1

Biosensors for Infectious Diseases-Fundamentals

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1.1 Introduction

The rapid growth in the urbanization processes and its association with inadequate city planning, poor management of sanitary conditions as well as water supplies, high population density, and interference in previously unaffected ecosystem leads to the spread of infectious diseases [1]. The term "infectious diseases" refers to medical conditions caused by a variety of pathogenic microorganisms, which include bacteria, viruses, fungi, and parasites. The diseases can spread from one organism to another through direct or indirect contact that results in a number of ailments, some of which are fatal [2]. Infectious disease outbreaks continue to put a heavy burden on the world's population despite the surge in medical advancements. They consistently pose challenges to international healthcare systems, raising ongoing concern about the rising frequency of epidemics throughout the world. It was reported, in 2016, the infectious diseases were responsible for one-fifth of all deaths that were officially recorded worldwide. In addition, socioeconomic and environmental issues, such as climate change, migration, and population increase, will probably make this scenario worse, particularly in overpopulated places. The need for early detection systems has grown as the possibility of more frequent epidemics and disease outbreaks has increased. An illustration of the necessity for early detection techniques to track diseases outbreaks is the continuing COVID-19 pandemic brought on by the rapid transmission of the novel coronavirus [3]. The success of measures for disease zoning, control, or eradication is greatly influenced by the rapid detection of a virus or antigen due to the threat posed by infectious diseases. All public-health programs must include both disease surveillance and diagnosis as essential elements. Prior to a virus outbreak having disastrous effects on the economy, people, and the environment, it is crucial to stop it from spreading or minimizing its speed [4]. Infectious diseases are

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categorized as (i) severe respiratory syndrome, which falls into the category of novel and previously unknown diseases, (ii) Foot and mouth diseases, on the other hand, fall into the category of recognized diseases that have risen in incidence, virulence, or in certain geographic range, and (iii) diseases such as avian influenza that are expected to become more prevalent in recent future [4]. In some cases, the diseases can spread through in a community in just a few hours, depending on the types of infectious diseases and the surrounding weather. The ongoing COVID-19 pandemic serves as a stark reminder: within two years of its emergence, more than 4.6 million lives have been lost, and the cost to the world economy is approaching US$7 trillion [5]. Finding the pathogens that cause infectious diseases is the first step in controlling them. By using an agar plate to grow bacteria on Petri's invention, Dr. Koch altered how we view diseases (i.e. the Petri dish). Laboratory culture-based detection of infectious agents has evolved into the "gold standard" in clinical microbiology. When combined with his novel microscopy, the technique enabled to link pathogens as the source of diseases commonly known as Koch's postulates [6]. Another significant development was introduced known as polymerase chain reaction (PCR), which includes the increase of detection limits of the infectious agents, even those that were slow-growing or uncultivable [7]. The diagnostic procedures are restricted only to the centralized medical laboratories due to the need for supporting infrastructure, such as highly skilled employees and capital equipment to perform PCR and culture assays. We need to make next technological leap to fast, economical, yet highly accurate diagnostic tests to better deal with infections that is emerging rapidly. The biosensor is one alluring device that can offer quick information on a disease outbreak [8]. It is commonly known that biosensors play a key role in environmental monitoring [9, 10], agriculture [11, 12], food and water analysis [13, 14], and medicine/clinical analysis [15, 16].

1.2 Biosensors Fundamental Aspects

Biosensors have a variety of definitions in the literature. However, according to 1999 IUPAC standards, they can be defined as a self-contained integrated receptor–transducer system that may provide specific quantitative or semiqualitative analytical information utilizing a biological recognition element [17]. Ideally, the biosensor should be a reagentless device that is typically employed in the detection process with the noble purpose of providing quick, accurate, and reliable information about the biochemical composition of its environment. It should also be able to respond continuously, reversibly, and without disrupting the sample. Different types of biosensors are available [18–21]. However, all of them essentially consist of a biological recognition component, or bioreceptor which interacts with the analytes to be detected and generates signals by the means of signal processing unit or transducer. A schematic representation of the typical components of biosensor is shown in Figure 1.1. An enzyme, antibody, nucleic acid (NA), cell/tissue, and hormones can be employed as bio-component. Its function is to selectively interact with the target analytes, and the outcome of the biochemical process is then turned into quantifiable signal through the transducer [22]. There are several types of transducing systems,

