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A Review of Biosensors and Their Applications

This paper reviews sensors with nano- and microscale dimensions used for diverse biological applications. A biosensor converts biological responses into electrical signals. In recent years, there have been significant advancements in the design and development of biosensors that generated a large spectrum of biosensor applications including healthcare, disease diagnosis, drug delivery, environmental monitoring, and water and food quality monitoring. There has been significant work to enhance the performance of biosensors by improving sensitivity, reproducibility, and sensor response time. However, a key challenge of these technologies is their ability to efficiently capture and transform biological signals into electric, optic, gravimetric, electrochemical, or acoustic signals. This review summarizes the working principle of a variety of biosensors in terms of their classification, design considerations, and diverse applications. Other lines of research highlighted in this paper are focused on the miniaturization of biosensing devices with micro and nano-fabrication technologies, and the use of nanomaterials in biosensing. Recently wearable sensors have had important applications such as monitoring patients with chronic conditions in home and community settings. This review paper mentions applications of wearable technology. Machine learning is shown to help discover new knowledge in the field of medical applications. We also review artificial intelligence (AI) and machine learning (ML)-based applications. [DOI: 10.1115/1.4063500]

Keywords: biosensor, nanomaterial, implantable devices, wearable sensor, medical devices, machine learning, artificial intelligence, artificial intelligence/machine learning, biological systems applications, biotechnology, medical devices and equipment, minimally invasive devices, sensors

Introduction

This extensive review presents different types of biosensors with nano and microscale dimensions used for biological applications. A biosensor is an analytical device, used for the detection of an analyte, that combines a sensitive biological component with a detector element (transducer) [1–3]. The sensitive biological element could be a bioreceptor, a biomimetic component, or a biologically derived material that interacts or binds with the analyte under study. A wide range of biological materials are used for the biosensors such as aptamers, tissue, microorganisms, organelles, mammalian cells, bacteria, enzymes, antibodies, and nuclei acids [3–15]. The transducer, which transforms the biological signal into a physio-chemical signal, has different detection options: electrochemiluminescence [16–19], optical [20,21], electrochemical [22,23], fluorescence [24,25], piezoelectric [26], etc., resulting from the interaction of the analyte with the sensitive biological element. Figure 1 provides an illustration of the principle of biosensors.

The use of biosensors was pioneered by Clark and Lyons [27]. In the early 1960s, they developed an electrode that could measure the oxygen concentration in blood. In this research, the electrode was introduced in perfusion blood during an open-heart surgery procedure. Biosensors have the capability to respond to specific biological signals and process them into measurable quantities for human comprehension. Recently, novel biosensors that can be implantable or wearable were developed [28]. In general, a biosensor consists of three main components. These include the biological sensing component for recognition of the biological signal, the transducer for converting the biological signal into an electric signal, and the signal processing system, which amplifies and displays the output in a desired format for human understanding [29]. The applications of biosensors are diverse; they have proven their usefulness in disease diagnosis in human healthcare delivery, agriculture, homeland security, food security, environmental, and industrial monitoring, as well as bioprocessing [28].

Biological sensors can monitor in real time, the vital signs of individual patients for a long period of time, and provide them with personalized health solutions. For achieving these goals, the biological sensors could be skin-integrated in wearable systems, or implantable medical devices. These biosensors are important to monitor different biophysical parameters of the patients such as; blood

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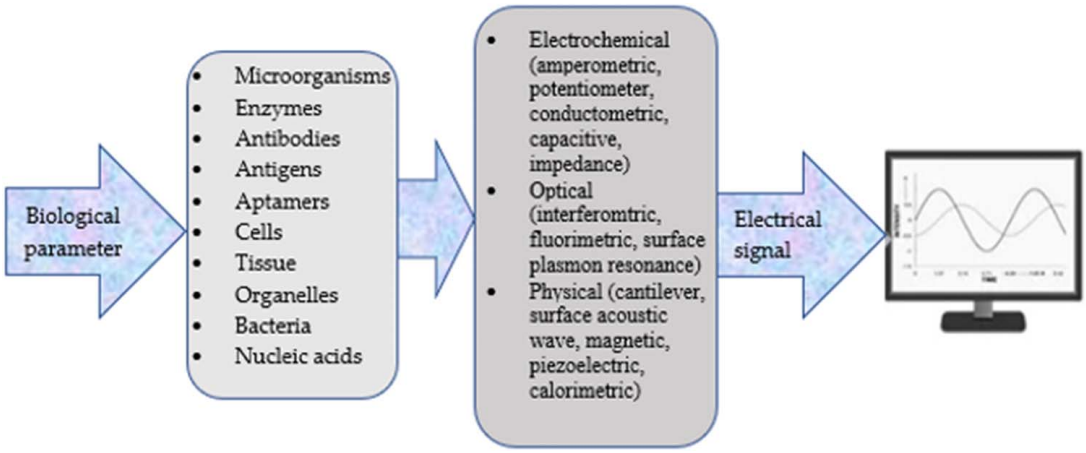

Fig. 1 Illustration of principal components of a biological sensor device: (1) bioreceptor–detector layer of immobilized biomaterial; (2) physicochemical transducer, (3) signal-conditioning and recording the signal for human interpretation

pressure, blood glucose level, heart electrical signals, pulse rate, and respiration rate [30]. The engineers and scientists have consistently collaborated to improve the biosensors' performance with emphasis on biocompatibility, specificity, reliability, durability, and consistency, as well as sensitivity for diagnosis, monitoring, and treatment of several health conditions.

In addition to real-time monitoring of patients and decisions connected to patient health complications, there is also the need for biosensors to simultaneously detect multiple analytes and/or respond to more than one stimulus, within biological fluids, within or outside the human body [29]. Unlike many other sensors used in other fields of application, biosensors (both implantable and non-implantable) are designed with unique features such as biocompatibility, biodegradability, and/or the ability to be bioresorbable, and miniaturization due to the biological environment in which they function. For instance, a skin-integrated device must be flexible, stretchable, lightweight, ultra-thin, and reliable. These devices can conform to the geometry and/or shape of the mounting surface. Furthermore, any regular movement or modification of the skin must be allowed without causing any discomfort to the patient [28].

This review paper is focused on several aspects of biosensing such as a general overview of biosensors, classification of biosensors based on the transduction methods, characteristics of biosensors, biosensor design considerations, biosensor applications, advancement in biosensors due the nanomaterials discovery, wearable biosensors, and machine learning application in biosensing.

General Overview of Biosensors

Biosensors have the capability of responding to the presence of a specific biological analyte, and the ability to quantify the analyte, subsequently translating it into a signal that is human-readable [3,31–33]. The sensory element is biochemical in nature, and the biosensor operation is based on reactions with the analyte of interest. A biosensor consists of three main components: (1) bioreceptor–detector layer of immobilized biomaterial; (2) physio-chemical transducer, which transforms the biological response into a measured electric signal; (3) electronic system for amplifying and recording the signal for human interpretation [34,35]. The bioreceptor is simply a biological molecule that comes into direct contact with the analyte of interest. Generally, it is immobilized on the active surface of the transducer. The responsibility of the bioreceptor is to detect the presence of the analyte and subsequently bind it. This results in physiological changes, which then also modify the physicochemical properties of the transducer in the vicinity of the biological receptor. This phenomenon leads to changes in the physical properties of the transducer, which are translated into an electrical signal for human understanding [36]. These main components of the biosensor are illustrated in Fig. 1.

According to Inshyna et al. [37], biosensors can be classified based on either the type of transducer or type of bioreceptor used for their construction. According to this classification, we have electrochemical, optical, calorimetric, piezoelectric, acoustic, and electronic biosensors. Furthermore, based on the type of bioreceptors, biosensors can also be grouped as follows: enzymatic, cellular, tissular, DNA sensors, immunosensors, and aptamer sensors [34,38,39].

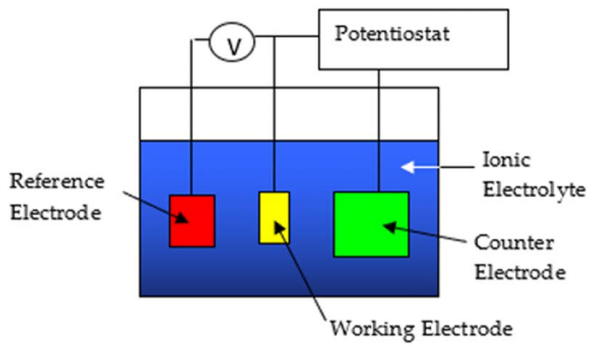

Fig. 2 Electrochemical measurements with a three-electrode potentiostat

Classification of Biosensors Based on the Transduction Methods

Electrochemical Transducers. Electrochemical biosensors exhibit high sensitivity, selectivity, and the capability to detect. Electrochemical biosensors are based on classical electrochemistry, with the electrodes introduced in an electrolyte. The electrochemical reaction occurs at the working electrode surface between bioreceptor and analyte producing detectable electrochemical signals in terms of voltage, current, impedance, and capacitance. The devices used for electrochemical measurements are relatively simple, easily miniaturized, require low power, and are sensitive for biological applications.

In experimental electrochemistry, the three-electrode cell is one of the most common configurations used to study electrochemical reactions. It consists of a counter electrode, working electrode, and reference electrode, as illustrated in Fig. 2. The electrode where oxidation/reduction takes place (where the potential is controlled) is the working electrode. The reference electrode has a stable potential; no current flows through it. The potential of the working electrode is measured relative to it. The potentiostat is

used to supply a constant potential to the working electrode, regardless of the chemical changes taking place on the working electrode at that time. Due to the advancement of microelectromechanical systems' (MEMS) microfabrication, the classic electrochemical cells could be miniaturized at microscale [40]. Figure 3 is an illustration of three electrodes miniaturized electrochemical cells that can be used for the detection of biomarkers in blood or biological fluids.

Based on the transduction principle, electrochemical biosensors are categorized as (a) voltametric, (b) amperometric, (c) impedimetric, (d) conductometric, and (e) potentiometric [42,43]. These sensors convert the information associated with electrochemical reactions (the reaction between an electrode and analyte) into an applicable qualitative or quantitative signal [41]. In this review, we will discuss voltametric and impedimetric biosensors because there are many applications for these sensors.

The working electrode could be a simple planar electrode or contain an array of micropillars fabricated on the planar working electrode. The micropillar electrode has a larger active area for detection to enhance the sensitivity of detection (Fig. 4).

Voltametric and amperometric techniques are characterized by applying a potential to a working electrode versus a reference electrode and measuring the current. The term voltammetry is used for those techniques in which the potential is scanned over a set potential range. The current response is usually a peak or a plateau that is proportional to the concentration of the analyte. In amperometry, changes in the current generated by the electrochemical oxidation or reduction are monitored directly with time, while a constant potential is maintained at the working electrode with respect to a reference electrode. The voltametric/amperometric biosensors generally are used for enzyme-linked immunosorbent assays (ELISA) detection, and there is extensive research in this area [40,44].

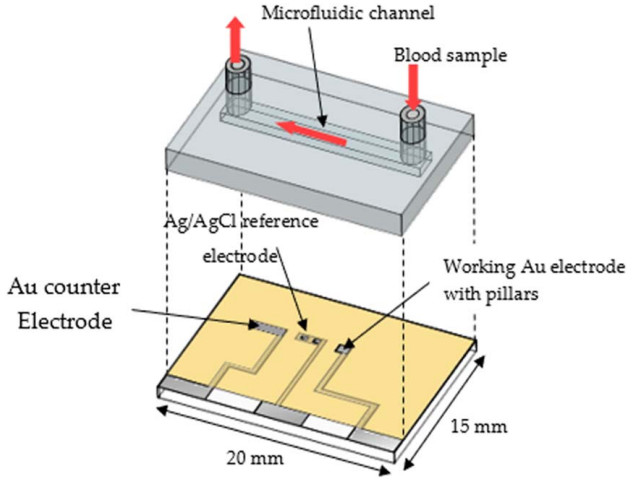

Fig. 3 Schematic of microfluidic system for testing blood biomarkers using microscale electrochemical electrodes. The working electrode could be planar or covered with tall pillars. Reproduced with permission from Pandikumar and Rameshkumar [41].

Impedimetric biosensors measure changes in conductance and capacitance at the sensor surface as the selective binding of the

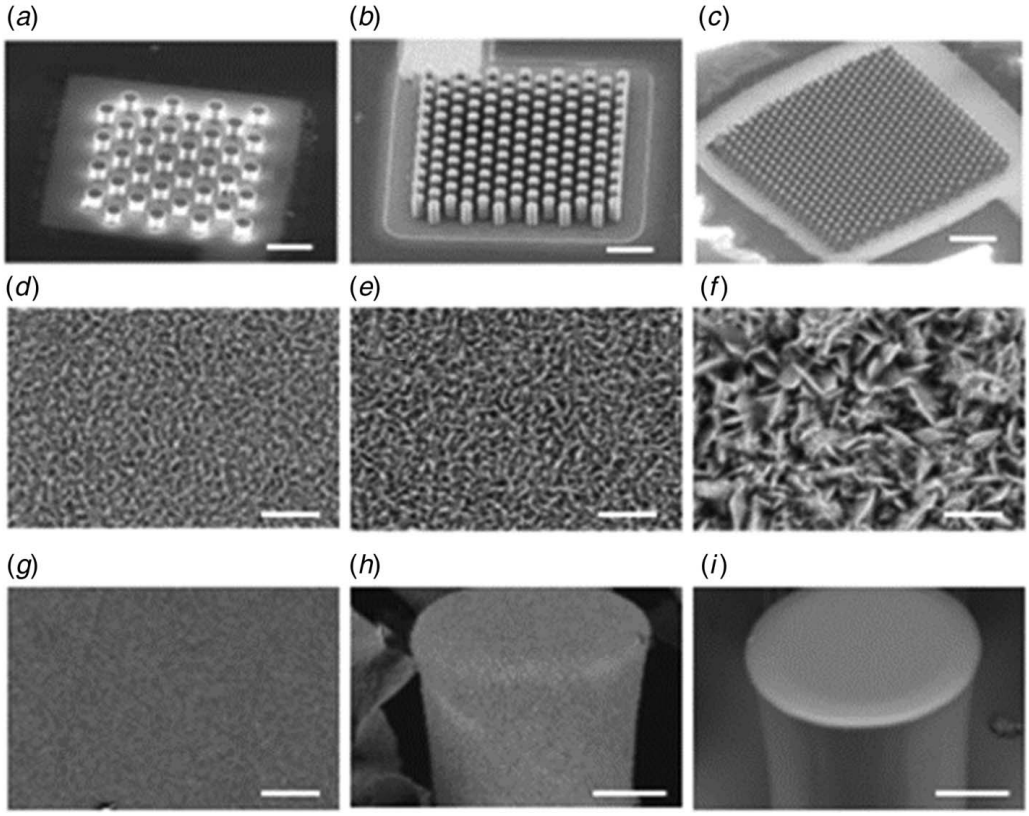

Fig. 4 Scanning electron microscopic images of the working electrodes. (*a*)–(c) Micropillar electrodes of diameter (*a*) Ø30 μm, (*b*) Ø20 μm, and (c) Ø10 μm. The scale bars are 100 μm. (*d*)–(*g*) The surface of the flat electrode modified with gold black at the current density of $-30\ \mu A/mm^2$ (*d*), $-60\ \mu A/mm^2$ (*e*), $-120\ \mu A/mm^2$ (*f*), and without the modification (*g*). The scale bars are 2.5 μm. (*h*) and (*i*) The surface of a micropillar of the Ø30 μm electrode modified with gold black at the current density of $-60\ \mu A/mm^2$ (*h*) and without the modification (*i*). The scale bars are 10 μm. Reproduced with permission from Numthuam et al. [40].

target occurs. In this way, the impedimetric transducers can detect biological molecules or the behavior of live cells. For applications regarding live cells, the impedimetric transducer is named Electric Cell-substrate Impedance Sensing (ECIS), which is a real-time and label-free detection method to analyze the behavior of cells. The ECIS technique was pioneered by Giaever and Keese [45–47] and has been extensively studied for over two decades due to its simple structure, easy operation, and sensitivity to many cell behaviors and properties [48–55]. The ECIS technique can measure cell attachment, proliferation, migration, invasion, and cell viability because the impedance measurements are directly responding to cell attachment, growth, and proliferation. When cells attach to the electrodes, cell attachments result in additional impedance to the circuit. Their insulating properties can be detected. The impedance values gradually increase until monolayer formation and then reach equilibrium when the cells are confluent and stable. Apoptotic cells lose the dielectric properties and tend to detach from the sensing electrodes. When the cells detach or lose the dielectric properties, the measured membrane impedance will decrease. As cells grow and cover the electrodes, information about the morphology of the cells and nature of the cell attachment can be extracted from the measured impedance [52–55].

