal that can be measured using diverse principles, structures, and geometry. Consequently, a sensor converts a physical parameter (temperature, humidity, index of refraction) into a signal that may be processed (e.g. optical, electrochemical (ECL), electrical, and mechanical) [4–7]. Fluorescence, absorbance, scattering, polarization, interference, color change, and luminescence are among the phenomena utilized in the development of sensors.

Sensors have been explored in the numerous sectors that include biomedicine, electronics, military applications, biochemical sensing, and environmental monitoring [8]. A wide variety of research articles on diverse sensing applications has been published in the recent few years due to advancement in various technologies. A biosensor structure is designed using a transducer, light source, and bioreceptor to detect an analyte. Clark reported a glucose oxidase solution encased in a semipermeable membrane as an electrode sensor for measuring the oxygen level in the blood in 1962 [9]. Updike and Hicks reported a sensor that entraps glucose oxidase solution within polyacrylamide gel in 1967 [10]. Guilbault and Montalvo reported a potentiometric sensor to detect the urease [11]. Then in 1972, 1975, 1976, and 1984, the ion-selective field effect transistor, immunosensor utilizing a potentiometric transducer, ECL glucose sensor, and fiberoptic sensor utilizing polymerization techniques were reported [12–15].

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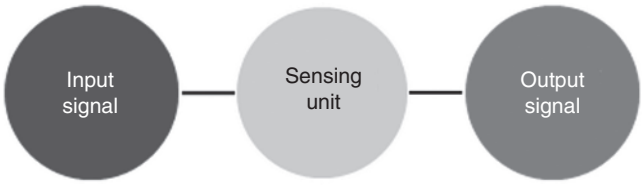

Figure 1.1 An illustration of components of a sensor structure.

Optical biosensors have been explored to detect the neurotransmitters that convey intercellular chemical messages within the nervous system [16, 17]. These neurotransmitters are generated by nerve cells that move to another part of the body and convey information in the form of chemicals such as acetylcholine, dopamine, serotonin, norepinephrine, gamma-aminobutyric acid, glutamate, endorphins, histamine, oxytocin, serotonin, and melatonin. Imbalances of these neurotransmitters are responsible for various neurological disorders such as Parkinson's disease, Alzheimer's, schizophrenia, depression, acetylcholine dysfunction, and altered levels of dopamine serotonin, and norepinephrine [18–25].

The emergence of the surface plasmon resonance (SPR) phenomenon advanced this research even more. Wood observed that reflected spectrum of light is associated with bright and dark bands as light passes through diffraction grating and become polarized [26]. Rayleigh and Fano explained this effect on the basis of the wave scattering from the diffraction grating [27]. Zenneck confirmed the existence of radio frequency waves at the metal-dielectric interface and presented the corresponding Maxwell's equation solution [28]. Otto offered a comprehensive and exact comprehension of the SPR phenomenon using experimental methods in 1968 [29]. Liedberg et al. demonstrated the first SPR-based sensor for measuring bimolecular interactions in 1983 [30]. In 1993, Jorgenson and Yee described a silver plasmonic metal-based fiberoptic sensor, in which the prism is replaced with fiber core to detect the sucrose solution [31]. Later, numerous biosensor designs, including an ECL glucose sensor, the utilization of various enzymes, antibodies, and aptamers for glucose and other biochemical detection, were reported [32, 33]. Technological advances have led to a diversity of biosensor designs [34, 35]. Before they may be used, enzymes must undergo a number of processes, including isolation and purification [36].

Figure 1.2 is a timeline of the development of various biosensor design and milestones. Researchers have studied transducer systems to detect air, soil, and water pollution, as well as numerous infections, toxins, and diseases [37–40]. Identifying ultrasensitive biosensors with sensitivities in the nano, femto, and Pico range is vital to detect diseases at the initial stages – including cancer, tuberculosis infection, cardiovascular disease, and Alzheimer's disease, which are responsible for so many deaths worldwide.

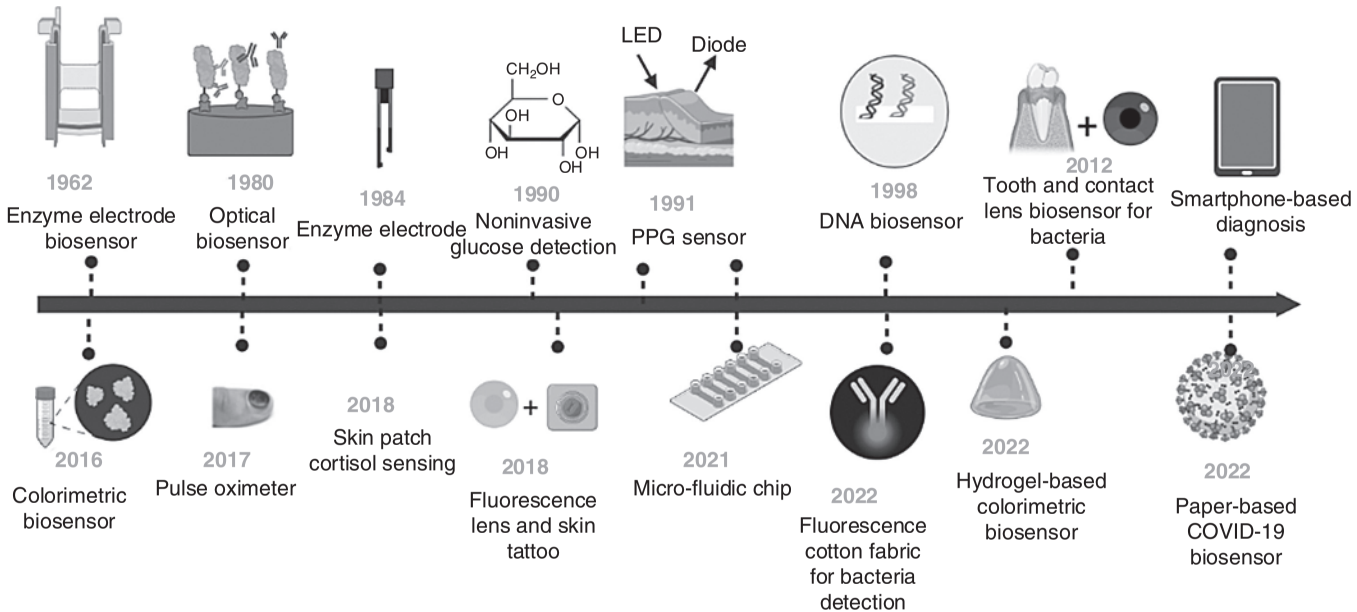

Figure 1.2 A schematic illustration of year-wise progress made in the field of biosensors.

In order to investigate plasmonic, ECL, surface-enhanced Raman scattering (SERS), chemiluminescence, and mass-based biosensors, researchers have investigated numerous methodologies [41–44]. The biosensors market, which includes thermal, ECL, piezoelectric, and optical sensors with applications in medical, food toxicity, bioreactors, agriculture, environment, home healthcare diagnostics, and point-of-care testing, was valued at US$24.9 billion in 2021 globally. It will reach up to US$49.6 billion through 2030 – an indication of an annual growth rate of 8.0% in the years 2022–2030 [45, 46].

Diabetes and cancer-related diseases have increased due to several factors, including environment, food habits, and daily lifestyle. In recent years, the demand for biosensors has rapidly increased due to their wide medical applications, their potential for early diagnosis, and the number of patients affected by diabetes [47]. Of all types of optical sensor designs, ECL glucose biosensors and lateral flow assay-based test for pregnancy have been commercialized most successfully in the global market. Fluorescence-based polymerase chain reactions (PCR) are used in nucleic acid-based tests due to its high specificity and sensitivity. Colorimetric biosensors are commonly used in serological tests that include lateral flow assays and enzyme-linked immunosorbent assays (ELISA) to detect different type of antibodies. Colorimetric methods have the drawback of low sensitivity values. Most plasmonic and refractive-index-based biosensors are still limited to lab research use only [48]. Figure 1.3 illustrates the market demand of different types of biosensors; the sizes of slices indicate the estimated share for each type of biosensor.

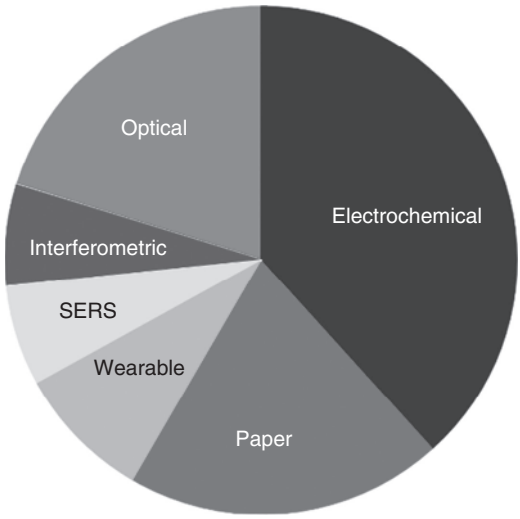

Figure 1.3 Commercialization and market pull of different types of biosensor platforms.