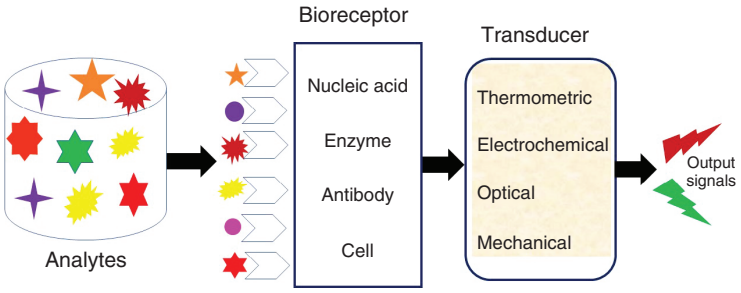

Figure 1.1 The schematic of biosensor concept representation.

including electrochemical, optical, piezoelectric, thermometric, and magnetic [23]. A "biosensor" is a device used to measure for analyte detection that combines a biological and physicochemical detector linked to a component. The design as well as function of biosensor determines the analyte detection. A noninvasive smartphone-based analyte biosensor can be tested on smartphones and other widely used devices. This enables rapid and cost-effective preliminary detection possible.

1.3 Classifications of Biosensor

In the late 1960s, Clarke and Lyons developed biosensors [24]. There are several perspectives to categorize biosensors, but the most frequently used two are biorecognition component and the signal transduction component. Based on the above two categories, biosensors classification is summarized in Table 1.1.

1.3.1 Biorecognition Perspective

Biosensors are categorized as nucleic acid, protein receptor-based immunosensors, enzymatic biosensors, and whole-cell biosensors based on the biological recognition component. The details of principles as well as examples are discussed in Sections 1.3.1.1–1.3.1.5.

1.3.1.1 Nucleic Acid Biosensors

A nucleic acid-based biosensor uses a complex DNA or RNA structure or an oligonucleotide with a known base sequence as detecting element. Nucleic acid biosensors can be used to find biological or chemical species, as well as DNA/RNA fragments. The analytes in the first application are DNA/RNA, and the hybridization reaction is used to detect it (a type of genosensor). In the second case, DNA/RNA acts as a receptor for particular biological/chemical species, such as drugs, contaminants, or target proteins [25]. A NA (natural and biomimetic forms of oligo- and polynucleotides) is integrated into nucleic acid (NA)-based biosensors as the biological recognition component. In DNA hybridization sensors, synthesized oligodeoxyribonucleotides are typically utilized as probes. The oligodeoxyribonucleotides are

Table 1.1 Classification of biosensors based on biorecognition elements and transduction perspective.

Biosensors category	Types	Examples
Bio-recognizing elements	Nucleic acid	Hybridization mechanism DNA-aptamers based
	Enzymes	Alcohol oxidase (Ethanol) Glucose oxidase (β-D-glucose)
	Protein receptors	Olfactory receptors Odorant-binding proteins
	Whole cells	β-galactosidase Green fluorescent protein
	Antibodies	Recombinant Polyclonal Monoclonal
Transduction through signals	Electrochemical	Potentiometric Impedimetric Voltametric Amperometric
	Optical	Surface plasmon resonance Absorbance-based Luminescence-based Reflectance-based
	Thermometric (Calorimetric)	Cholesterol oxidase Enzyme-glucose oxidase Enzyme-linked immune assay (ELISA)/thermometric ELISA (TELISA)
	Mass-sensitive	Electrochemical quartz crystal microbalance Piezoelectricity Chemical sensors
	Electrical	Dielectrophoresis Impedance based

immobilized to transducer surfaces using end-labels such as thiols, disulfides, amines, or biotin [26]. Especially, in the areas of clinical, environmental, and food analyses, DNA sensors have considerable potential for facilitating the accessibility of sequence-specific information [27]. The PCR and other amplification techniques, the effectiveness of the hybridization of the sequences, and the amount of background signal all play a role in determining the measurement sensitivity. Ionic strength, reaction temperature, and DNA computation circuit are some of the variables that affect the setting of specificity [28]. Biosensors based on DNA-aptamers have the ability to bind particular bacteria, viruses, proteins, and even small molecules and ions with exceptional specificity and affinity. As alternatives to antibodies, DNA-aptamers-based biosensors have been developed due to their low cost and great specificity [29].

1.3.1.2 Protein–Receptor Biosensor

Protein–receptor-based biosensors or non-catalytic proteins anticipate the protein's cell membranes to act as receptors are essential for biosensors. Multiple proteins work together and organize the sensing mechanism in the mammalian olfactory system. The olfactory receptor is a G-protein-coupled receptor (large protein family of receptors), and when a ligand molecule binds to the G-protein-coupled receptor, the second-messenger cascade of olfactory transduction is launched, which ultimately results in a cation influx through the ion channel associated with the system. Numerous studies have attempted to utilize this sensing capability of the membrane receptors for the development of biosensors since these receptors act as ligand-sensing elements [30]. There are 12 G-protein-coupled receptors that can sense and signal serotonin in humans [31].