The name "impedance spectroscopy" is derived from the fact that the impedance is generally determined at different frequencies rather than just one. The impedance spectroscopy measurements are generally performed using a small Alternative Current (AC) electric field over a wide frequency range (100–100 kHz). Thus, an impedance spectrum is obtained that allows the characterization of cell size, membrane resistance and capacitance, and cytoplasm conductivity as a function of frequency.

Determining the experimental values, for the capacitance and resistance of the cell membrane, enables cell electrophysiological information collection [52–55]. As an example, blocking the ion channels enables the cell membrane to act more capacitively. The capacitance and resistance characterizing a live cell are significantly different from those of a dead cell. While healthy cells adhere more securely to surfaces, as compared to unhealthy or dead cells, this results in a stronger capacitive coupling between the cells and underlying electrodes. When the cells die, the value of impedance reduces, due to the change in the membrane capacitance and resistance.

The ECIS technique has become convenient for various applications, such as: (1) monitoring cell migration and wound repair [56], (2) monitoring cell proliferation [57], (3) real-time continuous transepithelial electrical resistance (TEER) measurements [58], (4) monitoring the signal transduction pathways activated by G-protein-coupled receptors (GPCR) [59], (5) studying cell differentiation events [60], (6) assessing the cytotoxicity of a variety of toxicants [61], and (7) monitoring the cell attachment and spreading [62].

Recently, a review of the ECIS technique used for applications of two-dimensional cell culture was published in the literature [63]. For instance, ECIS has important applications in the study of cancer metastasis [49,53,64]. Mathematical models are used to simulate the impedance of cell monolayer and the influence of electrode dimensions on the detection sensitivity [54,55]. The cell

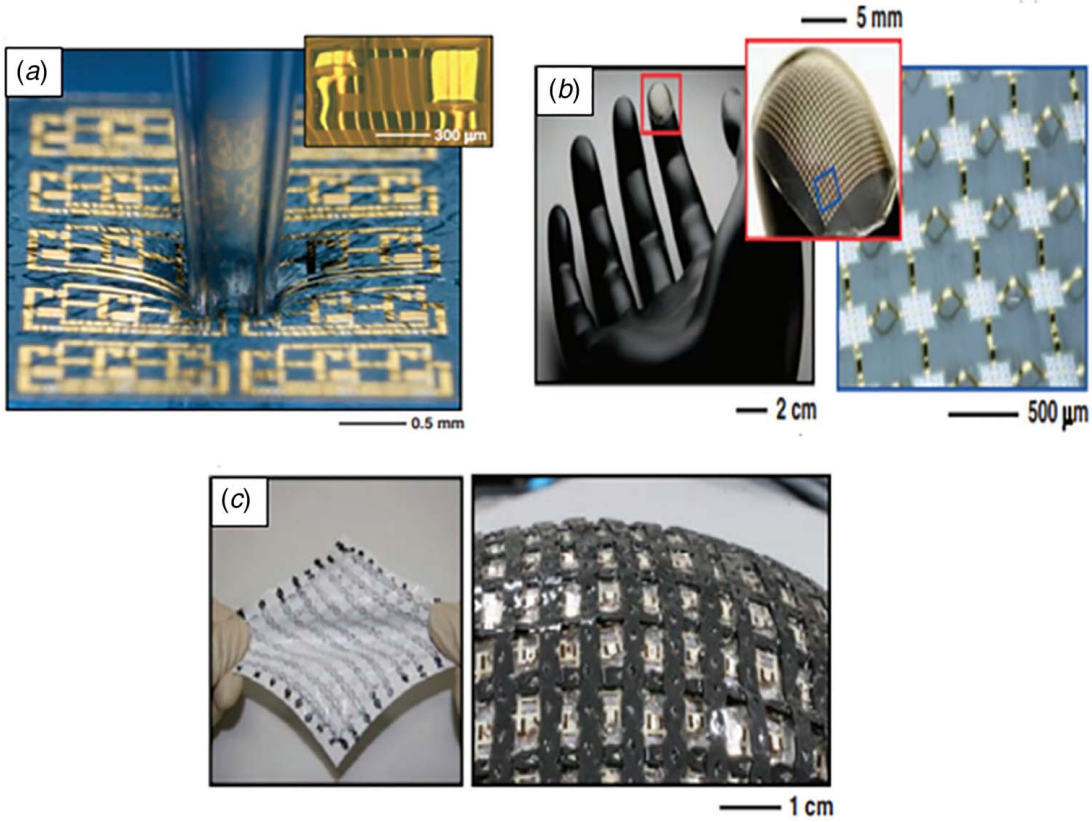

Fig. 5 Examples of stretchable electronics. (*a*) Stretchable silicon circuit in a wavy geometry, compressed in its center by a glass capillary tube (main) and wavy logic gate built with two transistors (top right inset). (*b*) Stretchable silicon circuit with a mesh design, wrapped onto a model of a fingertip, shown at low (left), moderate (center) and high (right) magnification. The red (left) and blue (center) boxes indicate the regions of magnified views in the center and right, respectively. The image on the right was collected with an automated camera system that combines images at different focal depths to achieve a large depth of field. (c) Array of organic transistors interconnected by elastic conductors on a sheet of PDMS in a stretched (left) and curvilinear (right) configuration.

viability was also tested using the ECIS technique, as reported in Ref. [65].

In the past decade, investigation into stretchable electronics has been widely conducted. Dr. John A. Rogers' group at the University of Illinois, Urbana-Champaign invented the stretchable electronics concept. According to Refs. [66,67], advanced mechanics and materials research have made possible the design of flexible electronics, such as integrated circuits with properties and functionalities comparable to acoustic sensors of the traditional silicon wafer-based ones. The advantages associated with stretchable electronic technology are its ability to conform to irregular surfaces and shapes without any distortion in their functions or deformation. Other advantages include the possibility of micro and nanoscale electronic designs that otherwise are not feasible with the conventional silicon wafer-based type. The advent of stretchable electronics has paved the way for the design of electronic eyeball cameras and deformable light-emitting displays. It is safe to say that soon, low-power sensors can be designed using flexible electronic technology together with piezoelectric materials. Figure 5 shows examples of stretchable electronics.

A stretchable biosensor with the ECIS technique was also demonstrated [68]. Authors reported that ECIS electrodes were embedded in a stretchable device and ECIS measurements on mammalian cells exposed to a cyclic strain were performed. The stretchable ECIS sensor was demonstrated to be capable of real-time monitoring the cell proliferation, while applying mechanical stimulation [68]. Figure 6 shows a stretchable ECIS sensor and details of the components.

Electrochemical biosensors have an important role in many clinical, environmental, industrial, pharmaceutical, defense, and security applications due to their superior sensitivity and selectivity. Recent developments in nanotechnology and material science, as well as being able to custom engineer the biorecognition component, will further push the development of useful and reliable electrochemical biosensor devices. The sometimes-limited shelf life and stability of the biorecognition component, as well as nonspecific binding, continue to be the biggest limitations for these types of biosensors. However, many strategies have helped to overcome or minimize these problems.

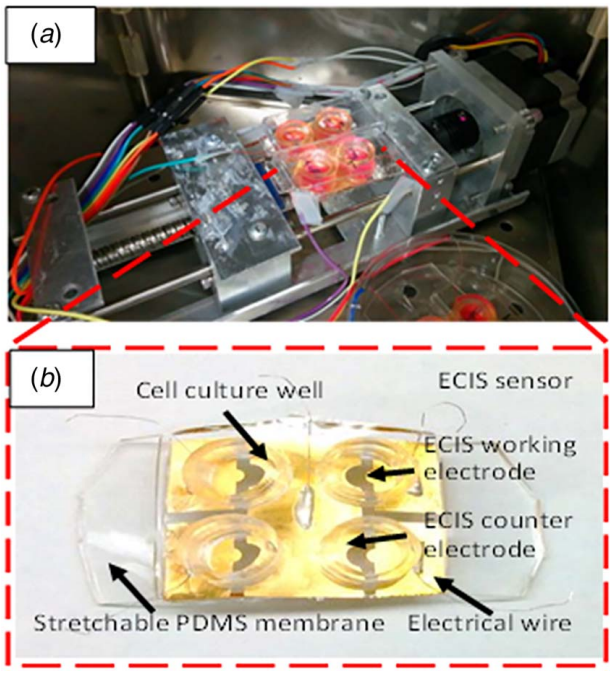

Fig. 6 Stretchable ECIS sensor. A linear motor was used to cyclically stretch the ECIS sensor. (*a*) The linear motor with the stretchable ECIS sensor mounted on it was placed inside the incubator; (*b*) stretchable ECIS sensor. Reproduced with permission from Zhang et al. [68].

Piezoelectric-Based Biosensors. The Quartz crystal microbalance (QCM) is a classic example of a piezoelectric biosensor. A standard QCM is based on a thin quartz plate with two aligned circular electrodes fabricated at the top and bottom surfaces of the piezoelectric substrate (Fig. 7). The QCM operates using thickness-shear mode. When an AC is applied between the top and bottom electrodes, the top and bottom surfaces of the piezo plate extend in the opposite direction parallel to the plate surface, which generate a thickness shear mode that propagates through the quartz substrate. Because of the high accuracy and stability of QCM measurements [69–75], this technique has become helpful for scientists, especially for viscosity and density sensing purposes. The drawback of the QCM measurements is the damping that occurs when the biological liquid is added to the top electrode, further decreasing the QCM sensibility. Generally, the QCM resonant frequency variations are monitored in real time and give information about the process that occurs at the piezoelectric crystal surface level.

The QCM operates in the resonant frequency range between 1 MHz and 20 MHz, although at higher frequencies the QCM provides good opportunities for enhancing the sensitivity of the detection. To achieve high resonant frequency, QCM biosensors create technological complications during microfabrication, because the piezoelectric substrate must be very thin [76]. Generally, the QCM detects biological molecules by measuring the changes in resonant frequency that occur when the antigen binds to the antibody receptor [77].

QCM detection offers stability, reusability, and cost-effectiveness. There are many research papers describing the biological detection with QCM. The QCM is an extremely sensitive mass sensor, capable of measuring mass changes in the nanogram range. This piezoelectric thickness-shear-mode resonator has been successfully employed for biological sensing applications, due to the minimal damping of the acoustic wave in liquid. The QCM's sensitive surface can be functionalized with different molecules that respond to different target analytes and have been tested with a wide range of biological applications. The adhesion [78,79] and viscoelastic [80–82] properties of mammalian cell monolayers

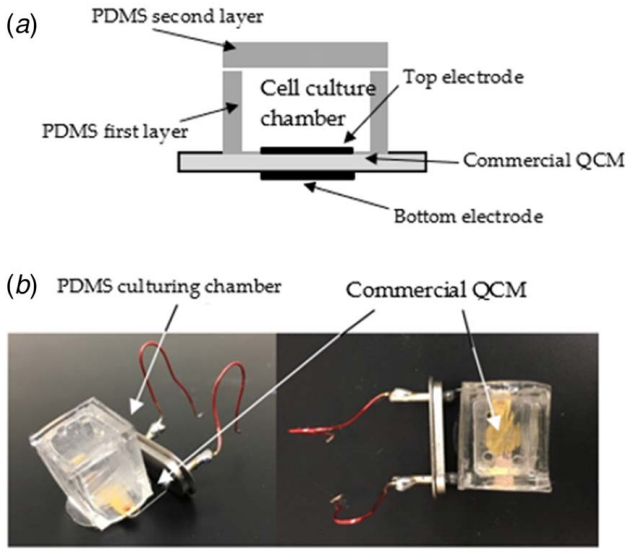

Fig. 7 Fabrication of culturing chamber for commercial QCM. (*a*) Cross-view of the PDMS chambers. Two layers of PDMS were used to obtain PDMS with tall dimensions. (*b*) Photographic images of the commercial QCM with the fabricated culturing chamber used for the experiments. Reproduced with permission from Lee et al. [69].

have been successfully characterized and reported using QCM resonators. QCM was previously used for virus detection. The QCM sensor was able to detect 1 nanogram of orchid virus [83,84]. QCM was also used for the detection of avian influenza virus [85].

An interesting application of the QCM is its combination with ECIS electrodes. Mammalian cells were in vitro cultured on the QCM and ECIS electrodes. This combination of ECIS and QCM devices was used as a water toxicity sensor. The mammalian cells were the sensorial element and their viability after exposure to the toxicant was monitored with both sensors: ECIS and QCM [70,71]. A commercial QCM was used to investigate live cells' activity in water-based toxic solutions. The QCM used in this research had a resonant frequency of 10 MHz and consisted of an AT-cut quartz crystal with gold electrodes on both sides. This QCM was transformed into a functional biosensor by integrating with polydimethylsiloxane (PDMS) culturing chambers (Fig. 7) [69].