1.2 Classification of Biosensors

Biosensors can be classified on the basis of bio-recognition elements (BREs), different types of transducers, and physical phenomenon. The enzymes, molecular imprinted polymers (MIP), antibodies, nucleic acids, cells, and aptamers have been explored as a biological recognition element to detect numerous analytes [49]. Types of transducers include ECL, optical, piezoelectric, thermal, and magnetic transducers that changes the form of signal. Various optical sensing techniques, such as the evanescent wave (EW) technique [50], fiber grating, SPR-based sensing, and SERS spectroscopy, are available for different applications [51]. ECL biosensors operate in potentiometric, amperometric, and conductometric mode while mass-based sensors can be magnetoelectric and piezoelectric.

1.3 Elements of Biosensors

Figures 1.4a and b show the necessary components of a biosensor, including BRE and transducers to process the signal and output display [52].

1.4 Bio-recognition Elements

BREs consist of nucleic acid (NA), lectins, enzymes, entire cells, antibodies, aptamers, bacteriophages, peptides, and molecularly imprinted polymers, as illustrated in Figure 1.4c [53]. Figure 1.4d depicts the many types of transducers. Bacteriophages are a type of pathogen that infects and replicates within bacteria by selectively attaching to tail-spike proteins. Peptides consist of a short segment of 12–15 amino acid residues that are stable in harsh environments, inexpensive, and simple to produce on a large scale. NA utilize genetic materials such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) as bioreceptors and aptamers are single-stranded DNA or RNA molecules [54]. Aptamers have a lower molecular weight, are readily produced at a low cost, and have excellent chemical stability [55]. Whole cells include microorganisms or cultivated tissues of multicellular organisms used in numerous biosensing applications due to its lower expenditures [56]. MIPs are artificial bioreceptors that are synthesized in the laboratory with binding sites designed corresponding to the target molecule [57].

1.4.1 Nucleic Acids

NAs are chains of linear polymers that consist of five nucleotides called bases: guanine, adenine, cytosine, uracil, and thymine. DNA is made up of a thymine base, while RNA uses uracil as a base. DNA is a unique genetic component of each

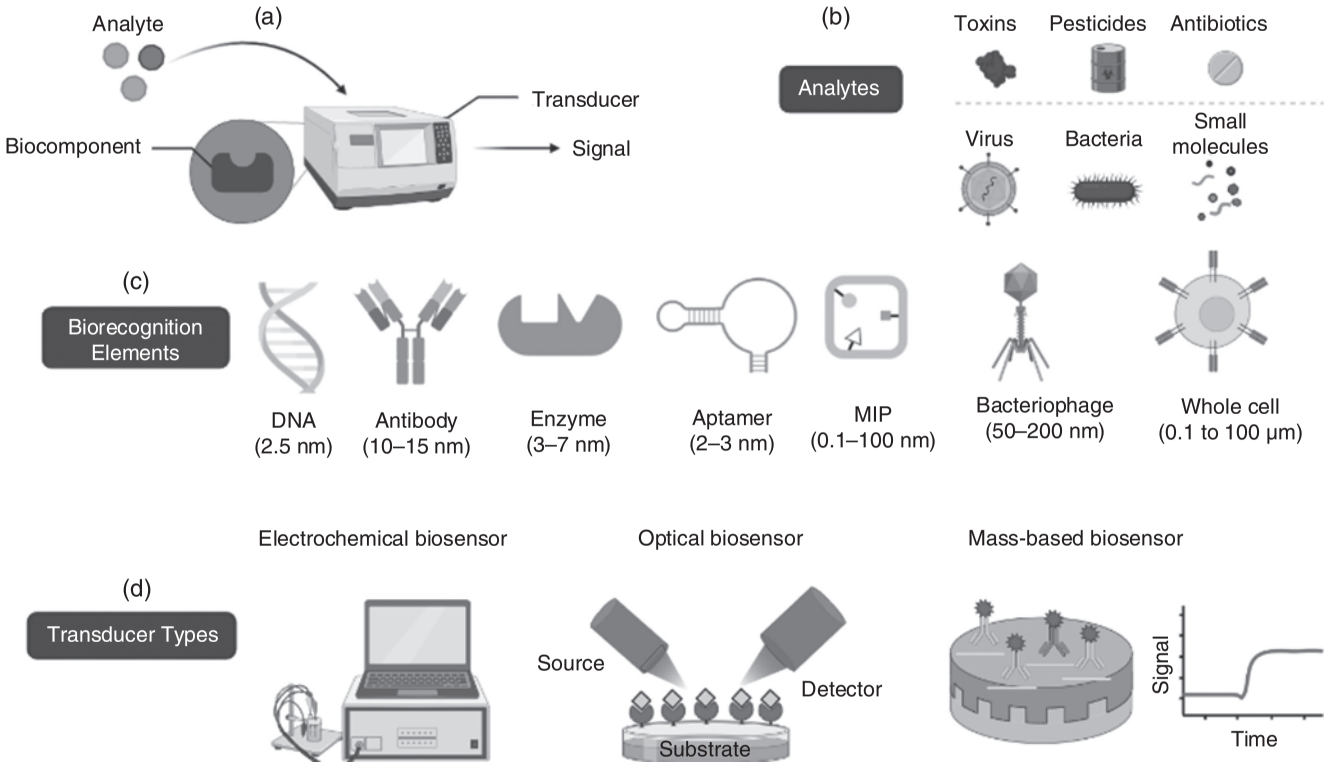

Figure 1.4 Schematic design of the (a) biosensor components (b) different analytes for sensing (c) bio-recognition elements (d) biosensor classification based on types of transducers.

individual organism. Due to its unique sequence and properties, NAs are used to design bioreceptors that match the complementary DNA of the concerned individual. The matching strand can be detected with different transducing mechanisms [54]. NA-based biosensor designs are simple, easy, fast, and low-cost, and they have high specificity to detect an analyte. Various NA biosensors have been reported to detect viruses, cancer cells, microorganisms, and biochemicals [58].

1.4.2 Aptamers

Aptamers are short sequences of oligonucleotides that form a three-dimensional structure that is very specific to the target molecules [55]. To synthesize the aptamers, various chemical or enzymatic procedures or a combination of chemical and enzymatic methods are used [59, 60]. Aptamers are chosen from the systematic evolution of ligands by exponential enrichment (SELEX) techniques using several repeatable steps. The production steps for a single-stranded DNA and its incubation are shown in Figure 1.5. Aptamers are selected using the repletion of various cycles, as these cycles increase the specificity toward the target [39].

1.4.3 Enzymes

Enzymes are target-specific, another type of BRE combined with an appropriate substrate that generates electrons and transfers them to a transducer. Proteins are widely explored enzymes, except RNA enzymes [62]. Enzymes are preferred as labels compared to other BRE, as they can be conjugated with antibodies or aptamers for bioreceptor purposes. Horseradish peroxidase (HRP) and beta-galactosidase are two examples of enzymes used in biosensor designing. Various enzymatic biosensors are also developed based on mass, plasmonic, ECL, thermistor, and piezoelectric techniques for different applications [63]. Enzyme immobilization in the biosensor design is advantageous as it can be used repetitively due to catalytic activity to detect the analyte as compared to the mobile enzyme [63]. Glucose and urease-based biosensors are well-known enzymatic biosensors, of which glucose biosensors are commercialized on different platforms due to their small detection limits and lifetimes.