1.3.1.3 Enzymatic Biosensor

The components of an enzymatic biosensor are an enzyme that detects and then reacts with the target analyte to produce a chemical signal, a transducer that converts the chemical signal into a physical signal, and an electronic amplifier that first prepares the signal before amplifying it [32]. Lactate, glucose, glutamate, and glutamine are few examples of the analytes that are essential to the metabolism of living beings. Glutamine and glucose help cells grow and function; lactate, which cells produce and use to measure how well their metabolism is working; and glutamate, an amino acid that is utilized by cells. For the detection of each of these analytes, a specific set of enzymes is required [33]. Interference is particularly difficult in biological samples since cells, proteins, small molecule metabolites and macromolecules, and electrochemical interferences are frequently present in the sample matrix. Hence, chemicals in the sample matrix have the potential to interfere with amperometric enzyme-based biosensors. According to the electron transfer mechanism used to measure the biochemical reaction or the degree of separation of the biosensor components (transducer, enzyme, mediators, and cofactors), amperometric enzyme biosensors are often categorized into three types. The existence of an enzyme is necessary in every step; thus, sensor performance depends on various factors, including working pH and temperature [34].

1.3.1.4 Whole-Cells Biosensors

A whole-cell biosensor is a kind of sensor that can find and recognize an element inside a cell or tissue. It is made up of several physical or chemical transducers and synthetic biomolecule recognition elements. Based on the differences in their molecular, cellular, and tissue sensing components, these biosensors can be divided into three groups. The reporting elements in the molecular-based biosensors are biologically active molecules such as enzymes, DNA, antigens, antibodies, and biofilms [35, 36]. The basic principle of a whole-cell biosensor is that it detects signals from its surroundings, such as small metabolites, chemicals, ions, temperature changes, or light, and then uses those signals to activate internal processing circuits [37, 38]. The applications of whole-cell biosensors include pharmacology, cell biology, environmental assessments, and toxicity. Drug delivery is one of the crucial applications of whole-cell biosensors [39].

1.3.1.5 Antibody-Based Biosensor

Antibodies can be utilized as bioreceptors in biosensors because of their selectivity. In vivo biosensor development has been aided by the incorporation of antibodies into biosensors. The antibody bioreceptors are traditionally mounted on the transducer surface in antibody biosensors. The analyte-containing solution is subsequently exposed to this [40]. All the molecules of antibodies follow the same structural principle, which is based on paired heavy and light polypeptide chains, and enable their integration into the immunoglobulin's common chemical class. Most of the time, immunoglobulin G (IgG) that predominates in serum uses biosensors [41]. The rapid and accurate identification of a variety of infections and related toxins is made possible by antibody-based sensors [42].

1.4 Transduction Through Signals

1.4.1 Electrochemical Biosensors

Electrochemical biosensors are one among the different types of biosensors, which have been utilized for various industrial applications since years [43]. According to the method of transduction, the electrochemical biosensors can be classified as amperometric, potentiometric, and impedimetric/voltametric. This type of biosensors analyzes interactions between the analyte and biorecognition element on the electrode surface to detect the changes in charge distribution and dielectric properties. Biological molecules, nucleic acids, proteins, disease biomarkers, and many more have been analyzed with the help of electrochemical biosensors [44].

1.4.2 Optical

Optical biosensors are one among the currently available various biosensing systems, which offer easy, portable, efficient, real-time, and cost-effective diagnostic tools with the advantages of sensitivity and specificity. Various innovative concepts like microelectronics, nanotechnologies, molecular biology, microelectrochemical systems, and biotechnology with chemistry are utilized to operate optical biosensors. It is highly essential for a simple, portable, and handheld optical biosensing instrument for the fast and accurate detection of harmful pathogens. Currently, the incorporation of intelligent nanomaterials in the form of gadgets offers significantly more sensitive and highly advanced sensors which may generate rapid results and help doctors and clinicians. Since years, optical biosensors have been developed for several applications. Over the past 10 years, a wide range of optical biosensing platforms, including surface plasmon resonance [45], interferometers [46], photonic crystals [47, 48], fiber-optics [49], and ring resonators [50], have studied for sensitive and label-free detection. The advantages of optical sensors are their sensitivity to electromagnetic interference, ability for remote sensing, capacity for minimization assays, inherent safety, and capability for multiplexed recognition within a

single device [51]. One of the most important limitations of widely used optical sensing systems is the penetration depth of the evanescent field, which is frequently less essential than the average size of the optical field [52].