Surface Acoustic Wave Devices. Surface acoustic wave sensors use piezoelectric materials to generate acoustic waves. Surface acoustic waves (SAW) are elastic waves that travel along the surface of the piezoelectric substrate, typically within 1–2 wavelengths from the surface and are sensitive to any modifications on its path of propagation. Anisotropic substrates like Lithium Niobate, Lithium Tantalate, Quartz, and Langasite are commonly used substrates for SAW generation. Parameters like crystal orientation, SAW velocity, coupling coefficient, permittivity and temperature coefficient of delay (TCD) determine the generation of SAW in these substrates [86].

SAW devices for liquid applications have attracted much attention due to their wide applications in the biological field [87–89]. Among various SAW devices, the wave-guided shear-horizontal (SH) SAW device, also referred to as the Love wave device, has been studied for liquid applications due to its high mass sensitivity and sensing capability in liquid environments. A Love mode surface acoustic wave device uses a piezoelectric substrate with inter-digital transducers (IDTs) to produce the surface-localized SH waves. A material layer with a slower acoustic velocity is deposited on the piezoelectric substrate to trap the acoustic energy near the surface and prevent energy loss into the bulk material. An essential application of the Love mode SAW is immunosensing specific biomarkers [87,90–93]. Other than immunosensors, SAW devices were used as mammalian cell and bacteria-based sensors [94]. In Ref. [95], a cell-based Love wave SAW biosensor was developed for real-time marine toxin testing.

A surface-horizontal surface acoustic wave (SH-SAW) device was developed for real-time monitoring of blood viscosity at room temperature. The device was tested with a liquid drop placed on the SAW delay-line path and demonstrated a sensitivity of 3.57 ± 0.3125 kHz shift per centipoise, enabling the potential for high-precision blood viscosity monitoring [96].

SAW sensors have been used in different applications. These include biosensing, chemical and gas sensing, microfluidics, and mechano-biological applications. For biological applications, SAW-based sensors are used for separating, identifying, and controlling biological targets; for instance, biomolecules, or proteins from bio-species, such as bacteria, fungi, or viruses. For chemical and gas sensing, the targeted chemical or gas molecule is attached to the functionalized surface and positioned between two electrodes. A perturbation of the resonant frequency is generated after the targeted biological material is sensed [97].

Electronic Biosensors Based on Field-Effect Transistors. These types of transducers employ the use of ion-sensitive silicon field-effect transistors (FET). The bio-sensitive layer is placed above the surface of an ion-sensitive membrane that forms a part of the gate of the field-effect transistor. Conventionally, FET-based biosensors with receptors (e.g., antibody) immobilized on the gate region above the active channel of the FETs face an intrinsic issue, that is the severe charge screening effect in high ionic strength solutions, such as in serum or blood samples, leading to low sensitivity for direct detection of protein in the physiological environment. Several research groups have reported that conventional FET-based biosensors can effectively detect proteins in a physiological salt environment, using AC signals in drain-source voltage (Vds), in conjunction with a reference electrode, in a relatively high frequency [98–101]. An extensive review of the FET presents diverse and interesting applications of this type of biosensor [102].

The FET transistors were demonstrated to feasibly measure Aβ fibrils in human serum with concentrations ranging from 100 pM to 10 μM [103]. C-Reactive protein (CRP) was sensed from 1 fM to 100 nM, demonstrating the high sensitivity of this type of biosensor [104]. Nanowires (NW) and nanoribbon (NR) were used in the fabrication of the FET biosensor. The detection in the subthreshold regime of NW FET sensor has the merit of not only improving the conductance response and signal-to-noise ratio but also better detection limit. The research showed that the detection limit of the NW FET device was improved from ~0.75 pM in the linear regime to ~1.5 fM in the subthreshold regime [105]. In comparison with the nanowire structure, the larger surface-to-volume ratio of NR was demonstrated to increase the efficient surface area for detection, where the sensing elements were immobilized and therefore proportionally improved the sensitivity of the NR-FET biosensors [106].

Optical Biosensors. Optical biosensors can detect luminescent, fluorescent, colorimetric, or other optical signals produced by the interaction of microorganisms with the analytes and correlate the observed optical signal with the concentration of target compounds. Optical biosensors have the biorecognition element integrated into an optical transducer system. They utilize enzymes, antibodies, aptamers, whole cells, and tissues as biorecognition elements. There are several types of optical biosensors based on optical waveguides, surface plasmon resonance (SPR), photonic crystals, and optical fibers [20,106,107]. Optical biosensors have been used for clinical diagnostics, drug discovery, food process control, and environmental monitoring.

Temperature Sensors. These transducers determine the quantity of heat generated by biological material [31]. An interesting application of the temperature sensor is based on bimaterial cantilever beams, which were employed as highly sensitive temperature sensors for biological applications [108,109]. The bicantilever beam temperature sensor was fabricated from composite materials and operated in deflection mode. To achieve the high sensitivity required for the detection of heat generated by a single mammalian cell, the cantilever beam temperature sensor was microprocessed with a length at the microscale and a thickness in the nanoscale dimension [110]. As a thermogenic sample, the brown fat cells (BFCs) that are related to metabolic heat production were employed. The cantilever beam deflection was measured under a conventional microscope, when six cells of BFCs were situated about 5 μm from the tip of cantilever beam, after the BFCs were thermal stimulated with flowing norepinephrine solution (NE). When the cantilever beam senses the heat, it bends due to the difference in the coefficient of the thermal expansion of the composite structure.

A second cantilever beam was included in a vacuum chamber and operated in the resonant frequency regime. The working principle of the vibrating cantilever beam temperature sensor is based on shifts in resonant frequency in response to temperature variations generated by mammalian cells [110]. The heat sensing of a single BFC cell was demonstrated using this resonant cantilever beam. The temperature measurements were performed by stimulating the activity of BFC by introducing NE solution (1 μM) in the microfluidic chamber that contains BFC culture. The cells were introduced in the microfluidic channel and some cells spontaneously attached to the sample stage side of the cantilever beam. Then, resonant frequency measurements of the cantilever beam side situated in vacuum were performed. The heat production was observed a few

Table 1 Principal types of biological sensors with transduction methods and applications

Sensor type	Transduction method	Applications	References
Electrochemical sensors	Voltammetry and amperometry	ELISA for detection of bone markers, DNA	[40,44]
	Impedance spectroscopy (ECIS)	Monitor cell migration, wound repair, cell differentiation, cell attachment, cancer metastasis, cell viability, cell proliferation, cell apoptosis	[49,53,56,57,60,61,65,68,69,111]
Piezoelectric sensors	QCM	Water toxicity, human skin odor, human urine analysis, cell adhesion viscosity properties of mammalian cell monolayer, detection of orchid virus, detection of avian influenza virus	[77–71,78–81,83,85]
Acoustic sensors	SAW device	Immunosensing of Biomarkers, Heavy metal toxicity of water, marine toxin detection	[87,90–95]
Optical sensor	Surface plasmon resonance (SPR)	Bacteria detection, Detection Biomarkers in oncology	[20,112,113]
Temperature sensor	Biomaterial cantilever beam deflection and resonant frequency	Heat generated by BFC	[108–110]
Electric sensor	FET	AB fibrils, C-reactive protein (CRP) and carcinoembryonic antigen detection, prostate-specific antigen (PSA)	[103–105]

minutes after adding NE, and the heat generation continued for approximately 23 min. A temperature change of 0.27 °C corresponds to 1 nJ of heat was measured.

Biosensors as analytical tools have several applications in different fields such as diagnostics, disease monitoring, and toxicity studies. The significant role of biosensors is illustrated in Table 1, which presents several biosensors with transduction methods and applications. The applications of these sensors are interesting, due to the advances and discoveries in the technological areas. There are still numerous challenges of biosensors despite many advances in technology. In some biosensors, a large amount of data are generated quickly at the output, and the analysis of these data requires further processing by an experienced user which can lead to errors. Processing by a person can take time to analyze data, which can greatly reduce the efficiency of the biosensor.

Recently, machine learning (ML) has allowed for enhancement in analytical capabilities of these various biosensing modalities [114]. ML, a subset of artificial intelligence (AI), is a framework allowing algorithms to learn automatically from data. For medical applications, it has been shown that such methods can not only significantly outperform human-engineered expert knowledge, but they are also able to discover new knowledge.

Characteristics of Biosensors

Due to their nature and mode of operation, biosensors are designed with unique characteristics and features upon which their usability and reliability depend.

Sensitivity. Sensitivity is the most important characteristic of a sensor. It is the detection limit, which is the minimal amount (or concentration) of analyte that can be detected. This characteristic shows the capacity of the sensor to capture any fluctuations occurring in the targeted analyte if it remains in the vicinity of the sensor. Highly sensitive sensors are affected by fluctuations at low scales such as nanogram and femtogram scales [107,112,115] has been reported that the sensitivity for glucose determination ranges from 0.048 to 3.36 mA L mol^{-1} cm^2.

Selectivity. Selectivity means that the sensor detects a certain analyte and does not react with added mixtures and contaminants. This characteristic of a biosensor is based on the ability to bind or communicate with the specific target analyte (molecule) in the presence of others in the same medium or test site. In implantable medical applications of biosensors, selectivity is one of the most important features of the device. This is because most of the analyte candidates in the bloodstream possess similar properties, and therefore, it is important that the bioreceptor part of the sensor communicate only with the analyte of interest [116,117].

Stability. The stability of a sensor refers to the signal drifting under constant conditions, which could cause errors. This feature of the biosensor ensures that it can withstand interference or noise from external factors during its operation. Noise in this case can be in the form of humidity that tends to affect the accuracy of the sensor signal in operation [118]. In addition, the temperature of the human body also impacts the effectiveness of the bioreceptor component of the sensor, thereby causing inconsistencies in the overall output of the sensor [119]. Other factors that affect the stability are the degradation of the bioreceptor over time and the affinity of the bioreceptor to the analyte.

Reproducibility. Due to the delicate conditions under which biosensing is required, it is necessary that a biosensor produces consistent output results, under the same or similar conditions, using the same analyte. This ability to show repeatable results, whenever the sample is measured, is an important quality of the transducer [118]. Consistent calibration of the biosensors after use in accordance with the manufacturer's instructions will ensure and enhance reproducibility and consistency of results.

Response Time. A biosensor's response time is the amount of time it takes to read and produce a signal after its bioreceptor meets the specific analyte [36,120]. For example, glucose oxidase–based sensors have a response time between 5 and 30 s [115].

Range or Linearity. The linearity of a biosensor is its ability to exhibit variation in its output proportional to different analyte concentrations. This is used to determine the resolution of the sensor, that is the measurement of the minimum change in the concentration of the analyte that can generate a corresponding response from the sensor. This feature is useful when sensing a wide range of concentrations for a specified analyte [118,119].

For mass production, it is important that the biosensing parameters are quantitatively validated [121,122]. The analytic hierarchy process was used, to perform a quantitative analysis of the signal produced by a carbon nanotube tube sensor, that consisted of 9.8% noise, and 10.1% error from external factors, which means that only about 80% of the normalized signal was corresponding to the real signal [122].

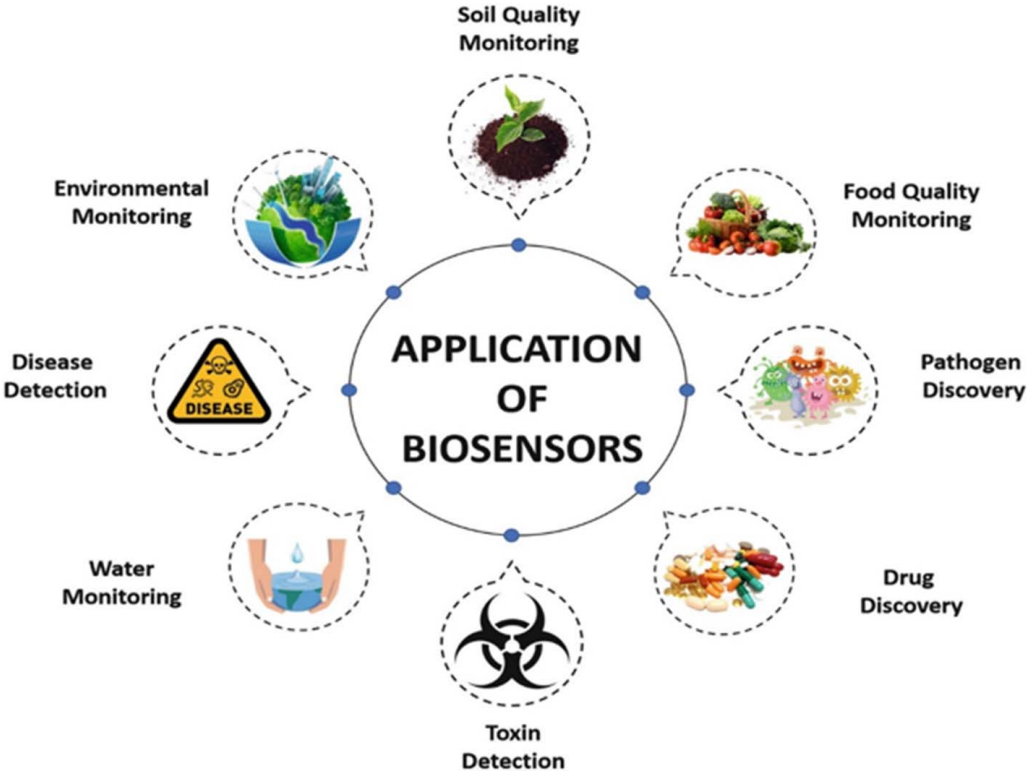

Fig. 8 Different applications of biosensors. Reproduced with permission from Singh et al. [130].

Limit of Detection

This characteristic of a biosensor describes the minimum quantity and concentration of analyte that the sensor can detect in the sample. This is mainly used to determine the quality of the sensor, and it is for this reason that many describe it as the most critical feature in the design and selection of biosensors. It is often determined indirectly through a linear calibration function formulated from a linear regression performed on a set of measurements of instruments against the concentration of the analyte [123].

Biosensor Design Considerations. In designing a biosensor, the principal thing is to identify and understand how the specific analyte of interest interacts with the bioreceptor (the component of the sensor that directly encounters the analyte). The following factors such as biological receptor selection, immobilization method, and transducer type must also be taken into consideration when designing a biosensor.