1.4.4 Antibodies

Antibodies are another class of bioreceptors. They can be polyclonal and monoclonal depending on their production method [64]. Antibodies are proteins generated by plasma cells and classified into five groups that depend on their structure of heavy chain constant region sequences. Their structure is Y-shaped, formed from heavy and light chains, as shown in Figure 1.6. Binding sites specific to

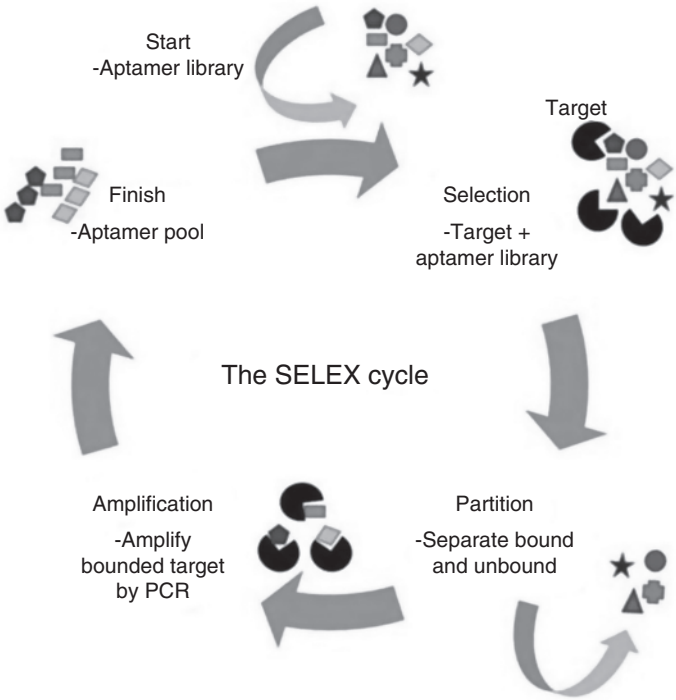

Figure 1.5 Stepwise diagram of the SELEX technique to choose the specific aptamers from the library that includes the separation of bound and unbound targets, target amplification, and generation of a specific aptamer. *Source:* [61]/with permission of Elsevier.

antigens, known as epitopes, can be classified as monoclonal or polyclonal. Monoclonal antibodies can bind to a single epitope while polyclonal antibodies target different epitopes. The production cost and time for making monoclonal antibodies are both higher than for polyclonal antibodies. As compared to other bioreceptors, antibodies involve high costs and stability challenges requiring low-temperature storage. Monoclonal antibodies act as the primary bio-recognition element and polyclonal antibodies act as the secondary bio-recognition element.

Most antibodies are produced by living organisms. Antibodies contain different numbers of epitopes that can be single or multiple [65]. Recombinant antibodies can also be synthesized in the lab with the help of synthetic genes; they are monoclonal in nature. Polyclonal antibodies suffer from high cross-reactivity as compared to monoclonal antibodies due to multiple epitopes. Instead of polyclonal antibodies, monoclonal antibodies are used to design highly specific biosensors because they bind only one epitope. The most important steps during the use of

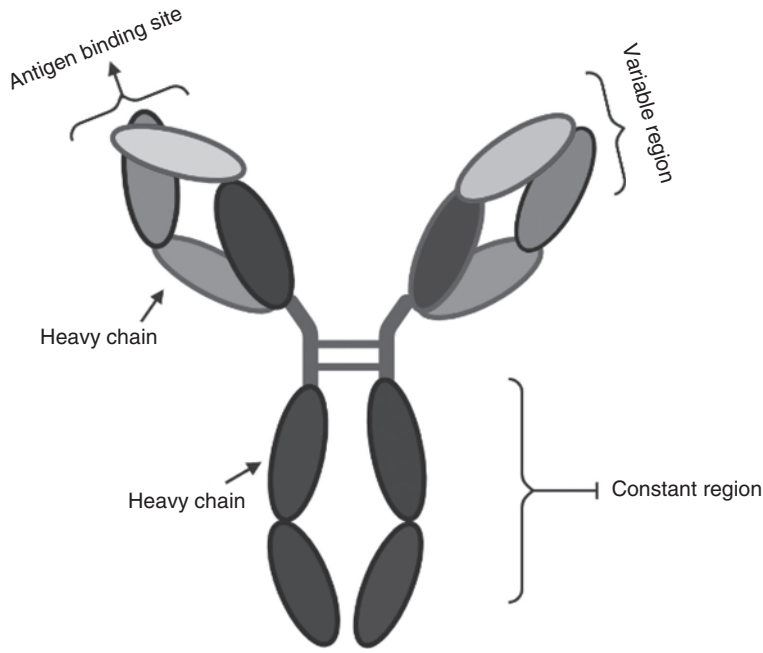

Figure 1.6 Structure of a Y-shaped antibody.

antibodies as a BRE are their immobilization and control of orientation on the surface without damaging their activity and specificity, as this affects the various performance factors, including the limit of detection (LOD), sensitivity, and figure of merit (FOM) [66].

1.4.5 Bacteriophages

A bacteriophage belongs to a family of viruses that contaminate bacteria and are used as BREs to detect the pathogen, cancer biomarkers, tuberculosis, and other pathogenic diseases. Phages are very specific in nature and can affect a single bacterial species. T4, M2, Φ29, and MS2 are a few examples of commonly used phages. A polyhedral head, collar of short length, and a helical tail are the basic components of a phage. Bacteriophages are found in nature and can be used at high pressure, temperature, and pH values. Several biosensor designs have been reported that consider the bacteriophage as a BRE for various types of bacteria detection [67–70]. Pathogenic bacteria (PathoBact) cause infection that consists of single cells with diameter and length in the range of a few μm [71]. PathoBacts have different shapes and can survive in a harsh environment. Bacteria are

prokaryotic microorganisms, without membrane-bound organelles such as a nucleus or mitochondria [72]. The five PathoBacts *Pseudomonas Aeruginosa, Klebsiella Pneumoniae, Staphylococcus Aureus, Escherichia Coli,* and *Streptococcus Pneumonia* were responsible for 13.7 million global deaths in 2019 among 33 investigated PathoBacts [73]. The main structure components of bacteria are DNA, cell wall, ribosomes, capsule, cytoplasm, flagellum, and pili.

Gram-positive and Gram-negative bacteria are classified based on response of bacteria to Gram staining. Gram-positive bacteria don't change from crystal violet color and thus remain purple while Gram-negative bacteria turn red due to different thickness of outermost peptidoglycan cell wall that are made from glucose molecules and connected three short peptide chains [74]. In Gram-positive bacteria, the peptidoglycan layer is 30–100 nm thick; this layer is 1–3 nm thick for Gram-negative bacteria surrounded by extra lipopolysaccharides layer [75]. Microscopy, culture, cytological, biochemical test methods, Gram staining, hemagglutination assays, ELISA, and western blotting (serological tests) are conventional; and polymerase chain reaction, fluorescence in situ hybridization, next-generation sequencing, spectroscopic, CRISPR technology, loop-mediated isothermal amplification, microarray technology, and biosensors are advanced method to detect the PathoBacts [76, 77]. The advanced methods are highly sensitive, can select specific target stable, and have short detection time, low cost, simple structures, and less sample preparation. These advantages overcome the drawbacks of conventional methods [78]. Biosensors are advanced emerging and competitive techniques for detecting pathogens and other analytes [79–82]. They involve ECL, piezoelectric, and optical platforms to detect various microorganisms. However, it is important to mention that each technique suffers from several challenges to commercialize it for various applications as it is in the developing stage.

Bacteriophages have been explored in various biosensing applications focused to detect the microorganism due to their chemical and physical properties. They do not require labeling, which creates advantages of reduces cost, time, high sensitivity, widespread availability (food, soil, water, and environment) and specificity. Various biosensor designs using phages to detect the analytes have been reported so far. Figure 1.7 shows a SERS and colorimetric technique combined biosensor that detects *Salmonella Enteritidis* using F5–4 bacteriophage as a bioreceptor and [83].

1.4.6 MIPs

Diagnostic techniques ELISA, PCR, and cell culture require BRE, trained specialists, complex instruments, and sample preparation. They include mimicking various BRE that include NA, proteins, amino acids, cells, peptides, viruses, and