1.4.3 Thermometric (Calorimetric)

Biosensor systems that are capable of adapting new goals are in high demand nowadays. The enzymes used in enzyme-linked immunosorbent assays (ELISAs) produce heat as a result of an enzyme-catalyzed reaction, making it simple to customize and modify a calorimeter to detect enzymes as indicators of antigen [53]. Hydrogen peroxide is widely used as a substrate in ELISA tests given that it contains a variety of reaction enzymes and high reaction enthalpy ($98\,kJ\,mol^{-1}$) (like catalase or horseradish peroxidase) [54]. Chemical reactions catalyzed by enzymes generate heat. ELISAs with optical-based detection have been developed for point-of-care application, although they lack quantitative data or require materials with specified optical properties [55]. An ELISA with a calorimetric readout of the heat produced by the enzyme reaction was initially developed by Mattiasson et al. and was called thermometry enzyme-linked immunosorbent assay (TELISA) [56]. The first TELISA calorimetric biosensor monitored with flow-through columns needs enormous sample amounts larger than finger prick, ambient temperature, and immobilized enzymes. Clinically relevant levels of phenylalanine and herceptin have been found in serum is one successful development of exceptionally sensitive nanocalorimeter TELISA systems [57].

1.4.4 Mass-Sensitive

A wide range of biosensors can be developed using mass-sensitive devices and the imprinting approach. They work as optical sensors for detecting numerous physiological activities [58]. The piezoelectric effect, which was discovered by Pierre and Jacques Curie in 1880, serves as the foundation for all mass-sensitive devices [59]. The function of a piezoelectric platform, also known as a piezoelectric crystal, or sensor component, is based on the theory that oscillations change when a mass is bonded to the surface of the piezoelectric crystal [60]. The sensing technique adopted everywhere is the change of mass and subsequent change in resonance frequency of the oscillating quartz plate. This is due to the analyte's morphological, optical, and functional characteristics not interfering with the resonating transducer's detection principle [61]. From the analytical chemistry standpoint, piezoelectricity is particularly suited for the development of physical sensors and biosensors. Piezoelectricity is particularly suited for the development of physical sensors and biosensors from an analytical chemistry standpoint. The principle of these assays can be explained by providing a simplified description. For example, two electrodes apply alternating voltage to the surface of the biosensor or sensor to excite it. When a crystal is placed in an oscillating circuit, alternating voltage causes it to oscillate mechanically and the frequency of the oscillations can be measured [62]. Analytes

or other masses attached to the surface of crystal, or more precisely, the surface of electrodes poisoned on the crystal, create an oscillating frequency shift [63].

1.4.5 Electrical

Conventional methods for identifying medical complications are time consuming, cost effective, and required skilled personnel for analysis. Electrical biosensors are regarded as a clear choice in diagnostic applications due to their portability for screening, cost, usability, and online monitoring. In addition, electrical biosensors are utilized to detect targets in different matrices in real time, be selective, and without preparing samples. Over time, electrical biosensors have been developed employing various transducer technologies, such as field-effect transistors, interdigitated electrodes, and microelectrodes [64]. Due to advancements in the conversion of molecular analytical signals into electrical signals, significant efforts have been made to develop and enhance the sensitivity of electrical biosensors to detect dengue virus DNA. This type of electrical biosensors has been designed with the transducers of nanoscale structures, such as nanotubes, nanoparticles, and nanowires as the dimension is comparable to the feature sizes of chemical and biological species to be detected. Silicon nanowires are highly demonstrated due to their unique mechanical, optical, and electrical characteristics as well as high biocompatibility and high surface-to-volume ratio. These are also shown to have excellent electrical detecting capacities with good electron or hole transit in the detection. The synthesis of silicon nanowires involves either top-down or bottom-up approach [65]. Furthermore, compared to other devices, the electrical detection based on silicon nanowire has a higher influence on conductance, and faster response of detection. Due to the linear output, low power needs, good resolution with ultra-low-level sensitivity up to parts per trillion or sub-pico or femto molar range, electrochemical biosensors are recognized as being exceptionally sensitive forms of transducers. The repeatability and precision are also quite good. Point-of-care and point-of-need electrochemical sensors are also available for deployment [66]. Surface modification with nanomaterials helps electrochemical biosensing applications [67]. Nowadays wireless nanowire-based biosensors is helpful technology in diagnosing infectious diseases [68–72].