Biological Receptor Selection. The biological receptor, being an important component of the sensor, is required to be highly sensitive and selective. These features enable it to (a) selectively interact with only the targeted biomolecule in the presence of others and (b) be able to capture the exact characteristics or behavior of the analyte. Understanding and acknowledging the advantages and disadvantages as well as the nuances in the biosensor applications play a major role in the selection and/or design of an appropriate receptor [124,125].

Immobilization Method Selection. Immobilization is the process of depositing a biological molecule onto a surface, in this case, a transducer. Various methods/techniques are used in the process. In general, the choice of method used is primarily determined by the physicochemical properties of the surface under consideration [126]. Some of the methods include adsorption, entrapment, covalent attachment, microencapsulation, and cross-linking [31,127]. The most popular method used is adsorption because it is simple and inexpensive. The disadvantage is that the deposition done by this method is usually affected by experimental conditions like ionic strength, temperature, and pH due to the weak van der Waals forces forming the bonding [128,129].

Transducer Element Selection. The sensitivity of a biological sensor greatly depends on its transduction method. In many applications, high sensitivity and low limit of detection are requested for monitoring a particular analyte of interest. However, in applications where selectivity is important to distinguish between the target analyte and other biological components, sensitivity could be affected. Therefore, finding a good balance between these features in designing or selecting a transducer element is indispensable [127,128].

Fields of Biosensor Applications

A few decades ago, when in situ testing and monitoring of biological materials was not possible, samples were taken to labs for analysis. Aside from the fact that this practice provides scientists and engineers with enough time and a convenient environment for the necessary analysis, this tends to be quite expensive and time-consuming, and requires consistent recruiting and training of highly skilled experts to achieve the testing. With the development of biosensors, their applications are in different fields such as medicines, environment, food safety, defense, and drug discovery. Figure 8 illustrates different fields of application of biosensors.

Medical Applications. For medical applications, biosensors are designed to interact with the biomolecules of the organism they are residing in. The application of biosensors in the medical field has experienced rapid growth over the years. This is due to the ease with which it has made diagnosis, testing, and monitoring of medical conditions in patients. For instance, Electrochemical biosensing systems coupled with Graphene Quantum Dots (GQDs)

Table 2 Nanomaterials-based biosensor transduction type and applications

Nanomaterials	Transducer type	Biosensing application	References
Nanoparticle (NP) AuNPs, AgNPs, magnetic nanoparticles	Localized surface plasmon resonance (LSPR), ELISA	Medical imaging, drug delivery, protein and DNA detection, virus detection	[35,152–154]
Nanorods	Surface plasmon resonance (SPR), electrochemical detection, FET	Protein and DNA detection, phosphate detection	[155–158]
Nanowire (NW)	Conductive transduction, FET, SPR	Disease diagnostics, Drug delivery, protein and DNA detection, immunoglobulin detection	[159–162]
Quantum dot (QD)	Resonance energy transfer (FRET)	Detection of organic compounds, pharmaceutical analytes, cancer biomarkers, virus	[163–167]
Carbon nanotubes (CNT)	Bioenzymatic electrochemical Biosensors, near-infrared (NIR) optical sensing, FET, conductive transduction	Glucose monitoring, fructose, galactose detection, DNA, and cancer biomarkers detection	[150,168,169]
Dendrimer	Fluorescent sensing	Disease diagnostics, drug delivery	[170–174]

biosensors have been proven to enhance the early detection of cancerous cells, as well as monitor the biomarker concentrations of the affected area. This helps medical practitioners to differentiate between normal and cancerous cells [131]. Optical biosensors are also reported by Kaur et al. [132] as an efficient tool for diagnosing different types of cancers in real time owing to their low sensitivity and low detection limit. They are also used to monitor and control blood sugar levels, as well as monitor cardiovascular conditions in real time during and after surgical procedures. Other medical applications include diabetes control and pathogen detection [133]. It was reported by Bohunicky et al. [134] that biosensors can help in early detection of cancer. This can be achieved by constantly monitoring certain protein levels as well as secretions from tumors. This will go a long way to help mitigate the pain and subsequent death of a large number of people carrying the disease.

Cardiovascular disease is the leading cause of death globally. Hence, researchers and medical practitioners have developed various techniques, such as immunoaffinity column assays, fluorometric assays, and enzyme-linked immunosorbent assays for sensing, monitoring, and managing cardiovascular problems [135–137]. However, with the use of biosensors, these expensive and time-consuming techniques can be avoided in case of early detection, monitoring, and treatment of cardiac problems. The emergence of biosensors provides a significant number of advantages over conventional diagnosis assays mentioned because they are established on electrical measurements and employ biochemical molecular recognition elements with the desired selectivity with respect to a particular biomarker under consideration [138,139].

Environmental Applications. With the adverse environmental pollution comes health problems for those in the immediate vicinity. As discussed prior, sensitivity and selectivity are key features of biosensors that could continuously scan the environment to sense the presence and the quantity of chemical agents, organic pollutants, potentially toxic elements, and pathogens that might pose a health hazard. Typical biosensors for environmental applications make use of antibodies, aptamers, nucleic acids, and enzymes as biological receptors. These biosensors include immunosensors, aptamer sensors, and enzymatic biosensors. Biosensors can also detect pollutants by measuring color, light, fluorescence, or electric current as reported by Refs. [140–145].

Application in the Food Industry. In the food industry, biosensors are employed as quality assurance tools. They are useful from the crop-growing stage to the processing of the food. Biosensors are also

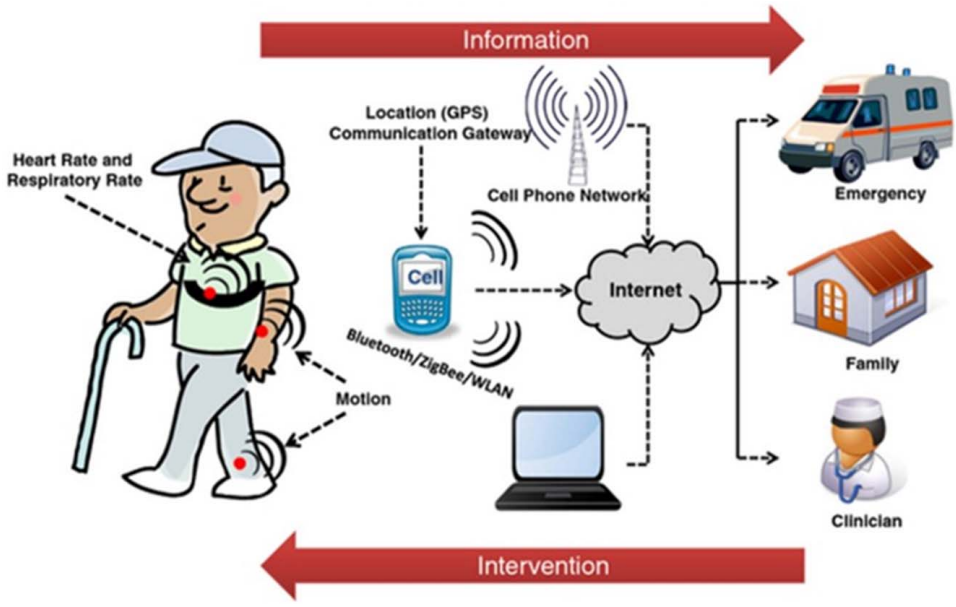

Fig. 9 Illustration of a remote health monitoring system based on wearable sensors. Health-related information is gathered via body-worn wireless sensors and transmitted to the caregiver via an information gateway such as a mobile phone. Caregivers can use this information to implement interventions as needed. Reproduced with permission from Patel et al. [176].

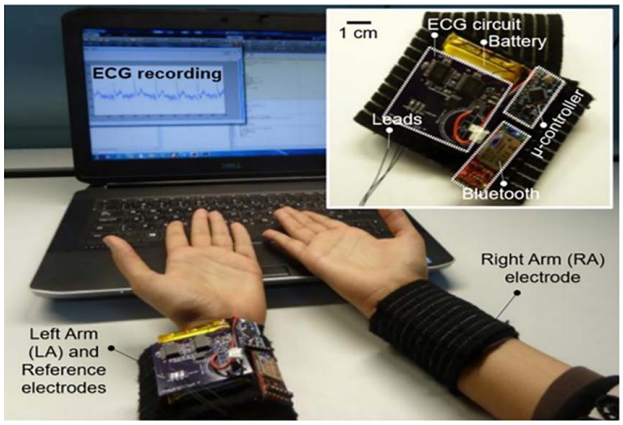

Fig. 10 Real-time demonstration of ECG measurement using the prototype graphene-clad textile embedded wearable wristband with integrated electronics. Reproduced with permission from Yapici and Alkhidir [185].

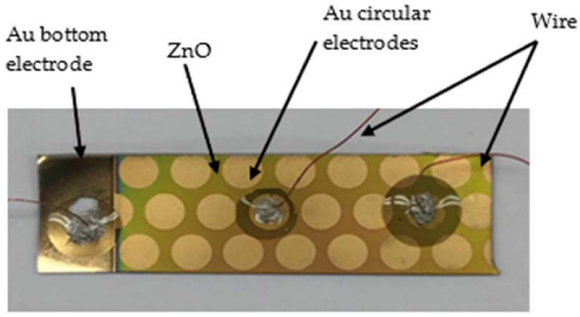

Fig. 11 Image of the fabricated ZnO power generator. It is fabricated by a thin layer of ZnO with Au power collection electrodes fabricated on both sides of the ZnO film. The substrate of the stretchable power generator is PDMS [157]. Reproduced with permission from Voiculescu et al. [187].

used for automation in food processing facilities for sorting food and reducing the time and cost of this food process. Biosensors can detect low concentrations of different chemicals in food. Moreover, biosensors are used to detect, monitor, and quantify the contamination of food from other sources such as container surfaces [146–149].

Advancements in Biosensors Due to Nanomaterials Discovery. Using nanomaterials, the sensitivity and performance of biosensors can be significantly improved [150]. Nanomaterials with at least one of their dimensions varying in a range from 1 to 100 nm display unique properties as compared to their bulk because their nanometer size enhances their physical properties (electrical, electrochemical, optical, and magnetic). Generally, the nano biosensors use nanomaterials in combination with microscale-size transducers.

The nanoparticles used for biosensors are nanoparticles with the capability of high detection sensitivity such as AuNPs, AgNPs, quantum dots (QDs), magnetic nanoparticles, nanowires, nanotubes or nanoribbons with very high surface area, nanomaterials with high electron conductivity such as carbon nanotubes (CNTs), Au nanowires, thin films at nanoscale such as graphene, polymeric materials as dendrimers, and photonic crystals (PC) [150]. An extensive presentation and classification of nanosensors showing their characteristics, detection mechanism, and application of biological nanosensors is given in Ref. [151]. Examples of nano biosensors'

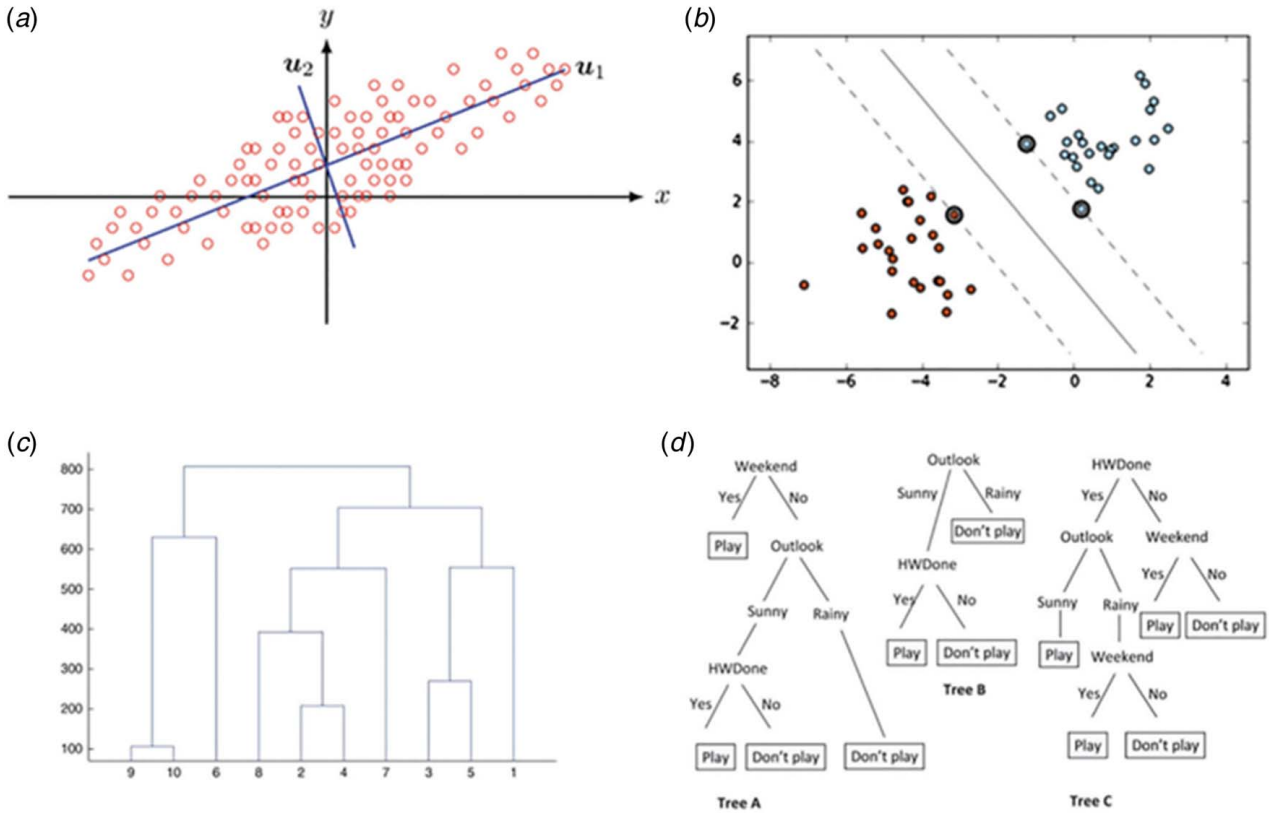

Fig. 12 Schematic illustrations of machine learning algorithms. (*a*) PCA. Reproduced with permission [184]. Copyright 2016, Springer Nature. (*b*) SVM. Reproduced with permission [191]. Copyright 2018, Springer Nature. (*c*) HCA. Reproduced with permission [186]. Copyright 2015, John Wiley and Sons. (*d*) RFs of three trees. Reproduced with permission under the terms of the Creative Commons Attribution License [192]. Copyright 2014, The Authors. Published by Taylor & Francis.

