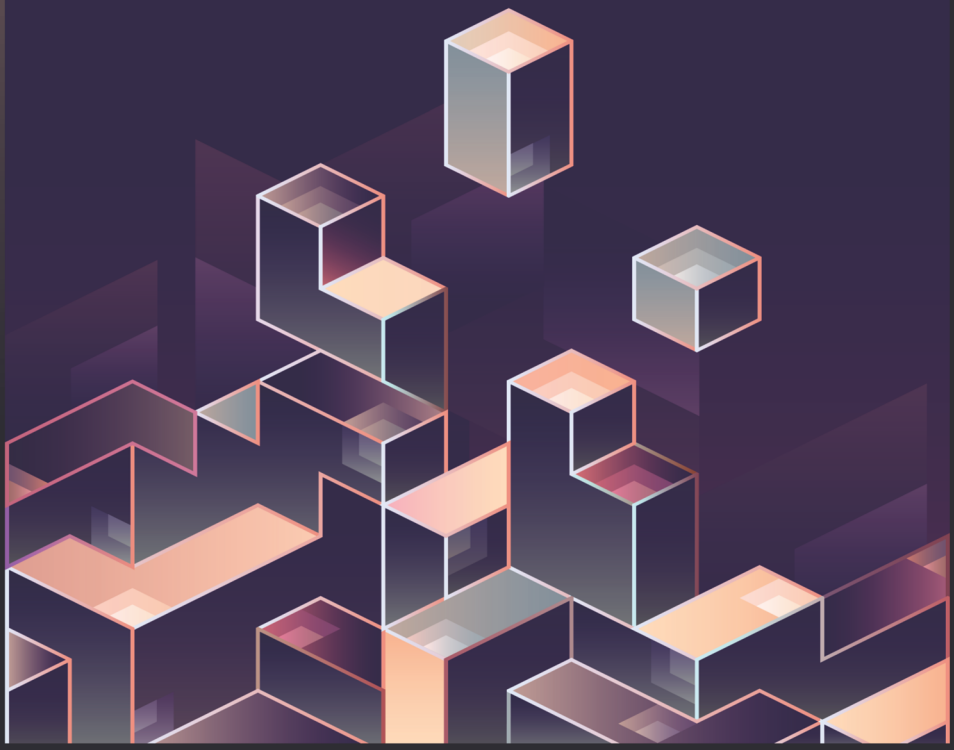
Nanomaterials-Based Sensing Platforms

Towards the Efficient Detection of Biomolecules and Gases



Aneeya K. Samantara | Sudarsan Raj | Satyajit Ratha
Editors

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Edited by

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Abbreviations

0D	zero-dimensional
1D	one-dimensional
2D	two-dimensional
3D	three-dimensional
A/D	analog to digital
AA	ascorbic acid
AC	acetaminophen
ACh	acetylcholine
ADHD	attention deficit hyperactivity disorder
AFM	atomic force microscopy
Ag	silver
Al	aluminum
AQ	anthraquinone
Au	gold
BOD	biological oxygen demand
C_2H_5OH	ethanol
CD	cyclodextrin
CDRs	complementarity-determining regions
CH_4	methane
Chits	chitosan
Cl_2	chlorine
CNF	carbon nanofiber
CNTs	carbon nanotubes
CO	carbon monoxide
CO_2	carbon dioxide
CPC	circular photonic crystal
CPs	conducting polymers
CR-GO	chemically reduced graphene oxide
CR-GO/GC	reduced graphene oxide modified glassy carbon
CTCs	circulating tumor cells
Cu_2O	cuprous oxide
Cu_2ZnSnS_4	CZTS
CuO	copper oxide