1.5 Conclusions

Due to benefits including high selectivity and sensitivity, the potential for downsizing, portability, low cost, and quick reaction, biosensors have increased their influence over the past 50 years in a variety of sectors, including therapeutic applications. The intricacies of numerous biological processes in health and disease are now being clarified by recent developments in biomarkers discovery and biotechnology, highlighting novel targets for diagnosis and treatments. This is crucial in the case of

infectious diseases because of the continued high number of projected fatalities, the threat of pandemics and epidemics, the emergence and reemergence of diseases, and the drug resistance of pathogens. Therefore, having reliable diagnosis techniques available is essential. This study discusses current methods for diagnosing viral diseases, ideas about biomarkers, and ligand selection, in addition to emphasizing the prospects of biosensor technology. Additionally crucial to the democratization of diagnosis are biosensors. Due to their high cost, centralized nature, and need for trained specialists to operate, many present systems are inaccessible to a sizeable portion of the global population. Because of this, the potential for cost savings, mobility, and simplicity is greatly appreciable, particularly in the case of diseases that are often ignored. The future also seems optimistic. It is possible that developments in disciplines like genetics, epigenetics, chemistry, biochemistry, physiology, and bioinformatics will help to better understand the subtleties of biological processes in both health and sickness. Particularly in diagnosis and treatments, or possibly both, new research targets are becoming available and existing ones are becoming better understood (i.e. theragnostic). Therefore, combining these discoveries with innovative technologies like biosensors could alter the current scenario of medical diagnosis.

References

1 Neiderud, C.J. (2015). How urbanization affects the epidemiology of emerging infectious diseases. *Infection Ecology & Epidemiology* 5 (1): 27060.

2 Sarwar, M. (2015). Insect vectors involving in mechanical transmission of human pathogens for serious diseases. *International Journal of Bioinformatics and Biomedical Engineering* 1 (3): 300–306.

3 Jiménez-Rodríguez, M.G., Silva-Lance, F., Parra-Arroyo, L. et al. (2022). Biosensors for the detection of disease outbreaks through wastewater-based epidemiology. *TRAC Trends in Analytical Chemistry* 155: 116585. https://doi.org/10.1016/j.trac.2022.116585.

4 Pejcic, B., De Marco, R., and Parkinson, G. (2006). The role of biosensors in the detection of emerging infectious diseases. *Analyst* 131 (10): 1079–1090.

5 Cheon, J., Qin, J., Lee, L.P., and Lee, H. (2022). Advances in biosensor technologies for infection diagnostics. *Accounts of Chemical Research* 55 (2): 121–122.

6 (a) Weiss, R.A. (2005). Robert Koch: the grandfather of cloning? *Cell* 123 (4): 539–542;bFredericks, D.N. and Relman, D.A. (1996). Sequence-based identification of microbial pathogens: a reconsideration of Koch's postulates. *Clinical Microbiology Reviews* 9 (1): 18–33.

7 Siqueira, J.F. Jr. and Rôças, I.N. (2005). Exploiting molecular methods to explore endodontic infections: part 1 – current molecular technologies for microbiological diagnosis. *Journal of Endodontics* 31 (6): 411–423.

8 Chatterjee, N., Manna, K., Mukherjee, N., and Saha, K.D. (2022). Challenges and future prospects and commercial viability of biosensor-based devices for disease diagnosis. In: *Biosensor Based Advanced Cancer Diagnostics* (ed. R. Khan, A. Parihar, and S.K. Sanghi), 333–352. Academic Press https://doi.org/10.1016/B978-0-12-823424-2.00013-2.

9 Long, F., Zhu, A., and Shi, H. (2013). Recent advances in optical biosensors for environmental monitoring and early warning. *Sensors* 13 (10): 13928–13948.

10 Rodriguez-Mozaz, S., de Alda, M.J.L., Marco, M.P., and Barceló, D. (2005). Biosensors for environmental monitoring: a global perspective. *Talanta* 65 (2): 291–297.

11 Mufamadi, M.S. and Sekhejane, P.R. (2017). Nanomaterial-based biosensors in agriculture application and accessibility in rural smallholding farms: food security. In: *Nanotechnology* (ed. R. Prasad, M. Kumar, and V. Kumar), 263–278. Singapore. https://doi.org/10.1007/978-981-10-4573-8_12: Springer.

12 Smart, A., Crew, A., Pemberton, R. et al. (2020). Screen-printed carbon-based biosensors and their applications in agri-food safety. *TRAC Trends in Analytical Chemistry* 127: 115898.

13 Khansili, N., Rattu, G., and Krishna, P.M. (2018). Label-free optical biosensors for food and biological sensor applications. *Sensors and Actuators B: Chemical* 265: 35–49.