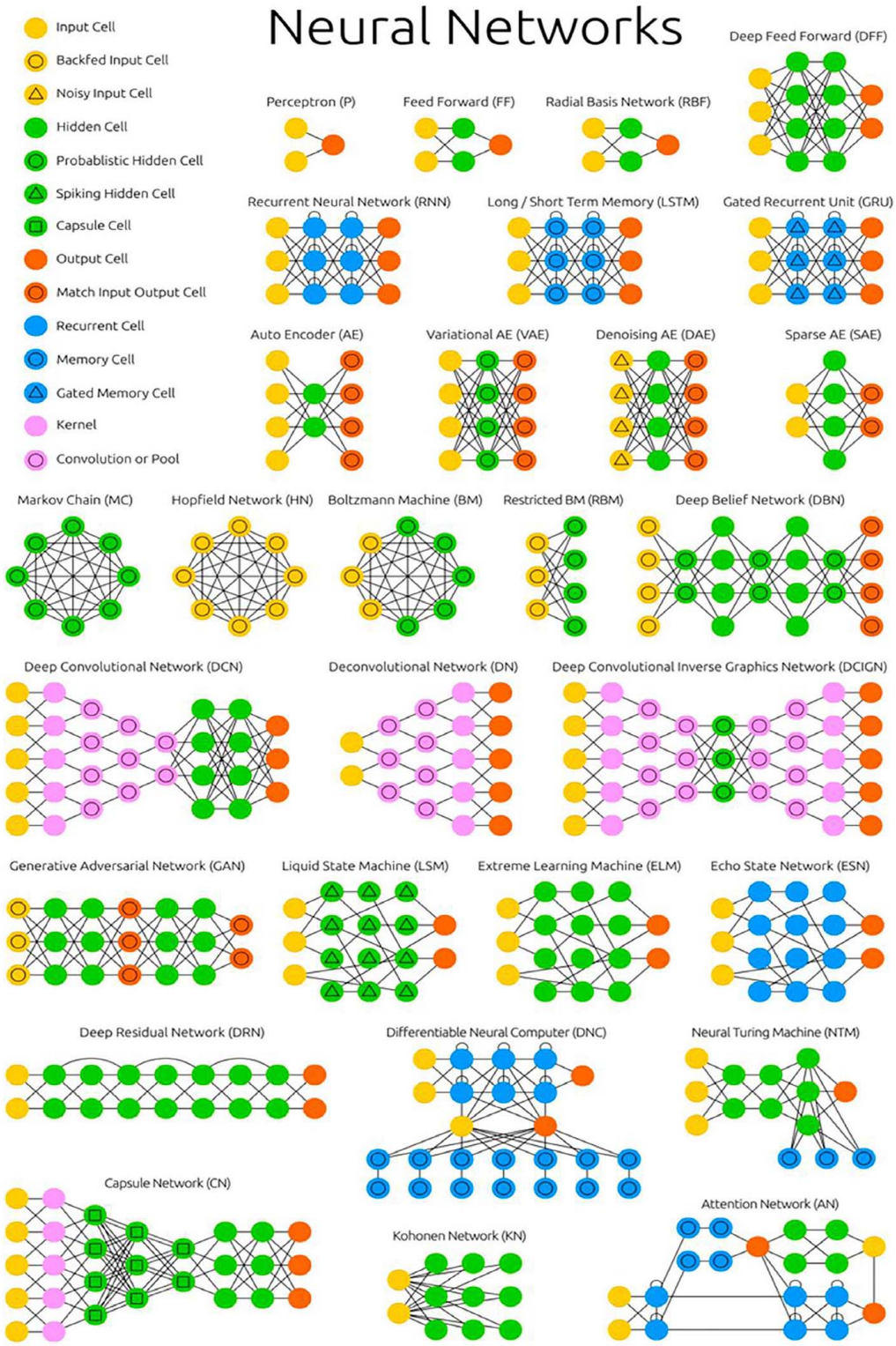

Fig. 13 Schematic illustrations of the latest Neural Network Architecture [193]

applications include the environment as well as the industrial sites, detection of ultra-low concentrations of potentially dangerous substances, detection of biochemicals in cellular organelles and medical diagnosis, and monitoring of physical and chemical phenomena in humanly unfriendly environments [151].

The research for nanosensors started in the last decade, and the progress shown in this area has been remarkable. Currently, there is extensive research on the nanoscale phenomena, discovery of nanomaterials, and continuing progress in nanotechnology fabrication tools that will generate further achievements in the field of nanosensors. This can be achieved through the enhanced performance of existing nanosensors and the discovery of novel types of nanosensors based on novel nanomaterials and detection techniques. Table 2 presents the main types of nanomaterials used for nanosensors, transduction methods, and applications of biological nanosensors.

Wearable Biosensors. Wearable biosensors and smartwatch technologies have taken health, exercise, and sleep monitoring to a few notches higher in recent years. Their emergence has made the measurement of a combination of physiological data, such as heart rate, heart rate variability, respiration rate, and other vital signals easy to archive due to their user-friendliness. With wearable biosensors, the physiological conditions of the patients are continuously monitored in real-time [175], as illustrated in Fig. 9. These wearable devices worn by patients enable medical personnel to take necessary actions before the effects of the change of the monitored parameters get dangerous. Modern optical and electrochemical-based wearable sensors are made of flexible electronics, wireless data transmission, and self-powering capability [177,178]. Gao et al. [179] have designed a fully integrated wearable sensor for monitoring perspiration to detect glucose, Na^+, and K^+ in patients. Yetisen et al. [180] developed a minimally invasive dermal tattoo realized on the skin-based colorimetric biosensor, that is able to detect changes in glucose and pH. Another interesting idea is to detect glucose levels in the tears. Elsherif et al. [181] have developed a wearable contact lens-based sensor for monitoring real-time glucose levels. Several tattoo-based biosensors have been researched with relatively minimal invasion procedures. In this technique, different types of dyes that changed colors in response to pH levels and other stimuli were used [182,183].

A low-cost and high-accuracy wearable piezoelectric-based sensor for blood pressure monitoring was also developed [184]. The piezoelectric sensor was mounted on the subject's wrist above the radial artery and was demonstrated as suitable for continuous, long-term blood pressure-monitoring applications.

Yapici et al. [185] took advantage of the impeccable conductive properties of graphene-clad textiles to develop a fully wearable, cloth-based smart medical garment for monitoring in real-time and for long periods of time the electrocardiogram (ECG) activity of the human body. Figure 10 illustrates the placement of the ECG sensors on the left and right hand and the recording of the electrical signal of the heart [185].

Piezoelectric ZnO was used for the fabrication of a wearable and stretchable piezoelectric power generator, that could harvest energy from the movements of the body (Fig. 11) [186]. The microfabricated power generator had a thickness in the micrometer scale to be attached to the skin or garments and stretched by the natural movements of arms, legs, or neck. This power generator demonstrated a maximum power output of 200 μW. It is expected that energy harvested by this device could power wearable sensors [157]. Obviously, wearable sensors with their current capabilities and esthetic packaging features have come to stay, and they will continue to be the basis on which further biosensing devices and their applications will be developed.

Machine Learning Applications in Biosensing

Data processing and interpretation is an integral part of biosensing. Conventionally, mathematical models are the tools deployed in data processing in most biosensors. However, for multianalyte-based sensors, this technique has become limited due to their inability to process data beyond two and three dimensions [188].

This has led to the introduction of more sophisticated data processing techniques such as preprocessing and machine learning algorithms in modern biosensing technologies. Neural and non-neural network models are subdivisions of machine learning algorithms, typically used in the design of biomedical signals [188,189].

Data Preprocessing. Like many data mining projects, careful cleaning of the raw data or signal received by a biosensor is critical in enhancing accuracy and efficiency. Typical data manipulation techniques used in the preprocessing stage are normalization, standardization, image analysis, transformation, as well as data metric synthesis [190]. The number and type of preprocessing techniques required largely depend on the nature of the raw data received.

Non-Neural Algorithms. Several choices of non-neural ML algorithms are used in the processing of biomedical signals detected by biosensors. The most popular ones are Principal Component Analysis (PCA) and Linear discriminant analysis (LDA), and Random Forests (RFs), hierarchical cluster analysis (HCA), support vector machine (SVM), and decision trees (DTs). The schematic illustrations of these algorithms are shown in Fig. 12.

Neural Algorithms. The Neural Algorithm is identical to the neuron network of living organisms, such as the human brain. This algorithm consists of a structured network of artificial neurons that are activated one after the other in a defined pattern [188]. The amount of data required to train a neural network is huge, and this is an inherent disadvantage as compared to the non-neural type of algorithm. In most cases, it is challenging to incorporate neural networks into biosensors for the purposes of data collection for physiological monitoring biosensors. Wearable and noninvasive biosensors have helped overcome the issue. Neural networks are subdivided into categories: (1) the Feedforward Neural Network (FNN), (2) Recurrent Network (RNN), and (3) Convolution Network (CNN). Figure 13 illustrates the latest architecture of the Neural Network [193].

In conclusion, the application of machine learning in biosensing technology, and its applications will certainly enhance the need to make them autonomous while improving their accuracy.

Conclusions

This review paper presented biosensors, their applications, and recent advancements in the use of Machine Learning techniques. Several types of biosensors with their transduction methods were discussed with a focus on electrochemical, thermometric, QCM and acoustic biosensors, and wearable biosensors.

Nanomaterials used for biosensing were also introduced. Nanomaterials became important components in bioanalytical devices since they were demonstrated to enhance the performance of biosensors in terms of sensitivity and detection limits down to single-molecule detection. The specific properties of nanomaterials could improve the performance of the classic transduction methods. The combination of different nanomaterials, each with different characteristics, could increase the performances of biosensors even more. Due to the vast number of different nanomaterials, all with their specific properties, only a few examples of nano biosensors were mentioned in this review paper to highlight the principal advantages of such materials. We also discussed biosensors based on nanomaterials, AI, ML, their challenges, and the potential to revolutionize the biosensors industry. Technological advancement in the field led to the development of wearable devices for continuous and real-time monitoring of physiological signals. Their successful applications depend less on technological issues and more on the challenges of practical ethical, legal, and social issues, regarding data collection and usage.

The biosensor industry is interested in integrating the miniaturized biosensors in personalized point-of-care (POC) devices, because of their reliable, sensitive, and fast detection of biomolecules with portable features. The recent advances in the camera and processor of smartphones are being integrated with biosensing applications, and this could increase the precision of healthcare diagnoses. Recently developed wireless technologies are better than their wired counterparts, but they require more innovation in the design of low-power ICs. IC fully integrated within the smartphone eliminates the need for external hardware and the processor unit, so there is a need for more fully integrated smartphone-based sensors for personalized health care. In conclusion, the combination

of biosensors, nanomaterial-based technology, and smartphone technology can improve POC-based devices for better health care.

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Author Contribution Statement

All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

No data, models, or code were generated or used for this paper.

References

[1] Turner, A., Karube, I., and Wilson, G. S., 1987, *Biosensors: Fundamentals and Applications*, Oxford University Press, New York.

[2] Urban, G. A., 2008, "Micro-and Nanobiosensors—State of the Art and Trends," Meas. Sci. Technol., **20**(1), p. 012001.

[3] Banica, F.-G., 2012, *Chemical Sensors and Biosensors: Fundamentals and Applications*, John Wiley & Sons, New York.

[4] Crivianu-Gaita, V., and Thompson, M., 2016, "Aptamers, Antibody ScFv, and Antibody Fab'fragments: An Overview and Comparison of Three of the Most Versatile Biosensor Biorecognition Elements," Biosens. Bioelectron., **85**, pp. 32–45.

[5] Škrlec, K., Štrukelj, B., and Berlec, A., 2015, "Non-Immunoglobulin Scaffolds: A Focus on Their Targets," Trends Biotechnol., **33**(7), pp. 408–418.

[6] Jost, C., and Plückthun, A., 2014, "Engineered Proteins With Desired Specificity: DARPins, Other Alternative Scaffolds and Bispecific IgGs," Curr. Opin. Struct. Biol., **27**, pp. 102–112.

[7] Brient-Litzler, E., Plückthun, A., and Bedouelle, H., 2010, "Knowledge-Based Design of Reagentless Fluorescent Biosensors From a Designed Ankyrin Repeat Protein," Protein Eng., Des. Sel., **23**(4), pp. 229–241.

[8] Miranda, F. F., Brient-Litzler, E., Zidane, N., Pecorari, F., and Bedouelle, H., 2011, "Reagentless Fluorescent Biosensors From Artificial Families of Antigen Binding Proteins," Biosens. Bioelectron., **26**(10), pp. 4184–4190.

[9] Ballerstadt, R., and Schultz, J. S., 2000, "A Fluorescence Affinity Hollow Fiber Sensor for Continuous Transdermal Glucose Monitoring," Anal. Chem., **72**(17), pp. 4185–4192.

[10] Schultz, J. S., Mansouri, S., and Goldstein, I. J., 1982, "Affinity Sensor: A New Technique for Developing Implantable Sensors for Glucose and Other Metabolites," Diabetes Care, **5**(3), pp. 245–253.

[11] Schultz, J. S., and Sims, G., 1979, "Affinity Sensors for Individual Metabolites," Biotechnol. Bioeng. Symp., (9), pp. 65–71.

[12] Vollmer, F., and Yang, L., 2012, "Review Label-Free Detection With High-Q Microcavities: A Review of Biosensing Mechanisms for Integrated Devices," Nanophotonics, **1**(3–4), pp. 267–291.

[13] Rizzuto, R., Pinton, P., Brini, M., Chiesa, A., Filippin, L., and Pozzan, T., 1999, "Mitochondria as Biosensors of Calcium Microdomains," Cell Calcium, **26**(5), pp. 193–199.

[14] Bragadin, M., Manente, S., Piazza, R., and Scutari, G., 2001, "The Mitochondria as Biosensors for the Monitoring of Detergent Compounds in Solution," Anal. Biochem., **292**(2), pp. 305–307.

[15] Gupta, R., and Chaudhury, N., 2007, "Entrapment of Biomolecules in Sol–Gel Matrix for Applications in Biosensors: Problems and Future Prospects," Biosens. Bioelectron., **22**(11), pp. 2387–2399.

[16] Juzgado, A., Soldà A., Ostric A., Criado A., Valenti G., Rapino S., Conti G., Fracasso G., Paolucci F., and Prato M., 2017, "Highly Sensitive Electrochemiluminescence Detection of a Prostate Cancer Biomarker," J. Mater. Chem. B, **5**(32), pp. 6681–6687.

[17] Valenti, G., Rampazzo, E., Biavardi, E., Villani, E., Fracasso, G., Marcaccio, M., Bertani, F., et al., 2015, "An Electrochemiluminescence-Supramolecular Approach to Sarcosine Detection for Early Diagnosis of Prostate Cancer," Faraday Discuss., **185**, pp. 299–309.