CV	cyclic voltammetry
DA	dopamine
DC	direct current
DLS	dynamic light scattering
DNA	deoxyribonucleic acid
DPV	differential pulse voltammetry
DTT	dithiothreitol
ECG	electrocardiography
EEG	electroencephalography
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EM	electromagnetic
F_c	constant fragment
FDA	Food and Drug Administration
FDTD	finite difference time domain method
FESEM	field emission scanning electron microscope
FET	field-effect-transistors
fMWCNTs	functionalized multi-wall carbon nanotubes
FOM	figure of merit
FRET	fluorescence resonance energy transfer
FWHM	full width at half maximum
g-C_3N_4	graphitic carbon nitride
GC	glassy carbon
GCE	glassy carbon electrode
GLAD	glancing angle deposition
Glu	glucose
GNP	graphene nanoplatelet
GNs	graphene nanosheets
GO	graphene oxide
GOD-HFs	glucose oxidase and hydroxyl fullerenes
GO_x	glucose oxidase
H_2	hydrogen
H_2S	hydrogen sulfide
hCG	human chorionic gonadotrophin
HCHO	formaldehyde
His	histidine
HIV	human immunodeficiency viruses
HPV	human papillomavirus

HRP	horseradish peroxidase
HS	hollow spheres
IDA	imidodiacetic acid
IEC	international electrochemical committee
IgG	immunoglobulin gamma
Igs	immunoglobins
In_2O_3	indium oxide
ISE	ion-selective electrode
ITO	indium tin oxide
Lac	laccase
LAMP	loop-mediated isothermal amplification
LD	levodopa
LED	light-emitting diode
LIG	laser-induced graphene
LNAs	locked-nucleic acids
LOD	limit of detection
LPG	liquefied petroleum gas
LSPR	localized surface plasmon resonances
MEMS	micro-electro-mechanical system
MIP	molecular imprinted polymers
miRNA	microRNA
MMP	matrix metallopeptidases
Mo	molybdenum
MON	metal oxide nanostructures
MOS	metal oxide semiconductor
MoS_2	molybdenum disulfide
MWCNTs	multi-walled carbon nanotube
NaCl	sodium chloride
NF	nafion
NGs	nano-generators
NH_3	ammonia
NHS	N-hydroxysuccinimide
NiCNFs	nickel nanoparticle loaded carbon nanofibers
nm	nanometer
NMOF	nano-metal-organic frameworks
NO	nitric oxide
NO_2	nitrogen dioxide
NPs	nanoparticles

NRs	nanorods
NTA	nitrilotriacetic acid
NW	nanowires
PCC	photonic crystal cavity
PDA	polydopamine
PDDA	poly diallyl dimethyl ammonium chloride)
PDMS	poly dimethyl siloxane
PI	polyimide
PI-BN	polyimide-boron nitride
PL	photoluminescence
PNA	peptide nucleic acid
PPd NS	porous pd nanostructures
ppm	parts per million
Ppy	polypyrrole
PSA	prostate-specific antigen
PSS	poly(sodium 4-styrene sulfonate)
Pt	platinum
Pt-DENs	dendrimer-encapsulated Pt nanoparticles
PVP	polyvinylpyrrolidone
QCM	quartz crystal microbalance
QDs	quantum dots
rGO	reduced graphite oxide
RI	refractive index
RIS	refractive index sensitivity
RIU	refractive index unit
RNA	ribonucleic acid
RRE	rev responsive element
SEM	scanning electron microscope
SIPs	surface imprinted polymers
SMOs	semiconductor metal oxides
SnO_2	tin oxide
SNR	signal to noise ratio
SOI	silicon-on-insulator
SPP	surface plasmon polarities
SPR	surface plasmon resonance
SPs	surface plasmons
SQUID	superconducting quantum interference devices
SWCNT	single-walled carbon nanotubes

TB	tuberculosis
TE	transverse electric
TEM	transmission electron microscope
THF	tetrahydrofuran
Thi	thionine
TIR	total internal reflection
TM	transverse magnetic
TR	tyramine
UA	uric acid
UV	ultraviolet
V_H	variable heavy
WO_3	tungsten oxide
XRD	X-ray diffraction
ZnO	zinc oxide

Preface

The growing interest in the early and reliable detection of several bio-molecules is due to the fact that the increasing set of bio-analytes are rather hard to detect and are of extremely small dimension, which requires the implementation of precise detection techniques. Traditional methods use enzyme-based methods to carry out the detection process. The most commonly used biosensors make extensive use of labels (such as enzymes and fluorescent or radioactive molecules attached to the targeted analyte). Thus, the final sensing output is completely dependent on the number of labels present in the analyte. These label-based detection techniques are thus labor- and cost-intensive as well as time-consuming. In addition, labeling of biomolecules can block active binding sites and alter the binding properties. As a result, this may adversely affect the affinity-based interaction between the recognition elements and the target molecules.