14 Leonard, P., Hearty, S., Brennan, J. et al. (2003). Advances in biosensors for detection of pathogens in food and water. *Enzyme and Microbial Technology* 32 (1): 3–13.

15 Masson, J.F. (2017). Surface plasmon resonance clinical biosensors for medical diagnostics. *ACS Sensors* 2 (1): 16–30.

16 Mascini, M. and Tombelli, S. (2008). Biosensors for biomarkers in medical diagnostics. *Biomarkers* 13 (7, 8): 637–657.

17 Thevenot, D.R., Toth, K., Durst, R.A., and Wilson, G.S. (1999). Electrochemical biosensors: recommended definitions and classification. *Pure and Applied Chemistry* 71 (12): 2333–2348.

18 Bai, Y., Xu, T., and Zhang, X. (2020). Graphene-based biosensors for detection of biomarkers. *Micromachines* 11 (1): 60.

19 Shah, J. and Wilkins, E. (2003). Electrochemical biosensors for detection of biological warfare agents. *Electroanalysis: An International Journal Devoted to Fundamental and Practical Aspects of Electroanalysis* 15 (3): 157–167.

20 Nigam, V.K. and Shukla, P. (2015). Enzyme based biosensors for detection of environmental pollutants – a review. *Journal of Microbiology and Biotechnology* 25 (11): 1773–1781.

21 García-Aljaro, C., Cella, L.N., Shirale, D.J. et al. (2010). Carbon nanotubes-based chemiresistive biosensors for detection of microorganisms. *Biosensors and Bioelectronics* 26 (4): 1437–1441.

22 Haupt, K. and Mosbach, K. (2000). Molecularly imprinted polymers and their use in biomimetic sensors. *Chemical Reviews* 100 (7): 2495–2504.

23 Kumar, S., Dilbaghi, N., Barnela, M. et al. (2012). Biosensors as novel platforms for detection of food pathogens and allergens. *BioNanoScience* 2 (4): 196–217.

24 Clarke, S.F. and Foster, J.R. (2012). A history of blood glucose meters and their role in self-monitoring of diabetes mellitus. *British Journal of Biomedical Science* 69 (2): 83–93.

25 Palchetti, I. and Mascini, M. (2008). Nucleic acid biosensors for environmental pollution monitoring. *Analyst* 133 (7): 846–854.

26 Thomas, S., Saji, K.J., and Jayaraj, M.K. (2022). An introduction to biosensors. In: *Nanomaterials for Sensing and Optoelectronic Applications* (ed. M.K. Jayaraj, P.P. Subha, and S. Thomas), 91–107. Elsevier.

27 Lucarelli, F., Tombelli, S., Minunni, M. et al. (2008). Electrochemical and piezoelectric DNA biosensors for hybridisation detection. *Analytica Chimica Acta* 609 (2): 139–159.

28 Stoecklein, N.H., Erbersdobler, A., Schmidt-Kittler, O. et al. (2002). SCOMP is superior to degenerated oligonucleotide primed-polymerase chain reaction for global amplification of minute amounts of DNA from microdissected archival tissue samples. *The American Journal of Pathology* 161 (1): 43–51.

29 Pfeiffer, F. and Mayer, G. (2016). Selection and biosensor application of aptamers for small molecules. *Frontiers in Chemistry* 4: 25.

30 Misawa, N., Osaki, T., and Takeuchi, S. (2018). Membrane protein-based biosensors. *Journal of the Royal Society Interface* 15 (141): 20170952.

31 Lengger, B., Hoch-Schneider, E.E., Jensen, C.N. et al. (2022). Serotonin G protein-coupled receptor-based biosensing modalities in yeast. *ACS Sensors* 7 (5): 1323–1335.

32 Ronkainen, N.J., Halsall, H.B., and Heineman, W.R. (2010). Electrochemical biosensors. *Chemical Society Reviews* 39 (5): 1747–1763.

33 Hertz, L. and Rothman, D.L. (2016). Glucose, lactate, β-hydroxybutyrate, acetate, GABA, and succinate as substrates for synthesis of glutamate and GABA in the glutamine–glutamate/GABA cycle. In: *The Glutamate/GABA-Glutamine Cycle* (ed. A. Schousboe and U. Sonnewald), 9–42. Cham: Springer.

34 Rocchitta, G., Spanu, A., Babudieri, S. et al. (2016). Enzyme biosensors for biomedical applications: strategies for safeguarding analytical performances in biological fluids. *Sensors* 16 (6): 780.

35 Bousse, L. (1996). Whole cell biosensors. *Sensors and Actuators B: Chemical* 34 (1–3): 270–275.

36 Gui, Q., Lawson, T., Shan, S. et al. (2017). The application of whole cell-based biosensors for use in environmental analysis and in medical diagnostics. *Sensors* 17 (7): 1623.