[18] Forster, R. J., Bertoncello, P., and Keyes, T. E., 2009, "Electrogenerated Chemiluminescence," Annu. Rev. Anal. Chem., **2**(1), pp. 359–385.

[19] Valenti, G., Fiorani, A., Li, H., Sojic, N., and Paolucci, F., 2016, "Essential Role of Electrode Materials in Electrochemiluminescence Applications," ChemElectroChem, **3**(12), pp. 1990–1997.

[20] Donzella, V., and Crea, F., 2011, "Optical Biosensors to Analyze Novel Biomarkers in Oncology," J. Biophotonics, **4**(6), pp. 442–452.

[21] Hiep, H. M., Endo, T., Kerman, K., Chikae, M., Kim, D.-K., Yamamura, S., Takamura, Y., et al., 2007, "A Localized Surface Plasmon Resonance Based Immunosensor for the Detection of Casein in Milk," Sci. Technol. Adv. Mater., **8**(4), pp. 331–338.

[22] Kotanen, C. N., Moussy, F. G., Carrara, S., and Guiseppi-Elie, A., 2012, "Implantable Enzyme Amperometric Biosensors," Biosens. Bioelectron., **35**(1), pp. 14–26.

[23] Lambrianou, A., Demin, S., and Hall, E. A., 2007, "Protein Engineering and Electrochemical Biosensors," Adv. Biochem. Eng. Biotechnol., **109**, pp. 65–96.

[24] Renard, M., Belkadi, L., Hugo, N., England, P., Altschuh, D., and Bedouelle, H., 2002, "Knowledge-Based Design of Reagentless Fluorescent Biosensors From Recombinant Antibodies," J. Mol. Biol., **318**(2), pp. 429–442.

[25] Mortellaro, M., and DeHennis, A., 2014, "Performance Characterization of an Abiotic and Fluorescent-Based Continuous Glucose Monitoring System in Patients With Type 1 Diabetes," Biosens. Bioelectron., **61**, pp. 227–231.

[26] Atay, S., Pişkin, K., Yılmaz, F., Çakır, C., Yavuz, H., and Denizli, A., 2016, "Quartz Crystal Microbalance Based Biosensors for Detecting Highly Metastatic Breast Cancer Cells via Their Transferrin Receptors," Anal. Methods, **8**(1), pp. 153–161.

[27] Clark, L. C. Jr, and Lyons, C., 1962, "Electrode Systems for Continuous Monitoring in Cardiovascular Surgery," Ann. N. Y. Acad. Sci., **102**(1), pp. 29–45.

[28] Rodrigues, D., Barbosa, A. I., Rebelo, R., Kwon, I. K., Reis, R. L., and Correlo, V. M., 2020, "Skin-Integrated Wearable Systems and Implantable Biosensors: A Comprehensive Review," Biosensors, **10**(7), p. 79.

[29] Perumal, V., and Hashim, U., 2014, "Advances in Biosensors: Principle, Architecture and Applications," J. Appl. Biomed., **12**(1), pp. 1–15.

[30] Lee, J.-H., 2015, Human Implantable Arrhythmia Monitoring Sensor With Wireless Power and Data Transmission Technique.

[31] Korotkaya, E., 2014, "Biosensors: Design, Classification, and Applications in the Food Industry," Foods Raw Mater., **2**(2), pp. 161–171.

[32] Karyakin, A., Ulasova, E., Vagin, M. Y., and Karyakina, E., 2002, "Biosensors: A Device Classification and Functional Characteristics," Sensor, **1**, pp. 16–24.

[33] Eggins, B. R., 2002, *Chemical Sensors and Biosensors*, John Wiley & Sons, New York.

[34] Monosik, R., Stredansky, M., and Sturdik, E., 2012, "Biosensors—Classification, Characterization and New Trends," Acta Chim. Slov., **5**(1), pp. 109–120.

[35] Martinkova, P., Kostelnik, A., Válek, T., and Pohanka, M., 2017, "Main Streams in the Construction of Biosensors and Their Applications," Int. J. Electrochem. Sci., **12**(8), pp. 7386–7403.

[36] Njagi, J. I., and Kagwanja, S. M., 2011, "The Interface in Biosensing: Improving Selectivity and Sensitivity," *Interfaces and Interphases in Analytical Chemistry*, ACS Publications, pp. 225–247.

[37] Inshyna, N. M., Chorna, I. V., Primova, L. O., Hrebenyk, L. I., and Khyzhnia, Y. V., 2020, Biosensors: Design, Classification and Application, IntechOpen, UK.

[38] Mousavi, S. M., Hashemi, S. A., Zarei, M., Amani, A. M., and Babapoor, A., 2018, "Nanosensors for Chemical and Biological and Medical Applications," Med. Chem., **8**(8), p. 2161.

[39] White, R. M., 1987, "A Sensor Classification Scheme," IEEE Trans. Ultrason. Ferroelectr. Freq. Control, **34**(2), pp. 124–126.

[40] Numthuam, S., Kakegawa, T., Anada, T., Khademhosseini, A., Suzuki, H., and Fukuda, J., 2011, "Synergistic Effects of Micro/Nano Modifications on Electrodes for Microfluidic Electrochemical ELISA," Sens. Actuators B, **156**(2), pp. 637–644.

[41] Pandikumar, A., and Rameshkumar, P., 2018, *Graphene-Based Electrochemical Sensors for Biomolecules*, Elsevier, New York.

[42] Brosel-Oliu, S., Abramova, N., Uria, N., and Bratov, A., 2019, "Impedimetric Transducers Based on Interdigitated Electrode Arrays for Bacterial Detection–A Review," Anal. Chim. Acta, **1088**, pp. 1–19.

[43] de Oliveira, O. N., Jr, Ferreira, L., Marystela, G., de Lima Leite, F., and Da Róz, A. L., 2016, *Nanoscience and Its Applications*, Elsevier-William Andrew, Oxford, UK.

[44] Ronkainen, N. J., Halsall, H. B., and Heineman, W. R., 2010, "Electrochemical Biosensors," Chem. Soc. Rev., **39**(5), pp. 1747–1763.

[45] Giaever, I., and Keese, C. R., 1991, "Micromotion of Mammalian Cells Measured Electrically," Proc. Natl. Acad. Sci. U. S. A., **88**(17), pp. 7896–7900.

[46] Mitra, P., Keese, C. R., and Giaever, I., 1991, "Electric Measurements Can be Used to Monitor the Attachment and Spreading of Cells in Tissue Culture," BioTechniques, **11**(4), pp. 504–510.

[47] Lo, C.-M., Keese, C. R., and Giaever, I., 1993, "Monitoring Motion of Confluent Cells in Tissue Culture," Exp. Cell Res., **204**(1), pp. 102–109.

[48] Keese, C. R., and Giaever, I., 1994, "A Biosensor That Monitors Cell Morphology With Electrical Fields," IEEE Eng. Med. Biol. Mag., **13**(3), pp. 402–408.

[49] Jiang, W. G., 2012, *Electric Cell-Substrate Impedance Sensing and Cancer Metastasis*, Springer Science & Business Media, Dordrecht, The Netherlands.

[50] Lo, C.-M., Keese, C. R., and Giaever, I., 1999, "Cell–Substrate Contact: Another Factor May Influence Transepithelial Electrical Resistance of Cell Layers Cultured on Permeable Filters," Exp. Cell Res., **250**(2), pp. 576–580.

[51] Lo, C.-M., Keese, C. R., and Giaever, I., 1995, "Impedance Analysis of MDCK Cells Measured by Electric Cell-Substrate Impedance Sensing," Biophys. J., **69**(6), pp. 2800–2807.
[52] Ayliffe, H. E., Frazier, A. B., and Rabbitt, R., 1999, "Electric Impedance Spectroscopy Using Microchannels With Integrated Metal Electrodes," J. Microelectromech. Syst., **8**(1), pp. 50–57.
[53] Han, A., Yang, L., and Frazier, A. B., 2007, "Quantification of the Heterogeneity in Breast Cancer Cell Lines Using Whole-Cell Impedance Spectroscopy," Clin. Cancer Res., **13**(1), pp. 139–143.
[54] Zhang, X., Li, F., Nordin, A. N., Tarbell, J., and Voiculescu, I., 2015, "Toxicity Studies Using Mammalian Cells and Impedance Spectroscopy Method," Sens. Bio-Sens. Res., **3**, pp. 112–121.
[55] Zhang, X., Wang, W., Nordin, A. N., Li, F., Jang, S., and Voiculescu, I., 2017, "The Influence of the Electrode Dimension on the Detection Sensitivity of Electric Cell–Substrate Impedance Sensing (ECIS) and Its Mathematical Modeling," Sens. Actuators B, **247**, pp. 780–790.
[56] Peitzman, E. R., Zaidman, N. A., Maniak, P. J., and O'Grady, S. M., 2015, "Agonist Binding to β-Adrenergic Receptors on Human Airway Epithelial Cells Inhibits Migration and Wound Repair," Am. J. Physiol. Cell Physiol., **309**(12), pp. C847–C855.
[57] MacKenzie, T. N., Mujumdar, N., Banerjee, S., Sangwan, V., Sarver, A., Vickers, S., Subramanian, S., et al., 2013, "Triptolide Induces the Expression of miR-142–3p: A Negative Regulator of Heat Shock Protein 70 and Pancreatic Cancer Cell Proliferation," Mol. Cancer Ther., **12**(7), pp. 1266–1275.
[58] Litkouhi, B., Kwong, J., Lot, C.-M., Smedley, J. G., McClane, B. A., Aponte, M., Gao, Z., et al., 2007, "Claudin-4 Overexpression in Epithelial Ovarian Cancer Is Associated With Hypomethylation and Is a Potential Target for Modulation of Tight Junction Barrier Function Using a C-Terminal Fragment of Clostridium Perfringens Enterotoxin," Neoplasia, **9**(4), pp. 304–314.
[59] Dorsam, R. T., and Gutkind, J. S., 2007, "G-Protein-Coupled Receptors and Cancer," Nat. Rev. Cancer, **7**(2), pp. 79–94.
[60] Alvarez, J. I., Dodelet-Devillers, A., Kebir, H., Ifergan, I., Fabre, P. J., Terouz, S., Sabbagh, M., et al., 2011, "The Hedgehog Pathway Promotes Blood-Brain Barrier Integrity and CNS Immune Quiescence," Science, **334**(6063), pp. 1727–1731.
[61] Banerjee, S., Sangwan, V., McGinn, O., Chugh, R., Dudeja, V., Vickers, S. M., and Saluja, A. K., 2013, "Triptolide-Induced Cell Death in Pancreatic Cancer Is Mediated by O-GlcNAc Modification of Transcription Factor Sp1," J. Biol. Chem., **288**(47), pp. 33927–33938.
[62] Kourtidis, A., Ngok, S. P., Pulimeno, P., Feathers, R. W., Carpio, L. R., Baker, T. R., Carr, J. M., et al., 2015, "Distinct E-Cadherin-Based Complexes Regulate Cell Behaviour Through miRNA Processing or Src and p120 Catenin Activity," Nat. Cell Biol., **17**(9), pp. 1145–1157.
[63] Voiculescu, I., Li, F., and Nordin, A. N., 2020, "Impedance Spectroscopy of Adherent Mammalian Cell Culture for Biochemical Applications: A Review," IEEE Sens. J., **21**(5), pp. 5612–5627.
[64] Mansor, A. F. M., Ibrahim, I., Zainuddin, A. A., Voiculescu, I., and Nordin, A. N., 2018, "Modeling and Development of Screen-Printed Impedance Biosensor for Cytotoxicity Studies of Lung Carcinoma Cells," Med. Biol. Eng. Comput., **56**(1), pp. 173–181.
[65] Voiculescu, I., Li, F., Liu, F., Zhang, X., Cancel, L. M., Tarbell, J. M., and Khademhosseini, A., 2013, "Study of Long-Term Viability of Endothelial Cells for Lab-on-a-Chip Devices," Sens. Actuators B, **182**, pp. 696–705.
[66] Rogers, J. A., Someya, T., and Huang, Y., 2010, "Materials and Mechanics for Stretchable Electronics," Science, **327**(5973), pp. 1603–1607.
[67] Khang, D.-Y., Jiang, H., Huang, Y., and Rogers, J. A., 2006, "A Stretchable Form of Single-Crystal Silicon for High-Performance Electronics on Rubber Substrates," Science, **311**(5758), pp. 208–212.
[68] Zhang, X., Wang, W., Li, F., and Voiculescu, I., 2017, "Stretchable Impedance Sensor for Mammalian Cell Proliferation Measurements," Lab Chip, **17**(12), pp. 2054–2066.
[69] Lee, K.-L., Ng, S., Li, F., Nordin, A. N., and Voiculescu, I., 2020, "MEMS Biosensor for Monitoring Water Toxicity Based on Quartz Crystal Microbalance," Biointerphases, **15**(2), p. 021006.
[70] Liu, F., Nordin, A., Li, F., and Voiculescu, I., 2014, "A Lab-on-Chip Cell-Based Biosensor for Label-Free Sensing of Water Toxicants," Lab Chip, **14**(7), pp. 1270–1280.
[71] Liu, F., Li, F., Nordin, A. N., and Voiculescu, I., 2013, "A Novel Cell-Based Hybrid Acoustic Wave Biosensor With Impedimetric Sensing Capabilities," Sensors, **13**(3), pp. 3039–3055.
[72] Li, F., Wang, J. H.-C., and Wang, Q.-M., 2007, "Monitoring Cell Adhesion by Using Thickness Shear Mode Acoustic Wave Sensors," Biosens. Bioelectron., **23**(1), pp. 42–50.
[73] Neumann, F., Madaboosi, N., Hernández-Neuta, I., Salas, J., Ahlford, A., Mecea, V., and Nilsson, M., 2018, "QCM Mass Underestimation in Molecular Biotechnology: Proximity Ligation Assay for Norovirus Detection as a Case Study," Sens. Actuators B, **273**, pp. 742–750.
[74] Voinova, M., Jonson, M., and Kasemo, B., 2002, "'Missing Mass' Effect in Biosensor's QCM Applications," Biosens. Bioelectron., **17**(10), pp. 835–841.
[75] Rodahl, M., and Kasemo, B., 1996, "Frequency and Dissipation-Factor Responses to Localized Liquid Deposits on a QCM Electrode," Sens. Actuators B, **37**(1–2), pp. 111–116.
[76] Pohanka, M., 2017, "The Piezoelectric Biosensors: Principles and Applications," Int. J. Electrochem. Sci., **12**(1), pp. 496–506.
[77] Yuwono, A. S., and Lammers, P. S., 2004, "Odor Pollution in the Environment and the Detection Instrumentation," Agric. Eng. Int.: CIGR J.
[78] Lucklum, R., and Hauptmann, P., 2003, "Transduction Mechanism of Acoustic-Wave Based Chemical and Biochemical Sensors," Meas. Sci. Technol., **14**(11), pp. 1854–1864.
[79] Kankare, J., 2002, "Sauerbrey Equation of Quartz Crystal Microbalance in Liquid Medium," Langmuir, **18**(18), pp. 7092–7094.
[80] Johannsmann, D., Mathauer, K., Wegner, G., and Knoll, W., 1992, "Viscoelastic Properties of Thin Films Probed With a Quartz-Crystal Resonator," Phys. Rev. B, **46**(12), pp. 7808–7815.
[81] Martin, S. J., Granstaff, V. E., and Frye, G. C., 1991, "Characterization of a Quartz Crystal Microbalance With Simultaneous Mass and Liquid Loading," Anal. Chem., **63**(20), pp. 2272–2281.
[82] Reed, C., Kanazawa, K. K., and Kaufman, J., 1990, "Physical Description of a Viscoelastically Loaded AT-Cut Quartz Resonator," J. Appl. Phys., **68**(5), pp. 1993–2001.
[83] Eun, A. J.-C., Huang, L., Chew, F.-T., Li, S. F.-Y., and Wong, S.-M., 2002, "Detection of Two Orchid Viruses Using Quartz Crystal Microbalance (QCM) Immunosensors," J. Virol. Methods, **99**(1–2), pp. 71–79.
[84] Afzal, A., Mujahid, A., Schirhagl, R., Bajwa, S. Z., Latif, U., and Feroz, S., 2017, "Gravimetric Viral Diagnostics: QCM Based Biosensors for Early Detection of Viruses," Chemosensors, **5**(1), p. 7.
[85] Wang, R., Wang, L., Callaway, Z. T., Lu, H., Huang, T. J., and Li, Y., 2017, "A Nanowell-Based QCM Aptasensor for Rapid and Sensitive Detection of Avian Influenza Virus," Sens. Actuators B, **240**, pp. 934–940.
[86] Morgan, D., and ProQuest, S. A. W. F., 2010, *With Applications to Electronic Communications and Signal Processing (Studies in Electrical and Electronic Engineering)*, Imperial College London.
[87] Zhang, F., Li, S., Cao, K., Wang, P., Su, Y., Zhu, X., and Wan, Y., 2015, "A Microfluidic Love-Wave Biosensing Device for PSA Detection Based on an Aptamer Beacon Probe," Sensors, **15**(6), pp. 13839–13850.
[88] Matatagui, D., Fontecha, J., Fernández, M., Gràcia, I., Cané, C., Santos, J., and Horrillo, M., 2014, "Love-Wave Sensors Combined With Microfluidics for Fast Detection of Biological Warfare Agents," Sensors, **14**(7), pp. 12658–12669.
[89] Yeo, L. Y., and Friend, J. R., 2014, "Surface Acoustic Wave Microfluidics," Annu. Rev. Fluid Mech., **46**(1), pp. 379–406.
[90] Mitsakakis, K., Tserepi, A., and Gizeli, E., 2009, "SAW Device Integrated With Microfluidics for Array-Type Biosensing," Microelectron. Eng., **86**(4–6), pp. 1416–1418.
[91] Lee, S., Kim, K.-B., and Kim, Y.-I., 2011, "Love Wave SAW Biosensors for Detection of Antigen-Antibody Binding and Comparison With SPR Biosensor," Food Sci. Biotechnol., **20**(5), pp. 1413–1418.
[92] Fu, C., Jung, I., Yang, S.-S., and Lee, K., 2012, "Towards Optimised Wireless Love Wave Biosensor With High Sensitivity," Micro Nano Lett., **7**(12), pp. 1202–1205.
[93] Josse, F., Bender, F., and Cernosek, R. W., 2001, "Guided Shear Horizontal Surface Acoustic Wave Sensors for Chemical and Biochemical Detection in Liquids," Anal. Chem., **73**(24), pp. 5937–5944.
[94] Gammoudi, I., Tarbague H., Othmane A., Moynet D., Rebière D., Kalfat R., and Dejous C., 2010, "Love-Wave Bacteria-Based Sensor for the Detection of Heavy Metal Toxicity in Liquid Medium," Biosens. Bioelectron., **26**(4), pp. 1723–1726.
[95] Zhang, X., Fang, J., Zou, L., Zou, Y., Lang, L., Gao, F., Hu, N., et al., 2016, "A Novel Sensitive Cell-Based Love Wave Biosensor for Marine Toxin Detection," Biosens. Bioelectron., **77**, pp. 573–579.
[96] Lee, K.-L., Kowach, G., Li, F., and Voiculescu, I., 5911, "Liquid Viscosity Sensor Using a Surface Acoustic Wave Device for Medical Applications Including Blood and Plasma," Sensors, **23**(13), p. 2023.
[97] Mandal, D., and Banerjee, S., 2022, "Surface Acoustic Wave (SAW) Sensors: Physics, Materials, and Applications," Sensors, **22**(3), p. 820.
[98] Kulkarni, G. S., and Zhong, Z., 2012, "Detection Beyond the Debye Screening Length in a High-Frequency Nanoelectronic Biosensor," Nano Lett., **12**(2), pp. 719–723.
[99] Laborde, C., Pittino F., Verhoeven H. A., Lemay S. G., Selmi L., Jongsma M. A., and Widdershoven F. P., 2015, "Real-Time Imaging of Microparticles and Living Cells With CMOS Nanocapacitor Arrays," Nat. Nanotechnol., **10**(9), pp. 791–795.
[100] Woo, J.-M., Kim, S. H., Chun, H., Kim, S. J., Ahn, J., and Park, Y. J., 2013, "Modulation of Molecular Hybridization and Charge Screening in a Carbon Nanotube Network Channel Using the Electrical Pulse Method," Lab Chip, **13**(18), pp. 3755–3763.
[101] Munje, R. D., Muthukumar, S., Panneer Selvam, A., and Prasad, S., 2015, "Flexible Nanoporous Tunable Electrical Double Layer Biosensors for Sweat Diagnostics," Sci. Rep., **5**(1), pp. 1–11.
[102] Vu, C.-A., and Chen, W.-Y., 2019, "Field-Effect Transistor Biosensors for Biomedical Applications: Recent Advances and Future Prospects," Sensors, **19**(19), p. 4214.
[103] Hideshima, S., Wustoni, S., Kobayashi, M., Hayashi, H., Kuroiwa, S., Nakanishi, T., and Osaka, T., 2018, "Effect of Human Serum on the Electrical Detection of Amyloid-β Fibrils in Biological Environments Using Azo-Dye Immobilized Field Effect Transistor (FET) Biosensor," Sens. Bio-Sens. Res., **17**, pp. 25–29.
[104] Chu, C.-H., Nishita, M., Park, S.-Y., Nishio, T., Kamizaki, K., Wang, Z., Tamada, K., et al., 2017, "Beyond the Debye Length in High Ionic Strength Solution: Direct Protein Detection With Field-Effect Transistors (FETs) in Human Serum," Sci. Rep., **7**(1), pp. 1–15.