However, label-free biosensing techniques-based on optical and/or electrochemical recognition techniques are free from any such biomarkers or labels. Rather, they make use of several intrinsic properties such as molecular weight, size, charge, electrical impedance, dielectric permittivity, or refractive index (RI), to detect their presence in a sample. Since there will be no biomarkers or labels here, the detection process will be much faster in comparison to traditional enzyme-based biosensing. Also, this would allow for the real-time and reliable detection of a wide range of analytes depending upon their specific set of inherent physicochemical properties.

Optical biosensors, especially SPR-based techniques, are of significant importance. And if combined with the latest fiber-optical systems, this could readily provide an effective tool to carry out a cost-effective, fast, and reliable sensing platform for a wide range of applications. This book deals with the brief history behind the sensing technology and also emphasizes a broad range of biosensing techniques-based on optical and

electrochemical response methods. Starting from the traditional enzyme-based biosensing method to functionalized nanostructure-based sensors; this book also provides a detailed overview of some of the advanced sensing methodologies-based on photonic crystal cavity (PCC)-based sensing devices.

—**Aneeya Kumar Samantara, PhD**
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Introduction

Detection of biomolecules and the underlying mechanism of the interactions among them are critical for several fields of interest such as cell biology, the pharmaceutical industry, and medical diagnosis, etc. The different kinds of interactions shown by the biomolecules, analytes, and protein molecules provide basic yet important information regarding the functions of a typical cell. This can be exploited by scientists to find out whether specific interactions can be guided to perform the proliferation of cancerous cells. This could also help in the diagnosis of the concerned cancerous cell growth. However, the development of such techniques would require high-precision and fast response sensing devices. Most of the analytes consist of drug compounds, DNA oligomers, peptides, viral particles, enzymes, etc., that have ultra-small dimensions and are also present in a very low concentration in a given specimen. Also, larger bioanalytes such as bacteria, cells are generally stained with fluorescent dyes to mark them. But, the process itself results in the death of the specimen. Therefore, for larger and smaller analytes, fabrication of a precise and non-invasive sensing technique is imperative considering the growing demand for reliable, fast, and responsive medical diagnosis.

This book introduces key fundamental aspects of several biosensing techniques with a brief overview of the processes involved and their future perspectives. It contains eight chapters comprising various materials and methods that are critical for the development of next-generation sensing devices.

The first chapter provides detailed information regarding the current trends and the future development of biosensing techniques, along with few excerpts on the application part. This will provide us a clear picture about the current state of the biosensing techniques and whether significant improvement and/or upgradations are being made to make the same more effective in the long run. The second chapter emphasizes on the application of nanostructured materials for biosensing applications. Materials like graphene (GN) and carbon nanotube (CNT) are well-known for their excellent physicochemical properties and can revolutionize the

sensing technique. Also, there has been a specific mention about quantum dots (QDs) which has drawn significant interest due to its unique optical properties. In the third chapter, we will be dealing with some of the advanced sensing techniques-based on photonic crystal cavity (PCC)-based sensors and their wide range of applications. This chapter provides insights regarding some of the self-assembly techniques and fabrication methods that could help researchers to understand the potential of such cavity-based sensors for biomolecule detection. The fourth chapter consists of information regarding the sensing activities of metal oxide-based nanostructures towards the detection of gas molecules. The fifth chapter provides information regarding optical biosensors for diagnostic applications. Here, a detailed overview of the detection methods based on advanced techniques such as surface plasmon resonance (SPR) has been provided along with an emphasis on the rise of gold nanoparticles (AuNPs) as biosensors. The sixth chapter discusses the synthesis of materials and fabrication of various types of metal-free sensing platforms and elaborately presented the electrochemical sensing performance. On the other hand, the seventh chapter covers the gas sensing performances of various noble metal-based nanostructures. The eighth chapter concludes the book and discusses different aspects of noble metal-based sensing platforms for the electrochemical detection of various bio-analytes.