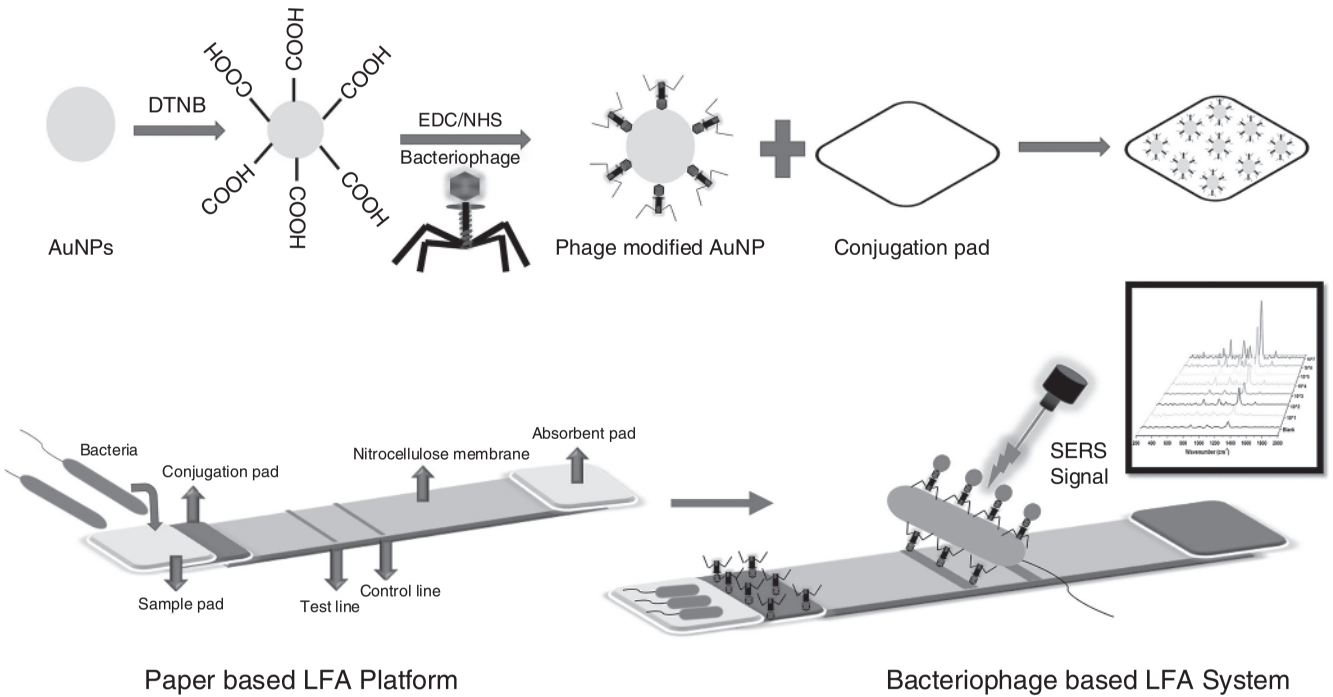

Figure 1.7 Graphic illustration of the F5-4 bacteriophage-based colorimetric lateral flow assay and SERS biosensor structure. *Source:* [83]/with permission of Elsevier.

bacteria that help to facilitate the easy isolation and investigation of complex samples. Molecular imprinting is a technique to develop the functionality of biomaterials into artificial materials, as naturally occurring materials are expensive and restricted in robustness with predefined specificity and selectivity [84]. MIP possesses better chemical stability, is temperature insensitive, requires less preparation time at a low cost, is easy to modify with chemicals, can be directly fabricated on the surface of the transducer, and has high physical and mechanical properties [85]. MIP synthesis involves reactive functional monomers that form specific complexes, cross-linkers for functional group immobilization on imprinted molecules, and initiators to shorten the cycle reaction in the usual way.

Functional monomer and target-based imprinting can be categorized in three ways that depend on their interaction: (i) covalent; (ii) semi-covalent; (iii) noncovalent imprinting, as shown in Figure 1.8 [86]. Figure 1.8a shows the stepwise synthesis of MIP, which includes self-assembly, polymerization, and template removal. Similarly, Figure 1.8b shows the commonly used ingredients that include initiators, functional monomers, and cross-linkers. Functional monomers are the polymers building block – for example, methacrylic acid (MAA), 4-vinyl pyridine (4-VP), acrylic acid (AA), 2-vinyl pyridine (2-VP) and cross-linkers involve trimethylolpropane-tri methacrylate (MBA), ethylene glycol dimethacrylate (EGDMA), divinylbenzene (DVB), and methylene acrylamide (TMPTM). An initiator is used to start the polymerization process, such as benzoyl peroxide (BPO), azobisisobutyronitrile (AIBN), and azodiisopentanyl (AIHN). Covalent imprinting uses a reverse bonding functional unit and template that distributes binding sites in a uniform mode [88]. Semi-covalent imprinting involves covalent and noncovalent polymerization approaches that can be achieved via covalent bonding as well as noncovalent methods [89]. During noncovalent bonding, interaction between functional monomer and sensing analyte is weak in nature that occur via ionic hydrogen bonding, and dipole interaction [90]. Out of these three imprinting techniques, noncovalent imprinting technique is most often used to synthesize the MIP, as shown in Figure 1.8b [91]. Numerous biosensor designs using MIP technology that include optical, ECL, and quartz crystal microbalance biosensors have been reported with improved performance for diverse analytes that include molecules from small to large in size [92]. Until recently, MIP-based biosensors have not been commercialized due to difficulties in large-scale MIP production, complete removal of templates, low selectivity, and less efficient synthesis methods [93].

1.4.7 Biosensors Based on Whole Cells

Biosensors that include whole cells employ different microbes that include viruses, bacteria, protozoa, fungi, and algae as bioreceptors [53]. These bioreceptors can self-replicate, are handled easily compared to plants and animal cells, are

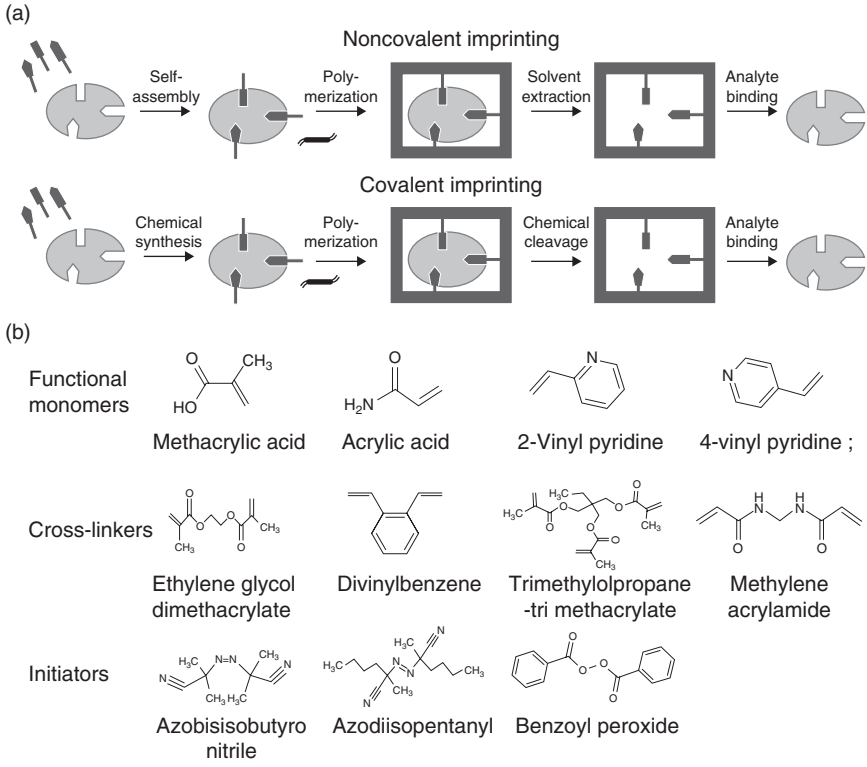

Figure 1.8 Graphic illustration of (a) various steps involved in covalent and noncovalent molecularly imprinted polymer technique. *Source:* [86]/MDPI/CC BY 4.0. (b) Some commonly used initiators, functional monomers, and cross-linkers during MIP fabrication. *Source:* [87]/Frontiers Media S.A/CC BY 4.0.

fast-proliferating, and do not require any extraction or purification methods to produce other bioreceptors such as antibodies [94]. Various biosensor designs based on whole cells have been reported that exhibit good sensitivity and specificity values to detect the different analytes [56, 95, 96]. Figure 1.9 shows the mechanism of a whole-cell-based biosensor that includes molecular bioreceptor immobilizing bacteria or live cells on the substrate to detect the specific target. The target binds itself to the surface of immobilized receptor that modulates the output signal or gene expression and can be measured using different transduction mechanism [96].

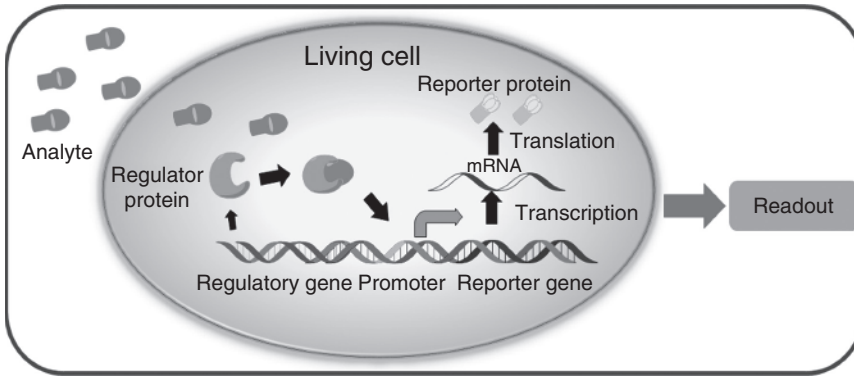

Figure 1.9 Biosensor design based on whole cell. *Source:* [96]/MDPI/CC BY 4.0.