[105] Gao, X. P., Zheng, G., and Lieber, C. M., 2010, "Subthreshold Regime Has the Optimal Sensitivity for Nanowire FET Biosensors," Nano Lett., **10**(2), pp. 547–552.
[106] Bao, Z., Sun, J., Zhao, X., Li, Z., Cui, S., Meng, Q., Zhang, Y., et al., 2017, "Top-Down Nanofabrication of Silicon Nanoribbon Field Effect Transistor (Si-NR FET) for Carcinoembryonic Antigen Detection," Int. J. Nanomed., **12**, p. 4623–4631.
[107] Tetyana, P., Shumbula, P. M., and Njengele-Tetyana, Z., 2021, "Biosensors: Design, Development and Applications, IntechOpen, UK.
[108] Voiculescu, I., Toda, M., Inomata, N., Ono, T., and Li, F., 2018, "Nano and Microsensors for Mammalian Cell Studies," Micromachines, **9**(9), p. 439.
[109] Sato, M. K., Toda, M., Inomata, N., Maruyama, H., Okamatsu-Ogura, Y., Arai, F., Ono, T., et al., 2014, "Temperature Changes in Brown Adipocytes Detected With a Bimaterial Microcantilever," Biophys. J., **106**(11), pp. 2458–2464.
[110] Inomata, N., Toda, M., and Ono, T., 2016, "Highly Sensitive Thermometer Using a Vacuum-Packed Si Resonator in a Microfluidic Chip for the Thermal Measurement of Single Cells," Lab Chip, **16**(18), pp. 3597–3603.
[111] Fan, J. A., Yeo, W. H., Su, Y., Hattori, Y., Lee, W., Jung, S. Y., Zhang, Y., et al., 2014, "Fractal Design Concepts for Stretchable Electronics," Nat. Commun., **5**(1), pp. 1–8.
[112] Wang, Y., Knoll, W., and Dostalek, J., 2012, "Bacterial Pathogen Surface Plasmon Resonance Biosensor Advanced by Long Range Surface Plasmons and Magnetic Nanoparticle Assays," Anal. Chem., **84**(19), pp. 8345–8350.
[113] Leatherbarrow, R. J., and Edwards, P. R., 1999, "Analysis of Molecular Recognition Using Optical Biosensors," Curr. Opin. Chem. Biol., **3**(5), pp. 544–547.
[114] Raji, H., Tayyab, M., Sui, J., Mahmoodi, S. R., and Javanmard, M., 2021, "Biosensors and Machine Learning for Enhanced Detection, Stratification, and Classification of Cells: A Review," arXiv, **24**(3).
[115] Stoytcheva, M., Zlatev, R., Velkova, Z., Valdez, B., and Ovalle, M., 2009, "Analytical Characteristics of Electrochemical Biosensors," Port. Electrochim. Acta, **27**(3), pp. 353–362.
[116] Van Steenis, H., Tulen, J., and Mulder, L., 1994, "Heart Rate Variability Spectra Based on Non-Equidistant Sampling: The Spectrum of Counts and the Instantaneous Heart Rate Spectrum," Med. Eng. Phys., **16**(5), pp. 355–362.
[117] Polatoğlu, İ., Aydın, L., Nevruz, B.Ç., and Özer, S., 2020, "A Novel Approach for the Optimal Design of a Biosensor," Anal. Lett., **53**(9), pp. 1428–1445.
[118] Bhalla, N., Jolly, P., Formisano, N., and Estrela, P., 2016, "Introduction to Biosensors," Essays Biochem, **60**(1), pp. 1–8.
[119] Wilkins, E., and Atanasov, P., 1996, "Glucose Monitoring: State of the Art and Future Possibilities," Med. Eng. Phys., **18**(4), pp. 273–288.
[120] Ali, J., Najeeb, J., Ali, M. A., Aslam, M. F., and Raza, A., 2017, "Biosensors: Their Fundamentals, Designs, Types and Most Recent Impactful Applications: A Review," J. Biosens. Bioelectron., **8**(1), pp. 1–9.
[121] Mohan, K. K., Prashanthi, K., Hull, R., and Montemagno, C. D., 2018, "Risk Assessment of a Multiplexed Carbon Nanotube Network Biosensor," IEEE Sens. J., **18**(11), pp. 4517–4528.
[122] Cai, L., Mohan, K. K., Prashanthi, K., and Montemagno, C. D., 2022, "Fabrication and Quantitative Performance Analysis of a Low-Cost, Flexible CNT Network-Based DNA Sensors Using Ink-Jet Printing," Sens. Bio-Sens. Res., **36**, p. 100498.
[123] Lavín, Á, Vicente, J., Holgado, M., Laguna, M., Casquel, R., Santamaría, B., Maigler, M., Hernández, A., and Ramírez, Y., 2018, "On the Determination of Uncertainty and Limit of Detection in Label-Free Biosensors," Sensors, **18**(7), p. 2038.
[124] Saha, K., Agasti, S. S., Kim, C., Li, X., and Rotello, V. M., 2012, "Gold Nanoparticles in Chemical and Biological Sensing," Chem. Rev., **112**(5), pp. 2739–2779.
[125] Chaubey, A., and Malhotra, B., 2002, "Mediated Biosensors," Biosens. Bioelectron., **17**(6–7), pp. 441–456.
[126] Nimse, S. B., Song, K., Sonawane, M. D., Sayyed, D. R., and Kim, T., 2014, "Immobilization Techniques for Microarray: Challenges and Applications," Sensors, **14**(12), pp. 22208–22229.
[127] Morales, M. A., and Halpern, J. M., 2018, "Guide to Selecting a Biorecognition Element for Biosensors," Bioconjugate Chem., **29**(10), pp. 3231–3239.
[128] Sassolas, A., Blum, L. J., and Leca-Bouvier, B. D., 2012, "Immobilization Strategies to Develop Enzymatic Biosensors," Biotechnol. Adv., **30**(3), pp. 489–511.
[129] Mohamad, N. R., Marzuki, N. H. C., Buang, N. A., Huyop, F., and Wahab, R. A., 2015, "An Overview of Technologies for Immobilization of Enzymes and Surface Analysis Techniques for Immobilized Enzymes," Biotechnol. Biotechnol. Equip., **29**(2), pp. 205–220.
[130] Singh, S., Kumar, V., Dhanjal, D. S., Datta, S., Prasad, R., and Singh, J., 2020, "Biological Biosensors for Monitoring and Diagnosis," *Microbial Biotechnology: Basic Research and Applications*, Springer, New York, pp. 317–335.
[131] Tabish, T. A., Hayat, H., Abbas, A., and Narayan, R. J., 2021, "Graphene Quantum Dot–Based Electrochemical Biosensing for Early Cancer Detection," Curr. Opin. Electrochem., **30**, p. 100786.
[132] Kaur, B., Kumar, S., and Kaushik, B. K., 2022, "Recent Advancements in Optical Biosensors for Cancer Detection," Biosens. Bioelectron., **197**, p. 113805.
[133] Tothill, I. E., 2009, "Biosensors for Cancer Markers Diagnosis," Semin. Cell Dev. Biol., **20**(1), pp. 55–62.
[134] Bohunicky, B., and Mousa, S. A., 2011, "Biosensors: The New Wave in Cancer Diagnosis," Nanotechnol. Sci. Appl., **4**, p. 1.
[135] Ooi, K. G.-J., Galatowicz, G., Towler, H. M., Lightman, S. L., and Calder, V. L., 2006, "Multiplex Cytokine Detection Versus ELISA for Aqueous Humor: IL-5, IL-10, and IFNγ Profiles in Uveitis," Invest. Ophthalmol. Vis. Sci., **47**(1), pp. 272–277.
[136] Caruso, R., Trunfio, S., Milazzo, F., Campolo, J., De Maria, R., Colombo, T., Parolini, M., Cannata, A., Russo, C., Paino, R., Frigerio, M., Martinelli, L., and Parodi, O., 2010, "Early Expression of Pro- and Anti-Inflammatory Cytokines in Left Ventricular Assist Device Recipients With Multiple Organ Failure Syndrome," ASAIO J, **56**(4), pp. 313–318.
[137] Caruso, R., Verde, A., Cabiati, M., Milazzo, F., Boroni, C., Del Ry, S., Parolini, M., Vittori, C., Paino, R., Martinelli, L., Giannessi, D., Frigerio, M., and Parodi, O., 2012, "Association of Pre-Operative Interleukin-6 Levels with Interagency Registry for Mechanically Assisted Circulatory Support Profiles and Intensive Care Unit Stay in Left Ventricular Assist Device Patients," J. Heart Lung. Transplant., **31**(6), pp. 625–633.
[138] Maurer, M., Burri, S., de Marchi, S., Hullin, R., Martinelli, M., Mohacsi, P., and Hess, O. M., 2010, "Plasma Homocysteine and Cardiovascular Risk in Heart Failure With and Without Cardiorenal Syndrome," Int. J. Cardiol., **141**(1), pp. 32–38.
[139] Watson, C. J., Ledwidge, M. T., Phelan, D., Collier, P., Byrne, J. C., Dunn, M. J., McDonald, K. M., et al., 2011, "Proteomic Analysis of Coronary Sinus Serum Reveals Leucine-Rich α2-Glycoprotein as a Novel Biomarker of Ventricular Dysfunction and Heart Failure," Circ. Heart Fail., **4**(2), pp. 188–197.
[140] Justino, C. I., Duarte, A. C., and Rocha-Santos, T. A., 2017, "Recent Progress in Biosensors for Environmental Monitoring: A Review," Sensors, **17**(12), p. 2918.
[141] Atkinson, A., and Haggett, B., 1993, "Whole Cell Biosensors for Environmental Monitoring," Sens. Rev., **13**(4), pp. 19–22.
[142] Nigam, V. K., and Shukla, P., 2015, "Enzyme Based Biosensors for Detection of Environmental Pollutants: A Review," J. Microbiol. Biotechnol., **25**(11), pp. 1773–1781.
[143] Tortolini, C., Mazzei, F., and Carlucci, L., 2012, "Electrochemical Biosensors for Environmental Monitoring," Int. J. Environ. Health, **6**(2), pp. 93–110.
[144] Rishpon, J., 2002, "Electrochemical Biosensors for Environmental Monitoring," Rev. Environ. Health, **17**(3), pp. 219–247.
[145] Hanrahan, G., Patil, D. G., and Wang, J., 2004, "Electrochemical Sensors for Environmental Monitoring: Design, Development and Applications," J. Environ. Monit., **6**(8), pp. 657–664.
[146] Manikandan, B., Ramar, M., and Munusamy, A., 2014, "Identification of Serum Component Involved in Generation of Neo-Lectin With Agglutinating and Phenoloxidase Activities in Human Serum," Hum. Immunol., **75**(1), pp. 34–40.
[147] Wei, N., Xin, X., Du, J., and Li, J., 2011, "A Novel Hydrogen Peroxide Biosensor Based on the Immobilization of Hemoglobin on Three-Dimensionally Ordered Macroporous (3DOM) Gold-Nanoparticle-Doped Titanium Dioxide (GTD) Film," Biosens. Bioelectron., **26**(8), pp. 3602–3607.
[148] Villalonga, R., Díez, P., Yáñez-Sedeño, P., and Pingarrón, J. M., 2011, "Wiring Horseradish Peroxidase on Gold Nanoparticles-Based Nanostructured Polymeric Network for the Construction of Mediatorless Hydrogen Peroxide Biosensor," Electrochim. Acta, **56**(12), pp. 4672–4677.
[149] Rana, J., Jindal, J., Beniwal, V., and Chhokar, V., 2010, "Utility Biosensors for Applications in Agriculture–A Review," J. Am. Sci., **6**(9), pp. 353–375.
[150] Singh, R. P., 2011, "Prospects of Nanobiomaterials for Biosensing," Int. J. Electrochem., **2011**, pp. 1–30.
[151] Abdel-Karim, R., Reda, Y., and Abdel-Fattah, A., 2020, "Review—Nanostructured Materials-Based Nanosensors," J. Electrochem. Soc., **167**(3), p. 037554.
[152] van den Berg, B., Wain, R., Dobson, C. M., and Ellis, R. J., 2000, "Macromolecular Crowding Perturbs Protein Refolding Kinetics: Implications for Folding Inside the Cell," EMBO J., **19**(15), pp. 3870–3875.
[153] Aldewachi, H., Chalati, T., Woodroofe, M., Bricklebank, N., Sharrack, B., and Gardiner, P., 2018, "Gold Nanoparticle-Based Colorimetric Biosensors," Nanoscale, **10**(1), pp. 18–33.
[154] Holzinger, M., Le Goff, A., and Cosnier, S., 2014, "Nanomaterials for Biosensing Applications: A Review," Front. Chem., **2**, p. 63.
[155] Cao, J., Sun, T., and Grattan, K. T., 2014, "Gold Nanorod-Based Localized Surface Plasmon Resonance Biosensors: A Review," Sens. Actuators B, **195**, pp. 332–351.
[156] Ibupoto, Z. H., Ali, S. M. U., Khun, K., Chey, C. O., Nur, O., and Willander, M., 2011, "ZnO Nanorods Based Enzymatic Biosensor for Selective Determination of Penicillin," Biosensors, **1**(4), pp. 153–163.
[157] Liu, G., Feng, D.-Q., Qian, Y., Wang, W., and Zhu, J.-J., 2019, "Construction of FRET Biosensor for Off-On Detection of Lead Ions Based on Carbon Dots and Gold Nanorods," Talanta, **201**, pp. 90–95.
[158] Ahmad, R., Ahn, M.-S., and Hahn, Y.-B., 2017, "ZnO Nanorods Array Based Field-Effect Transistor Biosensor for Phosphate Detection," J. Colloid Interface Sci., **498**, pp. 292–297.
[159] Ramanathan, K., Bangar, M. A., Yun, M., Chen, W., Myung, N. V., and Mulchandani, A., 2005, "Bioaffinity Sensing Using Biologically Functionalized Conducting-Polymer Nanowire," J. Am. Chem. Soc., **127**(2), pp. 496–497.
[160] Patolsky, F., Zheng, G., and Lieber, C. M., 2006, "Nanoscience and Its Applications," Analytical Chemistry, pp. 4261–4269.
[161] Kim, H.-M., Park, J.-H., and Lee, S.-K., 2019, "Fiber Optic Sensor Based on ZnO Nanowires Decorated by Au Nanoparticles for Improved Plasmonic Biosensor," Sci. Rep., **9**(1), pp. 1–9.