The above chapters provide a lucid understanding of the background and working principles of bio-sensing techniques-based on both traditional label-based and latest label-free methods. Furthermore, advanced concepts such as photonic crystal cavity-based sensing and nanostructure-based materials have been discussed in detail for a better understanding of the futuristic development in the field of biosensing.

CHAPTER 1

Biosensors: Current Trends and Future Perspectives

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ABSTRACT

A biosensor is an analytical device employed to sense analytes and associated changes in a given biochemical environment. The output is interpreted in the form of electronic signals read by an appropriate recognition system and an electrochemical transducer. The past few decades have witnessed the evolution of biosensors as well recognized sensitive and selective devices to record subtle changes in analytes of a various chemical or biological system. Due to such potential, biosensors have been implemented across disciplines of pure and applied sciences in some form or the other. Since their birth in the early 1960s, Extensive research and development has happened globally to enhance our existing knowledge on these devices. However, only a handful of biosensors have been commercialized and actively used, for example, the glucose monitors and pregnancy test kits. This chapter will provide details on the inception, evolution, current applications and the probabilistic future of this technology in the context of human health and disease.

1.1 BIOSENSORS AND THEIR UNDERLYING PRINCIPLE

1.1.1 HISTORICAL PERSPECTIVE ON THE BIRTH OF BIOSENSORS

In simple words, Biosensors can be defined as analytical devices that convert a biological or biochemical response to an electronic output. Biosensors have witnessed remarkable progress since their inception. Within the past 40 years, the direct or indirect applications of biosensors supported by research in both pure and applied sciences have established the impact of these devices. The history of biosensors dates to as early as the year 1906 when M. Cremer demonstrated that the concentration of an acid in a liquid is proportional to the electric potential between parts of the fluid located on opposite sides of a glass membrane (Cremer, 1906). Later, Søren Peder Lauritz Sørensen introduced the concept of pH, percentage of hydrogen ion concentration, in 1909, and an electrode for pH measurements was published in the year 1922 by W. S. Hughes. Between 1909 and 1922, Griffin and Nelson demonstrated enzyme immobilization on a surface of aluminum hydroxide and charcoal (1916). In 1956 Professor LeLand C. Clark, also known as the "father of biosensors," published his work on the development of the first true biosensor, an oxygen probe that could sense the changing oxygen concentrations in a given biochemical environment (2006). This electrode was named as "Clark Electrode" after Professor Clark (Heineman et al., 2006). Employing this invention, the first demonstration was performed using a dialysis membrane containing the enzyme glucose oxidase (GO_x) wrapped over the oxygen detection probe. In this demonstration, observers witnessed the ability of the probe to detect the changes in oxygen concentration in proportion to the activity of the enzyme GO_x (Heineman et al., 2006; Bhalla et al., 2016). Thus, the first biosensor was an "enzyme electrode" marking the activity observed during the scientific demonstration (Heineman et al., 2006; Bhalla et al., 2016). Later in 1967, Updike and Hicks used a similar principle employing the immobilization of enzyme GO_x in a gel (polyacrylamide gel) onto the surface of an oxygen electrode to facilitate rapid quantitative measurement of oxygen concentration (Bhalla et al., 2016). Soon, this innovation sparked a great interest and curiosity in the global scientific community. Only 2 years later, Guilbault and Montalvo developed glass electrode-based sensors to measure urea concentration (Guibault and Montalvo, 1969). Subsequently, from 1970 several authors began accepting and reproducing the idea of biosensors, based on the coupling of enzyme and

electrochemical sensors. A new set of sensors were proposed in 1971-based on a novel principle called ion-selective electrode (ISE) to detect the activity of beta-glucosidase enzyme for the formation of benzaldehyde and cyanide (Rechnitz and Llenado, 1971). This marked a transformative approach in the field where researchers attempted to employ various targets as receptors including, tissues, microorganisms, cellular organelles, cell surface receptors, enzymes, antibodies, nucleic acids, etc. (Bhalla et al., 2016). On the other hand, probable transducers included, electrochemical, optical, thermometric, magnetic, and others (Bhalla et al., 2016).