1.5 Sensing Techniques

1.5.1 ECL Biosensors

An ECL (ECL) biosensor is made up of an interface for the analyte reaction, a receptor for binding the target molecule through BRE, and a device known as transducer that alters the interaction signal to a measurable electrical signal. This signal can be measured in the form of impedance, current, voltage, and conductance. ECL biosensors measure changes in electrical properties that result from a specific biochemical reaction. The principle of electrochemistry involves the connection between chemical reaction such as oxidation and reduction into electrical energy. The detection of biomarkers involves the use of an electrode modified with target that specifically binds to the disease biomarker. As the biomarker binds to the target molecule, this attachment changes in the measurable electrical signal. Electrochemical impedance spectroscopy (EIS) is an example that measures the output electrical signal as target cancer cells binds to bioreceptors, such as their size and surface charge. EIS can be used to monitor cancer cell growth and invasion and to detect cancer biomarkers in blood samples [97, 98].

In ECL biosensors, electrodes are utilized as transducers and reaction sites that sense the analyte by reducing or oxidizing it [99]. Reference electrode and working electrode are two main components during ECL sensor design. Silver (Ag) and silver chloride (AgCl) are used to fabricate the reference electrode, which forms a connection with the electrolyte solution and is kept at a distance to maintain the potential at a stable value. Reference electrode using graphite, gold (Au), platinum (Pt), and compounds made from silicon (Si) have been reported so far.

ECL sensors are classified into amperometric, potentiometric, conductometric, field effect transistor, and impedimetric. Amperometric sensors measure the signal in the form of a current generated from ECL reaction, potentiometric sensors measure voltage generated at electrode surface, and impedimetric sensors measure impedance [100].

Clark reported using ECL biosensors to measure glucose solutions [63]. In the case of potentiometric ions in solution, BRE is measured after being converted to potential. Impedimetric biosensor measure the impedance to detect the presence of various analytes [101–105]. ECL biosensors have a short lifespan (i.e. 1–3 years), and components must be replacement. Some ECL sensor designs involve using electrolyte solutions to enhance performance and lifespan; however, refilling the solution regularly is another drawback. Figure 1.10 shows a manganese oxide-fluorescent polymer dot–based ECL biosensor to detect Madin-Darby canine kidney (MDCK) and MD Anderson-metastatic breast (MDAMB) cancer cells cancer cells [106].

1.5.2 Optical Biosensors

Light is used in optical biosensors to detect the various analytes that possess advantages such as high sensitivity with low detection limits, fast speed, and shorter detection time. Optical biosensors detect changes in the optical properties of a sample resulting from a chemical reaction. Output is measured using optical transducers (i.e. colorimetric). Other examples of optical biosensors for cancer detection include fluorescence, Raman spectroscopy, and light scattering [39, 107, 108]. The classification of various optical sensor designs and their descriptions based on underlying operational principles and sensing applications are discussed in detail.

1.5.2.1 Plasmonic Biosensors

With the growing demand for portable, reliable, fast-responding, and highly sensitive detection mechanisms, plasmonic biosensors that consist of surface plasmon resonance (SPR) and localized surface plasmon resonance (LSPR) have become a favorable alternative technology to detect the various biochemicals. In recent years, considerable progress has been witnessed in the field of plasmonic biosensors and their commercialization in the different application areas. More precisely, the unique properties of the SPR phenomenon are focused on a variety of applications such as the guiding of light, nanoscale manipulation, overcoming the difficulty to provide good resolution below the diffraction limit, and single molecule detection [109].

Prism-based Kretschmann's configuration and fiberoptic structures are widely explored for various applications [110]. A surface plasmon (SP) phenomenon is

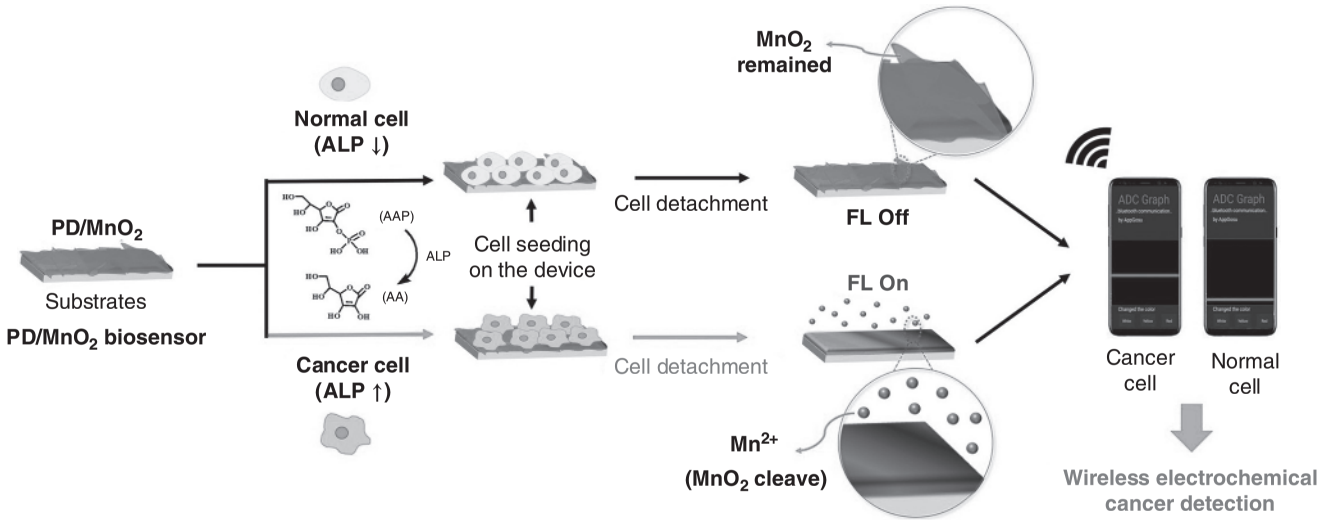

Figure 1.10 A fluorescent polymer dot-manganese oxide complex–based ECL sensor to detect the cancer cells. *Source:* [106]/with permission of Elsevier.

excited using a transverse magnetic wave whose electric field exists along the interface of two materials with opposite permittivity values fulfilled by metal and dielectric material. Figures 1.11a and b show penetration depth in metals (δ_m), dielectric (δ_s), and their numeric values in the case of most widely explored plasmonic metals Au and Ag [111]. As the wave vector and momentum of an oscillating charge are always greater than those of a massless photon, it is difficult to excite the surface plasmons' incident light directly, but the light can be excited by different techniques that increase their momentum.

Excitation methods include prism, Bragg, and fiber configuration. In these methods, the incident electromagnetic light is coupled through prisms for biosensing applications. For practical purposes, the Otto configuration was not found suitable, as it was not possible to maintain the few nm gaps between the metal layer and the prism material. Otto configuration was modified and reported by Kretschmann and Raether by depositing the plasmonic active metal layer on the base of prism [112]. This configuration has been explored for various applications and lays the foundation for rapid growth of prism-based SPR sensors. Figures 1.12a

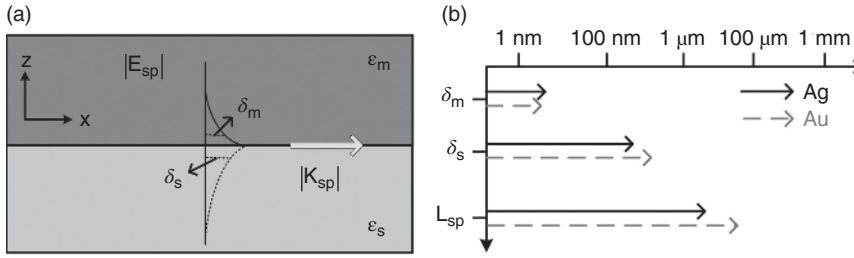

Figure 1.11 Schematic illustration of (a) surface plasmons existence at the interface of the metal and dielectric indication penetration depth in metals (δ_m), dielectric (δ_s) of the electromagnetic field and propagation length (L_{sp}) of surface plasmons; (b) numerical values of δ_m, δ_s, and L_{sp} for plasmonic active Ag and Au metals that are commonly used in biosensing applications.