[162] Zhang, H., Song, D., Gao, S., Zhang, H., Zhang, J., and Sun, Y., 2013, "Enhanced Wavelength Modulation SPR Biosensor Based on Gold Nanorods for Immunoglobulin Detection," Talanta, **115**, pp. 857–862.
[163] Pandit, S., Dasgupta, D., Dewan, N., and Prince, A., 2016, "Nanotechnology Based Biosensors and Its Application," J. Pharm. Innov., **5**(6), p. 18.
[164] Vashist, S. K., Venkatesh, A. G., Mitsakakis, K., Czilwik, G., Roth, G., von Stetten, F., and Zengerle, R., 2012, "Nanotechnology-Based Biosensors and Diagnostics: Technology Push Versus Industrial/Healthcare Requirements," Bionanoscience, **2**(3), pp. 115–126.
[165] Ma, F., Li, C.-C., and Zhang, C.-Y., 2018, "Development of Quantum Dot-Based Biosensors: Principles and Applications," J. Mater. Chem. B, **6**(39), pp. 6173–6190.
[166] Shojaei, T. R., Salleh, M. A. M., Sijam, K., Rahim, R. A., Mohsenifar, A., Safarnejad, R., and Tabatabaei, M., 2016, "Fluorometric Immunoassay for Detecting the Plant Virus Citrus Tristeza Using Carbon Nanoparticles Acting as Quenchers and Antibodies Labeled With CdTe Quantum Dots," Microchim. Acta, **183**(7), pp. 2277–2287.
[167] Hong, S., and Lee, C., 2018, "The Current Status and Future Outlook of Quantum Dot-Based Biosensors for Plant Virus Detection," Plant Pathol. J., **34**(2), pp. 85–92.
[168] Simon, J., Flahaut, E., and Golzio, M., 2019, "Overview of Carbon Nanotubes for Biomedical Applications," Materials, **12**(4), p. 624.
[169] Sireesha, M., Jagadeesh Babu, V., Kranthi Kiran, A. S., and Ramakrishna, S., 2018, "A Review on Carbon Nanotubes in Biosensor Devices and Their Applications in Medicine," Nanocomposites, **4**(2), pp. 36–57.
[170] Sandoval-Yañez, C., and Castro Rodriguez, C., 2020, "Dendrimers: Amazing Platforms for Bioactive Molecule Delivery Systems," Materials, **13**(3), p. 570.
[171] Liu, M., and Fréchet, J. M., 1999, "Designing Dendrimers for Drug Delivery," Pharm. Sci. Technol. Today, **2**(10), pp. 393–401.
[172] Satija, J., Sai, V., and Mukherji, S., 2011, "Dendrimers in Biosensors: Concept and Applications," J. Mater. Chem., **21**(38), pp. 14367–14386.
[173] Abbasi, E., Aval, S. F., Akbarzadeh, A., Milani, M., Nasrabadi, H. T., Joo, S. W., Hanifehpour, Y., et al., 2014, "Dendrimers: Synthesis, Applications, and Properties," Nanoscale Res. Lett., **9**(1), pp. 1–10.
[174] Zheng, Y., Li, S., Weng, Z., and Gao, C., 2015, "Hyperbranched Polymers: Advances From Synthesis to Applications," Chem. Soc. Rev., **44**(12), pp. 4091–4130.
[175] Purohit, B., Kumar, A., Mahato, K., and Chandra, P., 2020, "Smartphone-Assisted Personalized Diagnostic Devices and Wearable Sensors," Curr. Opin. Biomed. Eng., **13**, pp. 42–50.
[176] Patel, S., Park, H., Bonato, P., Chan, L., and Rodgers, M., 2012, "A Review of Wearable Sensors and Systems With Application in Rehabilitation," J. Neuroeng. Rehabilitation, **9**(1), pp. 1–17.
[177] Kim, J., Campbell, A. S., de Ávila, B. E.-F., and Wang, J., 2019, "Wearable Biosensors for Healthcare Monitoring," Nat. Biotechnol., **37**(4), pp. 389–406.
[178] Purohit, B., Vernekar, P. R., Shetti, N. P., and Chandra, P., 2020, "Biosensor Nanoengineering: Design, Operation, and Implementation for Biomolecular Analysis," Sens. Int., **1**, p. 100040.
[179] Gao, W., Emaminejad, S., Nyein, H. Y. Y., Challa, S., Chen, K., Peck, A., Fahad, H. M., et al., 2016, "Fully Integrated Wearable Sensor Arrays for Multiplexed In Situ Perspiration Analysis," Nature, **529**(7587), pp. 509–514.
[180] Yetisen, A. K., Moreddu, R., Seifi, S., Jiang, N., Vega, K., Dong, X., Dong, J., et al., 2019, "Dermal Tattoo Biosensors for Colorimetric Metabolite Detection," Angew. Chem., **131**(31), pp. 10616–10623.
[181] Elsherif, M., Hassan, M. U., Yetisen, A. K., and Butt, H., 2018, "Wearable Contact Lens Biosensors for Continuous Glucose Monitoring Using Smartphones," ACS Nano, **12**(6), pp. 5452–5462.
[182] Jia, W., Bandodkar, A. J., Valdés-Ramírez, G., Windmiller, J. R., Yang, Z., Ramírez, J., Chan, G., et al., 2013, "Electrochemical Tattoo Biosensors for Real-Time Noninvasive Lactate Monitoring in Human Perspiration," Anal. Chem., **85**(14), pp. 6553–6560.
[183] Bandodkar, A. J., Jia, W., Yardımcı, C., Wang, X., Ramirez, J., and Wang, J., 2015, "Tattoo-Based Noninvasive Glucose Monitoring: A Proof-of-Concept Study," Anal. Chem., **87**(1), pp. 394–398.
[184] Kong, X., Hu, C., Duan, Z., Kong, X., Hu, C., and Duan, Z., 2017, "Generalized Principal Component Analysis," *Principal Component Analysis Networks and Algorithms*, pp. 185–233.
[185] Yapici, M. K., and Alkhidir, T. E., 2017, "Intelligent Medical Garments With Graphene-Functionalized Smart-Cloth ECG Sensors," Sensors, **17**(4), p. 875.
[186] Köhn, H. F., and Hubert, L. J., 2014, "Hierarchical Cluster Analysis," *Wiley StatsRef: Statistics Reference Online*, pp. 1–13.
[187] Voiculescu, I., Li, F., Kowach, G., Lee, K. L., Mistou, N., and Kasberg, R., 2019, "Stretchable Piezoelectric Power Generators Based on ZnO Thin Films on Elastic Substrates," Micromachines, **10**(10), p. 661.
[188] Zhang, K., Wang, J., Liu, T., Luo, Y., Loh, X. J., and Chen, X., 2021, "Machine Learning-Reinforced Noninvasive Biosensors for Healthcare," Adv. Healthcare Mater., **10**(17), p. 2100734.
[189] Mitra, B., and Craswell, N., 2018, "An Introduction to Neural Information Retrieval," Foundations and Trends® in Information Retrieval, **13**(1), pp. 1–126.
[190] Berrar, D. P., Dubitzky, W., and Granzow, M., 2003, *A Practical Approach to Microarray Data Analysis*, Springer, New York.
[191] Chauhan, V. K., Dahiya, K., and Sharma, A., 2019, "Problem Formulations and Solvers in Linear SVM: A Review," Artif. Intell. Rev., **52**(2), pp. 803–855.
[192] Fawagreh, K., Gaber, M. M., and Elyan, E., 2014, "Random Forests: From Early Developments to Recent Advancements," Syst. Sci. Control. Eng., **2**(1), pp. 602–609.
[193] Leijnen, S., and Veen, F. V., 2020, "The Neural Network Zoo," Proceedings, **47**(1), p. 9.