1.1.2 BIOSENSORS FOR DISEASE

The progress made within a decade of the first "biosensor" led the scientific and medical community to collaborate towards a common idea-Can these "biosensors" or sensing devices be used in detection and diagnosis of various human diseases? Little did the scientific community foresee the power of these simple yet innovative devices during that time. Nevertheless, the idea majorly focused towards developing simplified, cost-effective and user-friendly devices. Due to this, biosensor technology has continued to evolve into an ever-expanding and multidisciplinary domain of innovation-driven science since its birth.

1.1.3 SENSORS VS. BIOSENSORS: WORKING PRINCIPLE

The working principle of a biosensor could be imagined similar to that of a classical sensing device (Figure 1.1(A)). Hence, the question is-What exactly is unique about biosensors and how different they are from the conventional sensing devices? Thus, it is important to gain a deeper insight to their structural components which makes them of functionally unique. The functional anatomy of a conventional sensing device includes components that will involve a sensing unit, a converter unit to convert the sensed signal into a digital format, and a display unit to interpret this converted signal to a user-friendly readable format (Figure 1.1(A)). So, to begin with the first component is a *sensor*: a device that can sense physical changes including, temperature, mass, humidity, light, and pressure. This change measured and captured by the sensor is analog in nature. To ensure proper interpretation, it is important to change the analog signal

into a specific electronic potential difference termed as "voltage." This analog signal is sensitive to fluctuations and constant changes that can be captured using a *transducer*, the second component of the sensing device. The transducer enables analog to digital (A/D) signal conversion that is efficient enough to capture and convert even the smallest of fluctuations in the analog readings. The transducers can be semiconductors, diodes or transistors (for temperature changes), capacitors (to measure pressure changes) or photodiodes or photoresistors (to detect light-based changes) (Yoon, 2016). Thereafter, the recorded signal is processed with a network of electronic components constituting an amplifier to capture signal changes, an electronic processor and a readable display unit to record the changes detected by the user (Figure 1.1(A)).

Although, the overall structure of a biosensor primarily overlaps with the principle of a general sensing device as described above however it differs significantly with a few unique features (Figure 1.1(B)). For example, the sensor used in a "biosensor" module is a sensitive biochemical element called *bioreceptor*, also otherwise known as a biomimetic material (Figure 1.1(B)). Bioreceptors prove superior in determining the differences in biochemical analytes (tissue changes, microbes, nucleic acid changes, etc.), which the conventional sensors (for temperature, pressure, etc.), fail to detect (Bhalla et al., 2016; Yoon, 2016). For example, to detect *E. coli* in a given sample, a voltage signal will be generated only when the bioreceptor (for instance, anti-*E. coli* antibody) will recognize and bind to the bacteria. As of today, the commonly used bioreceptors include nucleic acids (DNA, RNA) and antibodies that target proteins of interest. Second, the transducer of a biosensor primarily features electrochemical (measures voltage differences), optical, thermal (change of temperature) and piezoelectric (to measure antigens, nucleic acids, biomolecules, enzymes) (Yoon, 2016). Like the conventional sensing device, the third unit is the electronic module comprising of the electronic unit to record the changes detected by the user (Figure 1.1(B)).

1.2 CHARACTERISTICS OF A BIOSENSOR

A biosensor constitutes of unique components integral for its function. Therefore, the device should include components that harness optimized properties for the efficient detection of the analyte and its associated changes with minimal error.