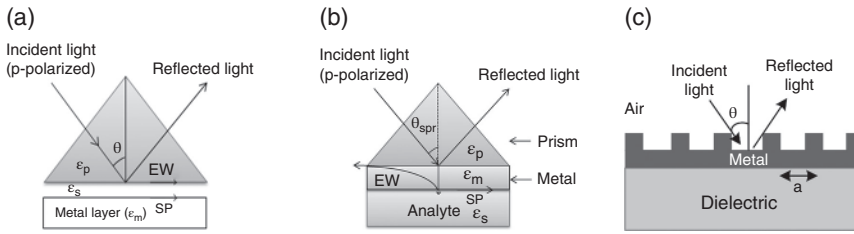

Figure 1.12 Schematic of light coupling in a plasmonic-based sensor using (a) Otto, (b) Kretschmann, and (c) Bragg grating configuration.

and b show the structure reported by Otto and Kretschmann for sensing purposes. SPR requires precise wave vector matching of incident light with surface plasmons at a specific angle known as resonance angle, denoted as θ_{SPR} [51]:

$$\frac{2\pi}{\lambda} n_{prism} \sin\theta_{SPR} = Real\left(\frac{2\pi}{\lambda}\sqrt{\frac{\varepsilon_m \varepsilon_s}{\varepsilon_m + \varepsilon_s}}\right) \tag{1.1}$$

Eq. (1.1) represents the evanescent wave-vector (k_{ev}), with dielectric permittivity (ε_s) and metal permittivity (ε_m). At resonance conditions, a decrease in intensity of reflected light is detected at resonance angle denoted as θ_{SPR}. This θ_{SPR} is responsive to any change in RI of sensing medium and shows angular shift ($\delta\theta_{SPR}$) for other analytes, which is the principle behind SPR sensing [112, 113]. Phase-matching condition with grating of holes or grooves having lattice constant a can be expressed as (Figure 1.12c).

$$\beta = \frac{2\pi}{\lambda} n_s \sin\theta \pm \nu \frac{2\pi}{a} \tag{1.2}$$

β, ν and n_s are the wave vector of surface plasmons (Eq. 1.2), diffraction order, and analyte RI. Fiberoptic-based sensors possess the advantages of small size, low cost, remote sensing, electromagnetic radiation immunity, long-term reliability, miniaturization, and online monitoring. Plasmonic sensors have been explored to detect the analytes such as gases, liquids, and various toxic materials. Furthermore, different strategies, transition metal dichalcogenides (TMDCs) [114], plasmonic nanocomposites [115], glass materials [116], and fiber geometries [117] have been used to improve the performance of SPR sensors in the visible to infrared region [118]. Discovery of other 2D materials and their unique properties has further triggered research in the field of SPR sensing [119]. Out of the four interrogation methods, wavelength and angular methods are most commonly used for the detection of various biochemical substances as they are simple to fabricate and provide superior resolution at a low cost [120]. Figure 1.13 shows the fiberoptic configuration used for various sensing applications.

Prism-based configurations utilize the phenomenon of total internal reflection (TIR) to excite SPs; therefore, a prism (due to its bulky size) can be replaced with a core of optical fiber for sensing purposes, as shown in Figure 1.13.

1.5.2.2 Interferometric Sensors

Interferometric sensors explore the interference phenomenon to measure the various quantities that include disease-related analytes, temperature, and humidity. Fabry-Perot (FPI), Mach-Zehnder (MZI), Sagnac, and Michelson interferometers are four types of interferometers used for many biochemical

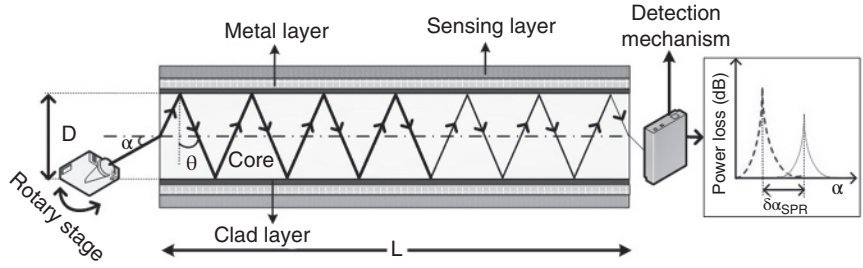

Figure 1.13 Schematic of fiberoptic configuration.

sensing applications. In interferometry, light is split into components that are further combined to produce maxima and minima series. The MZI interferometer is based on interference obtained by division of amplitude. Light can be split into its components using a beam splitter that covers the different path lengths and phases, which are further recombined with the help of another beam splitter [121]. Figure 1.14a shows the MZI interferometer structure that consist of laser light source, sensing arm with reference arm, input, output waveguide, and detector system.

In FPI, an etalon is used to separate the two surfaces that are parallel to each other by a certain distance. Incident and reflected light interfere multiple times at these parallel surfaces [125]. Figures 1.14b and c show the schematics of the FPI and Michelson interferometers. Michelson interferometers have the same principle of working as MZI, except for the reflector difference. In a Sagnac interferometer, a light beam travels with different polarizations along a loop fabricated using an optical fiber, as shown in Figure 1.14d [126]. The advantage of interferometric sensors lies in the fact that they can be applied via heavy optical components, optical fiber structures, and planar guides that involve mirrors as well as reflectors [127].

1.5.2.3 Colorimetric Sensors

Colorimetric sensors are widely used because changes are easily visible to the naked eye. They have easy use, low cost, high sensitivity, and high selectivity to detect the analytes. The sensors change color during interaction between analyte and ligand, having the advantage of parallel sensing [39]. Colorimetric sensors examine the chemical reaction of the analytes that yield high-sensitivity designs lying in the range of parts per billion to parts per trillion. Chemical properties detection is useful in toxic analytes because toxics are very reactive and can be detected easily with very low concentrations lying in the range of sub parts per million [128]. These days, colorimetric sensors are combined with different effects that include plasmonics, thin metallic layers, and 2D materials to improve biosensor performance. Figure 1.15 shows a AuNPs-based colorimetric Aptasensor to

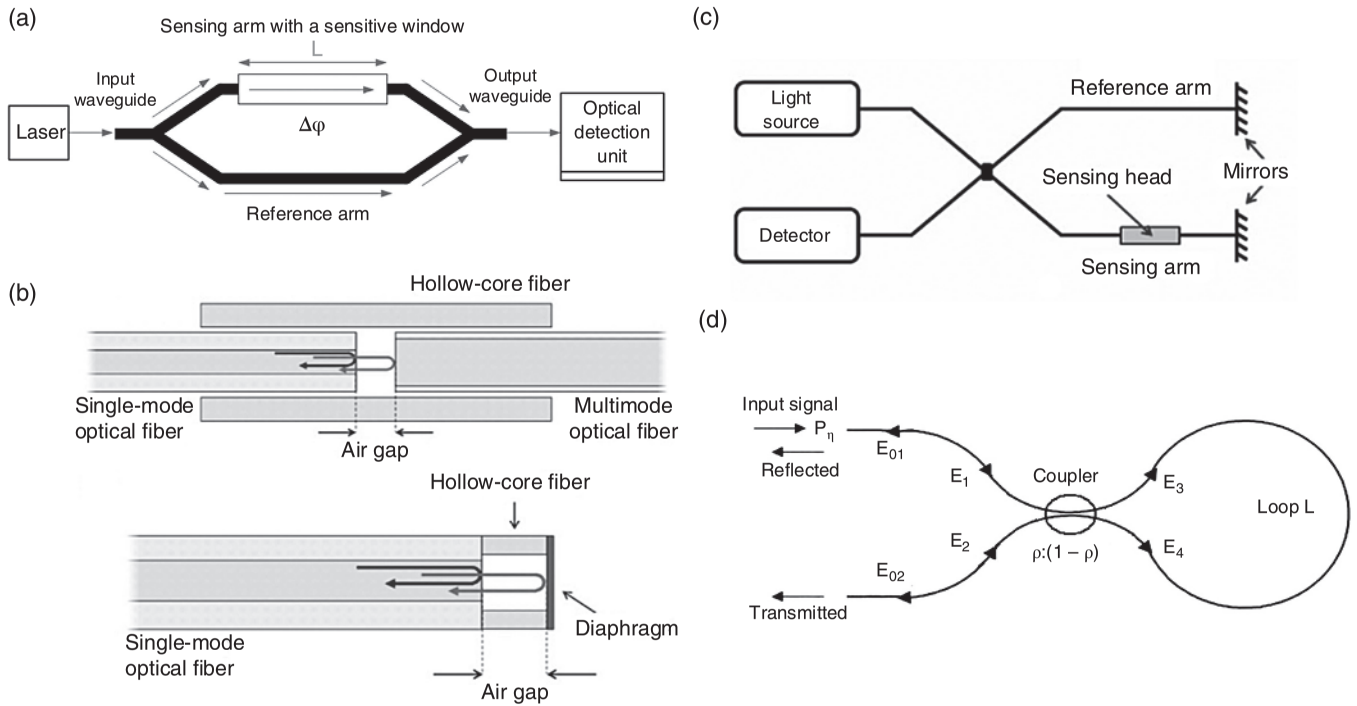

Figure 1.14 Schematic of (a) MZI-based biosensor design. *Source:* [122]/MDPI/CC BY 4.0. (b) FPI sensor. *Source:* [123]/Springer Nature/CC BY 4.0. (c) Michelson interferometric sensor. *Source:* [123]/Springer Nature/CC BY 4.0. and (d) Sagnac configuration. *Source:* [124]/with permission of Elsevier.