37 Liu, Q., Wu, C., Cai, H. et al. (2014). Cell-based biosensors and their application in biomedicine. *Chemical Reviews* 114 (12): 6423–6461.

38 Gu, M. B., Mitchell, R. J., & Kim, B. C. (2004). Whole-cell-based biosensors for environmental biomonitoring and application. Zhong, JJ. Biomanufacturing. Advances in Biochemical Engineering, 87. Springer, Berlin, Heidelberg. https://doi.org/10.1007/b13533 269-305.

39 Gupta, N., Renugopalakrishnan, V., Liepmann, D. et al. (2019). Cell-based biosensors: recent trends, challenges and future perspectives. *Biosensors and Bioelectronics* 141: 111435.

40 Zeng, X., Shen, Z., and Mernaugh, R. (2012). Recombinant antibodies and their use in biosensors. *Analytical and Bioanalytical Chemistry* 402 (10): 3027–3038.

41 Dzantiev, B.B. and Zherdev, A.V. (2013). Antibody-based biosensors. In: *Portable Biosensing of Food Toxicants and Environmental Pollutants* (ed. D.P. Nikolelis, T. Varzakas, A. Erdem, and G.-P. Nikole), 161–196. Boca Raton, FL: CRC Press Book.

42 Byrne, B., Stack, E., Gilmartin, N., and O'Kennedy, R. (2009). Antibody-based sensors: principles, problems and potential for detection of pathogens and associated toxins. *Sensors* 9 (6): 4407–4445.

43 Goud, K.Y., Kailasa, S.K., Kumar, V. et al. (2018). Progress on nanostructured electrochemical sensors and their recognition elements for detection of mycotoxins: a review. *Biosensors and Bioelectronics* 121: 205–222.

44 Goud, K.Y., Reddy, K.K., Khorshed, A. et al. (2021). Electrochemical diagnostics of infectious viral diseases: trends and challenges. *Biosensors and Bioelectronics* 180: 113112.

45 Kim, H.M., Uh, M., Jeong, D.H. et al. (2019). Localized surface plasmon resonance biosensor using nanopatterned gold particles on the surface of an optical fiber. *Sensors and Actuators B: Chemical* 280: 183–191.

46 Sharma, A., Mishra, R.K., Goud, K.Y. et al. (2021). Optical biosensors for diagnostics of infectious viral disease: a recent update. *Diagnostics* 11 (11): 2083.

47 Chen, Y.T., Liao, Y.Y., Chen, C.C. et al. (2019). Surface plasmons coupled two-dimensional photonic crystal biosensors for Epstein–Barr virus protein detection. *Sensors and Actuators B: Chemical* 291: 81–88.

48 Endo, T., Ozawa, S., Okuda, N. et al. (2010). Reflectometric detection of influenza virus in human saliva using nanoimprint lithography-based flexible two-dimensional photonic crystal biosensor. *Sensors and Actuators B: Chemical* 148 (1): 269–276.

49 Huang, J.C., Chang, Y.F., Chen, K.H. et al. (2009). Detection of severe acute respiratory syndrome (SARS) coronavirus nucleocapsid protein in human serum using a localized surface plasmon coupled fluorescence fiber-optic biosensor. *Biosensors and Bioelectronics* 25 (2): 320–325.

50 Guider, R., Gandolfi, D., Chalyan, T. et al. (2015). Sensitivity and limit of detection of biosensors based on ring resonators. *Sensing and Bio-sensing Research* 6: 99–102.

51 Luchansky, M.S. and Bailey, R.C. (2012). High-Q optical sensors for chemical and biological analysis. *Analytical Chemistry* 84 (2): 793–821.

52 Brecht, A. and Gauglitz, G. (1995). Optical probes and transducers. *Biosensors and Bioelectronics* 10 (9, 10): 923–936.

53 Nguyen, H.H., Lee, S.H., Lee, U.J. et al. (2019). Immobilized enzymes in biosensor applications. *Materials* 12 (1): 121.

54 Kazura, E., Mernaugh, R., and Baudenbacher, F. (2020). A capillary-perfused, nanocalorimeter platform for thermometric enzyme-linked immunosorbent assay with femtomole sensitivity. *Biosensors* 10 (6): 71.

55 Quesada-González, D. and Merkoçi, A. (2018). Nanomaterial-based devices for point-of-care diagnostic applications. *Chemical Society Reviews* 47 (13): 4697–4709.