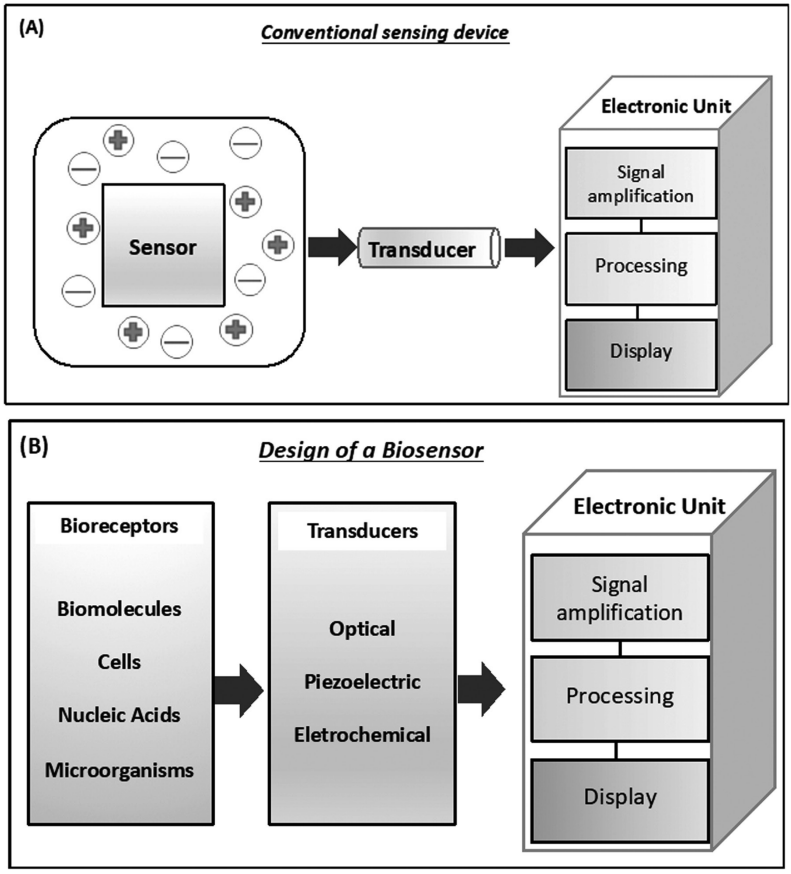

FIGURE 1.1 Schematic representations of functional components of biomolecule sensing devices. (A) Classical sensing device-sensor senses the charge-based changes in environment which are recorded by the transducer in connection. Thereafter, the transducer signals the charge recorded to the electronic unit for subsequent processing of data. (B) Design of a biosensor-sensors can include biomolecules to microorganisms which recognize the changes-based on the environment or specific analyte. The signal is thereafter processed by the specific type of transducer-based on the sensing method and transferred to the electronic unit for data processing and analysis.

Source: Adapted with permission from: Bhalla, Jolly, Formisano, and Estrela (2016).

1.2.1 SPECIFICITY AND SELECTIVITY

Selectivity and specificity enable a bioreceptor to detect a specific analyte in a given sample containing various biomolecules and other constituents

(Yoon, 2016; Holzinger and Goff, 2014). One can imagine the interaction of an antigen with the antibody which is of very specific and selective in nature. Considering this example, antibodies can be considered as bioreceptors that are clamped (attached) on the transducer's surface. A buffering solution (containing salts) with the antigen when exposed to the transducer allows the antibodies to interact only with its target antigens (Yoon, 2016). Hence, these features are an important consideration for designing of a biosensor.

1.2.2 PRECISION AND ACCURACY

Precision ensures to provide similar results each time an analyte is measured while accuracy ensures the digital readings obtained with a mean value nearest to the true value when an analyte is measured in multiple replicates (Bhalla et al., 2016). This property is further characterized by the reproducibility to generate identical responses for experiments conducted in replicates. Such properties are very much dependent on the quality of transducer and electronic components used in the given biosensor. Therefore, the accuracy in the obtained signals or digital readings provides high reliability and robustness towards the functioning of a biosensor.

1.2.3 LINEAR RANGE OF SENSING

The linearity or linear range of a biosensor can be defined as the range of analyte concentration changes to which the biosensor responds linearly. It is the feature that is indicative of the accuracy of the detected changes in the analyte (Gupta et al., 2017). This unique property of the biosensor helps to recognize the smallest of any change associated with the analyte during a given response of the biosensor (Gupta et al., 2017).

1.2.4 BIOSENSING STABILITY

Stability defines the degree of susceptibility to ambient changes occurring within the vicinity of the biosensing system (Bhalla et al., 2016; Yoon, 2016; Gupta et al., 2017). These changes can potentially induce drifts or biases in the output signal during measurement of analyte-associated changes. This results in error in the end results obtained. Stability of a biosensor also helps

to record changes with the analyte in long experimental conditions. Factors including the functioning of transducers and electronics, affinity of the bioreceptor (interaction between analyte and bioreceptor) may influence the stability of a biosensor. Therefore, appropriate tuning of electronics is required to ensure a stable response of the sensor.