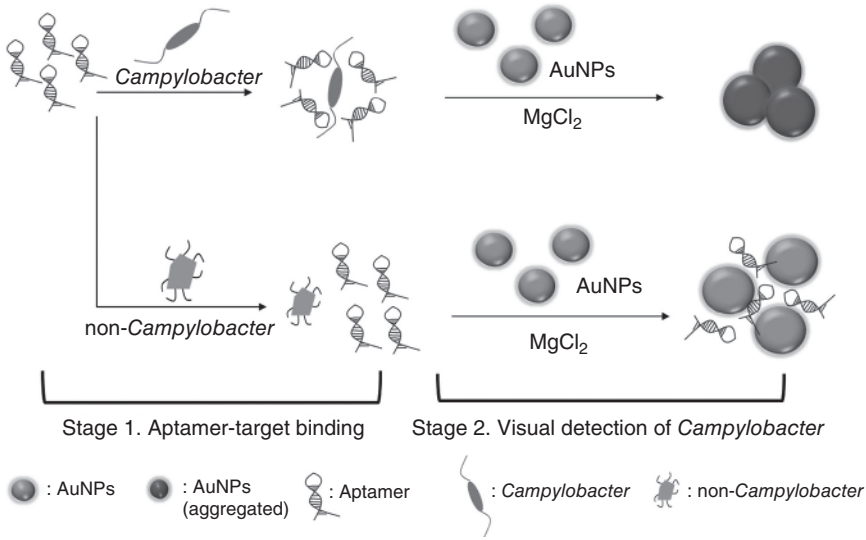

Figure 1.15 Schematic of AuNPs and aptamer-based colorimetric biosensor designs to detect campylobacteriosis that spread due to *Campylobacter jejuni* and *Campylobacter coli*. *Source:* [129]/with permission of Elsevier.

detect the foodborne disease campylobacteriosis that spread due to *Campylobacter jejuni* and *Campylobacter coli bacteria*. The biosensor structure includes gold nanoparticles functionalized with a specific aptamer that changes color and causes aggregation [129]. Colorimetric sensors have been widely explored to detect metal ions, toxics, biosamples, dyes, medicines, pesticides, and pollutants with high performance through the naked eye [130]. Two methods are commonly used to design colorimetric sensors: the first is direct binding (receptor-spacer-reporter), and the second is competitive binding–based sensors that include indicator displacement assays. In receptor-spacer-reporter–based sensor design, a spacer is used to bind the reporter and a receptor moiety. Binding of target with bioreceptor through the spacer changes output signal.

Indicator displacement assay sensor designs form a receptor-indicator assembly that generates competition among the target analyte and the indicator. As the indicator shows the displacement, a signal change is observed in the output signal [103].

1.5.2.4 SERS-Based Biosensors

The concept of inelastic scattering of incident light with a molecule that changes its frequency due to their interaction is used in SERS [131]. The output Raman signal is enhanced due to adsorption of molecules on the metal surface [131, 132].

This method enables the detection of a single molecule, ultra-sensitivity, high selectivity due to a narrow bandwidth of 0.1 nm, multiplexing detection in simple assay designs, a longer lifetime due to photo-bleaching resistance, and a lower detection limit. Various biosensing applications based on SERS have been reported so far [133–138]. SERS biosensors can be labeled or label-free. Labeled biosensors involve a target with an external Raman molecule, as shown in Figure 1.16 [140]. Label-free biosensor design involves direct interaction of the target with BRE; a shift in the Raman signal can be observed. Enhancing the Raman signal intensity depends on cross-section and the number of adsorbed molecules on the metal surface [138]. The electromagnetic and chemical enhancement mechanisms are two approaches responsible for Raman signal enhancement. During the interaction of the molecule with light in the electromagnetic mechanisms, a molecule is a point dipole that produces dipole moment, and charge distribution increases the field intensity near metal surface.

In case of chemical enhancement, a chemical interaction of metal and molecules generates the molecular polarizability. In addition, resonance due to incident light and the molecule's electron transition, resonance of the incident light molecule with the metal-molecule transition, and ground state of metal and molecule overlap with each other, leading to signal enhancement (the nonresonance effect).

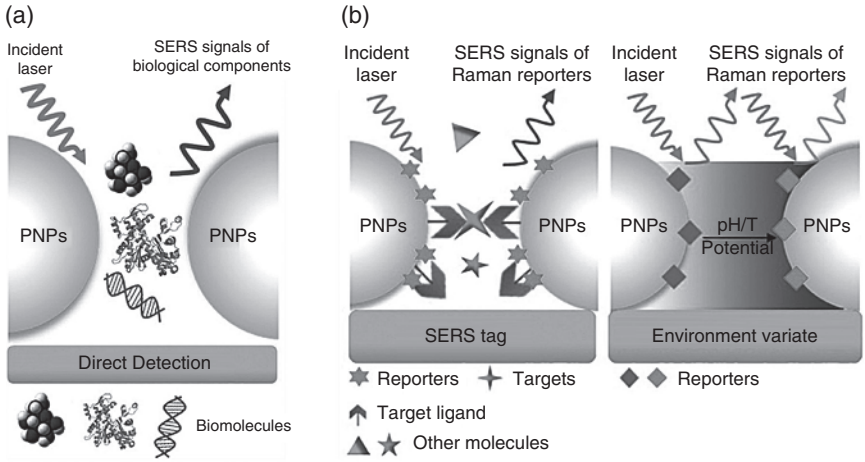

Figure 1.16 Schematic illustration of (a) label-free and (b) labeled SERS biosensors. *Source:* [139]/with permission of Elsevier.

The chemical effect contributes less as compared to the electromagnetic effect, and this effect is the least studied due to experimental quantification. The electromagnetic effect is independent of the analyte but depends directly on the metal roughness [139, 141].

1.5.2.5 Fluorescence-Based Biosensors

Fluorescence-based biosensors make use of light emitted by the fluorescent material as they absorb electromagnetic light depending on their state; they can be fluorescent in one state but not fluorescent in another state. For example, nicotinamide adenine dinucleotide + hydrogen (H) is fluorescent while NAD^+ does not emit light [142].

The absorbed photon has high energy as compared to released photon; therefore, a photon that excites dye has a lower wavelength as compared to an emitted photon. Dyes can be excited in the range of wavelengths (known as the "spectrum") as they are not excitable at a single wavelength. In the fluorescence technique, there is a light source to excite the light, a fluorophore that emits light after excitation, filters to filter wavelength, and a light detector to measure the intensity. Nucleic acids, flavin nucleotides, and green fluorescent proteins are some commonly used inherent fluorescent molecules for biosensing applications [144, 145]. Fluorescence biosensors are widely explored for various biochemical and other sensing applications. On the other hand, analytes or target molecules are nonfluorescent; therefore, these are labeled with fluorescent molecules to detect them easily using some reactive groups that include amino, hydroxyl, and carboxyl groups that form bonding with tag and target molecules [146, 147]. The requirement of a clear analyte solution to overcome interference and complex components makes it difficult to implement for commercial purposes [148]. Another drawback is that the binding site of the fluorescent tag suffers from photobleaching, and interaction of the tag with a specific target could lead to incorrect results. Fluorescence biosensors have less capability for multiplexing, a long detection time, and phototoxicity [39].

Figure 1.17 shows the fluorescently labeled biosensor used to detect the target molecule. Förster resonance energy transfer (FRET) is a distance-dependent interaction between two light-sensitive molecules (a donor and an acceptor fluorophore) that transfer energy in nonradiative way among each other. Fluorescence lifetime imaging is used to measure the fluorophores molecule decay time during fluorescence. Changes in fluorescence intensity measure the variation of light intensity emitted by the fluorophore molecule to investigate the molecular interactions. Fluorescence correlation spectroscopy measures the variation in intensity of a solution that comprises fluorescent molecules.