56 Mattiasson, B., Borrebaeck, C., Sanfridson, B., and Mosbach, K. (1977). Thermometric enzyme linked immunosorbent assay: TELISA. *Biochimica et Biophysica Acta (BBA)-Enzymology* 483 (2): 221–227.

57 Lubbers, B.R. (2015). Nano-calorimetry for point of care diagnostics. Doctoral dissertation. Biomedical Engineering, Nashville, Tennessee.

58 Mujahid, A. and Dickert, F.L. (2012). Molecularly imprinted polymers for sensors: comparison of optical and mass-sensitive detection. In: *Molecularly Imprinted Sensors* (ed. S. Li, Y. Ge, S.A. Piletsky, and J. Lunec), 125–159. Elsevier.

59 Tombelli, S. (2012). Piezoelectric biosensors for medical applications. In: *Biosensors for Medical Applications* (ed. S. Higson), 41–64. Woodhead Publishing.

60 Pohanka, M. (2018). Overview of piezoelectric biosensors, immunosensors and DNA sensors and their applications. *Materials* 11 (3): 448.

61 Dickert, F.L. and Hayden, O. (2001). Non-covalent molecularly imprinted sensors for vapours, polyaromatic hydrocarbons and complex mixtures. In: *Techniques and Instrumentation in Analytical Chemistry*, vol. 23 (ed. A. Janshoff and C. Steinem), 503–525. Elsevier.

62 García-Martinez, G., Bustabad, E.A., Perrot, H. et al. (2011). Development of a mass sensitive quartz crystal microbalance (QCM)-based DNA biosensor using a 50 MHz electronic oscillator circuit. *Sensors* 11 (8): 7656–7664.

63 Cheng, C.I., Chang, Y.P., and Chu, Y.H. (2012). Biomolecular interactions and tools for their recognition: focus on the quartz crystal microbalance and its diverse surface chemistries and applications. *Chemical Society Reviews* 41 (5): 1947–1971.

64 Bacher, G., Bhand, S., and Deshpande, S. (2022). Electrical biosensors for virus detection. In: *Advanced Biosensors for Virus Detection* (ed. R. Khan, A. Parihar, A. Kaushik, and A. Kumar), 241–259. Academic Press.

65 Nuzaihan, M., Hashim, U., Arshad, M.M. et al. (2016). Electrical detection of dengue virus (DENV) DNA oligomer using silicon nanowire biosensor with novel molecular gate control. *Biosensors and Bioelectronics* 83: 106–114.

66 Kaushik, A., Yndart, A., Jayant, R.D. et al. (2015). Electrochemical sensing method for point-of-care cortisol detection in human immunodeficiency virus-infected patients. *International Journal of Nanomedicine* 10: 677.

67 Radhakrishnan, S., Kim, B.S., and Dave, S. (2022). Surface modification with nanomaterials for electrochemical biosensing application. In: *Advanced Nanomaterials for Point of Care Diagnosis and Therapy* (ed. S. Dave, J. Das, and S. Ghosh), 101–120. Elsevier.

68 Panwar, R., Churi, H., and Dave, S. (2022). Point-of-care electrochemical biosensors using CRISPR/Cas for RNA analysis. In: *Biosensors for Emerging and Re-Emerging Infectious Diseases* (ed. J. Das, S. Dave, Radhakrishnan, and P. Mohanty), 317–333. Academic Press.

69 Sahoo, M., Gadnayak, A., Nayak, A. et al. (2022). Advantages of silicon nanowire-based biosensors as wireless technology for infectious disease diagnosis. In: *Biosensors for Emerging and Re-Emerging Infectious Diseases* (ed. J. Das, S. Dave, S. Radhakrishnan, and P. Mohanty), 407–417. Academic Press.

70 Xue, Q., Kan, X., Pan, Z. et al. (2021). An intelligent face mask integrated with high density conductive nanowire array for directly exhaled coronavirus aerosols screening. *Biosensors and Bioelectronics* 186: 113286. https://doi.org/10.1016/j.bios.2021.113286.

71 Dave, S. and Kirubavathy, S.J. (2022). Biosensors based on metal-organic framework (MOF): paving the way to point-of-care diagnosis. In: *Electrochemical Applications of Metal-Organic Frameworks* (ed. S. Dave, R. Sahu, and B.C. Tripathy), 255–267. Elsevier.

72 Sahoo, S., Nayak, A., Gadnayak, A. et al. (2022). Quantum dots enabled point-of-care diagnostics: a new dimension to the nanodiagnosis. In: *Advanced Nanomaterials for Point of Care Diagnosis and Therapy* (ed. S. Dave, J. Das, and S. Ghosh), 43–52. Elsevier.