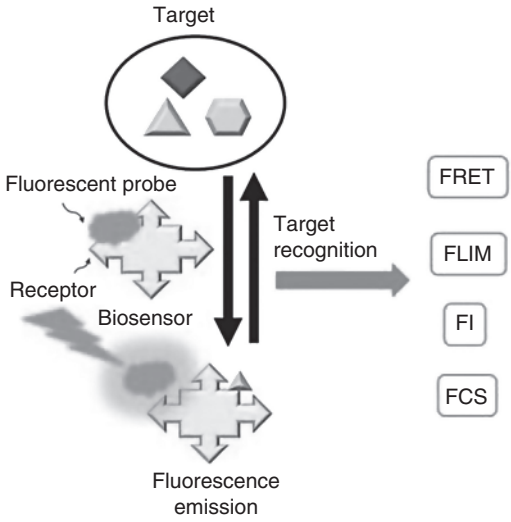

Figure 1.17 Schematic picture of a fluorescence-based sensing mechanism that involve molecular interaction methods Förster resonance energy transfer (FRET), fluorescence lifetime imaging (FLIM), changes in fluorescence intensity (FI), and fluorescence correlation spectroscopy (FCS). *Source:* [143]/MDPI/CC BY 4.0.

1.5.2.6 Photonic Crystal-Fiber–Based Biosensors

A photonic crystal consists of nanostructures arranged in periodic order that interact with incident light according to their wavelength and periodicity. PCF structures can be fabricated in all three possible dimensions using different techniques that change the refractive index in a periodic manner. PCFs are being implemented on different sensing platforms for various applications. PCF consists of small air holes that confine the light fabricated along the length of fiber. Two effects called photonic bandgap and index guiding effects are responsible for guiding the light in PCFs [149]. The effective RI of the core is higher than clad-effective RI in index guiding mechanism. In the core region, air holes are arranged in a periodic manner such that it makes the core effective RI more than air hole surrounding them. The size of clad air hole is kept large as compared to core region surrounding air holes. There is contrast RI difference between core and clad that guides the light via total internal reflection phenomenon inside the core [150]. The operating principle of PCF and traditional optical fiber is almost the same except for a higher effective RI contrast between core and cladding, which leads to much stronger confinement for different applications. In a photonic bandgap PCF, the light is confined by a photonic bandgap generated using the microstructured cladding [66]. Different materials, which include silica, polymers, chalcogenides, and glasses, are used to fabricate the PCFs. Figure 1.18 shows that various types of PCF structures are explored to detect the different analytes that include DNA, RNA, viruses, bacteria, and various diseases [151–154].

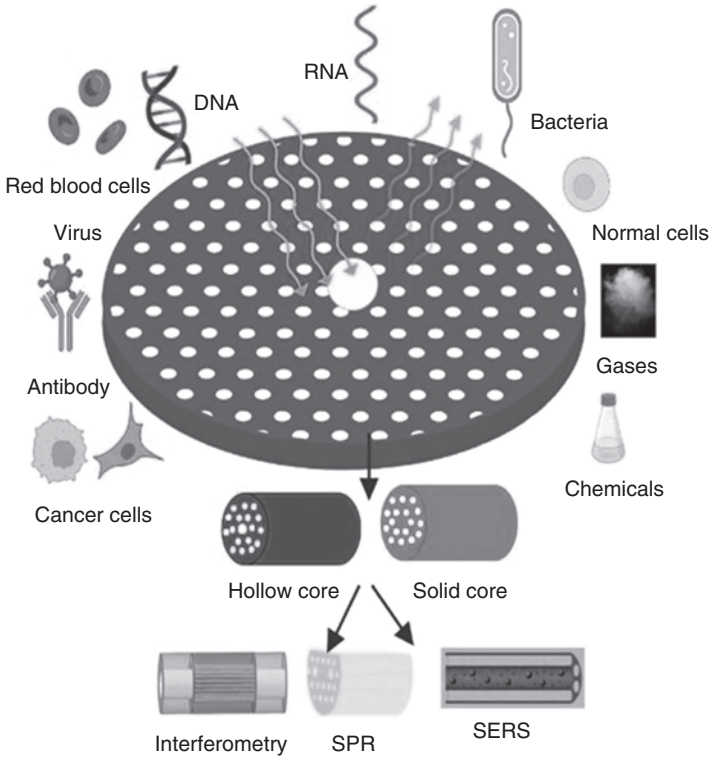

Figure 1.18 Schematic demonstration of different types of PCFs for numerous analytes detection. *Source:* [28] with permission of Elsevier.

1.5.3 Mass Biosensors

Mass-based biosensors can measure the changes in the mass of the crystal as it vibrates on applying an electric field. It can be piezoelectric and magnetoelastic according to the crystal type. For example, quartz crystal microbalance biosensors measure changes in resonance frequency that result from the binding of a cancer biomarker to an immobilized receptor. Other examples of mass-based biosensors for cancer detection include surface acoustic wave (SAW) biosensors and micro-cantilever biosensors [155, 156]. Piezoelectric biosensors include quartz crystal microbalances that consist of thin quartz layers sandwiched between a pair of electrodes and surface acoustic-based devices. On the application of electric voltage mechanical vibrations are generated due to excitation of the structure. The crystal resonant frequency and the deposited layer near the surface are connected to each other and expressed in eq. (1.3). The frequency of vibration decreases as

the deposit attaches to the crystal surface. The frequency of vibration becomes proportional to the mass of the deposit material as its thickness becomes very thin and rigid. Therefore, the mass of the deposit can be determined using the Sauerbrey relation. In surface-acoustic wave-based sensor design, guided sound-waves travel parallel to the elastic material surface with decaying displacement amplitude inside the material and are confined to within roughly one wavelength of the surface. Surface-acoustic wave-based devices activate at ultrasonic frequencies in the substrate.

$$\Delta f = -\frac{2 f_0^2}{A\sqrt{\rho_q \mu_q}} \Delta m \tag{1.3}$$

In eq. (1.3), the symbols f_o, Δf, Δm, A, $\rho_q \mu_q$ represents the fundamentals mode resonant frequency, change in normalized frequency, mass, piezoelectrically active crystal area, quartz density, and crystal shear modulus [157]. In piezoelectric biosensors, piezoelectric crystal is modified with bioreceptors, as mechanical stress is applied that generate electric charge and binding of analyte on crystal surface produce change in mass that can be measured at transducer in the form of

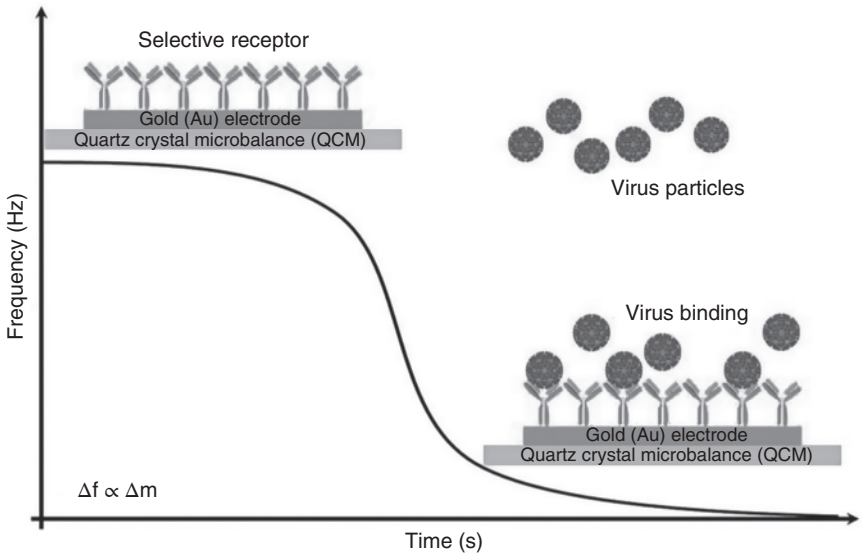

Figure 1.19 Schematic of frequency vs. time plot and structure of Au and quartz crystal–based biosensor to detect the virus. As virus binds to bioreceptor surface, it changes the mass, which changes the frequency that can be selected with diverse techniques. *Source:* [158]/MDPI/CC BY 4.0.

electrical signal [61]. In magnetoelastic biosensors, a magnetic field is used to excite the sensor by generating the magnetic flux through amorphous ferromagnetic ribbons or wires. As no direct connection is required, the sensing coil can be placed at a distance, so magnetoelastic biosensors can be used for wireless monitoring. Figure 1.19 shows the structure of a quartz crystal and Au-based biosensor and a change in frequency can be observed after binding of virus with bioreceptor in frequency vs. time plot [159, 160].

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