1.2.5 SENSITIVITY

The sensitivity of a biosensor defines its ability to detect the least amount of analyte and associated changes (Gupta et al., 2017). This is important since the concentrations of various analytes occur in the range of nanograms to femtograms in a given biological system.

1.3 TYPES OF BIOSENSORS

The classification of biosensors broadly depends on the transducers used in its design (Yoon, 2016; Kubicek-Sutherland et al., 2017). This is because of the transducers that enable the isolation and immobilization of the analyte to its electrical component. Therefore, biosensors can be categorized-based on the biological or the transduction elements used in their designing (Kubicek-Sutherland et al., 2017). Biological elements include enzymes, antibodies, tissue samples, microorganisms, etc., while transducers include components that are based on the recognition of mass, electrochemical, and optical properties (Figure 1.2).

1.3.1 OPTICAL BIOSENSORS

Optical biosensors utilize optical fibers to allow detection of analytes-based on absorption, fluorescence or scattering of light (Yoon, 2016; Kubicek-Sutherland et al., 2017). This type of biosensor enables the measurement of both catalytic and affinity reactions. Biochemical or molecular reactions induce a change in the fluorescence or absorbance concurrent with a change in refractive index (RI) of the surface-immobilized with varied density of bioreceptors and analytes. Optical biosensors can be utilized for *in vivo* applications, including the precision of recording the changes inside a living biological cell.

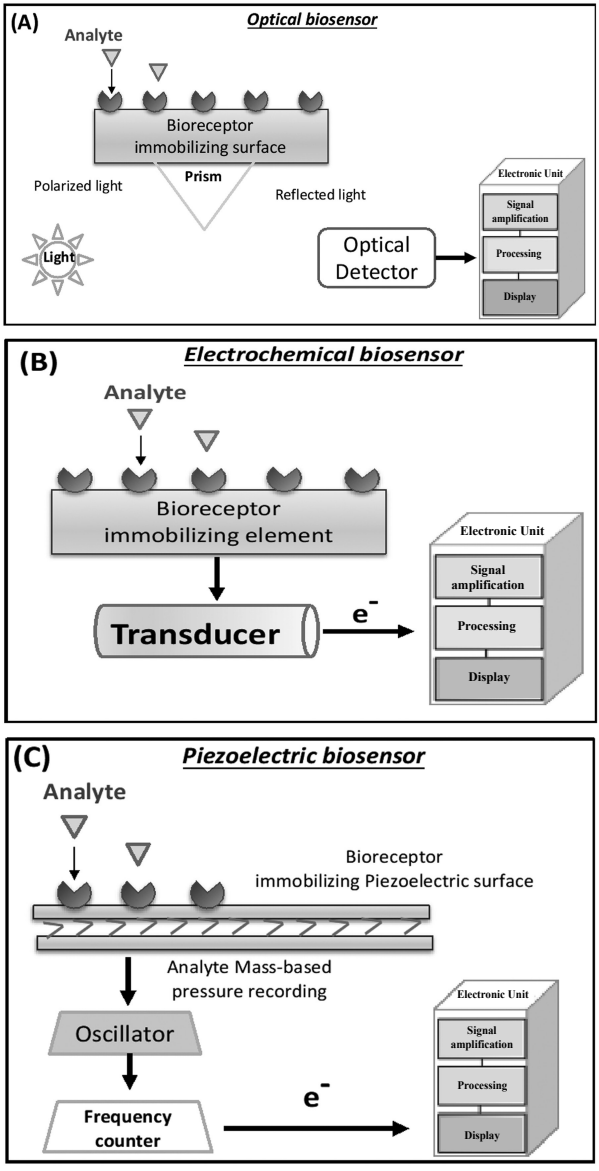

FIGURE 1.2 Classification of commercially available biosensors-based on the transducing element. (A) Optical biosensor-allows the detection of analytes-based on the properties of light. (B) Electrochemical biosensor-transduction of electrical signals produced as a result of bioreceptor-analyte interaction allows efficient detection of analyte-associated changes. (C) Piezoelectric biosensor-functions-based on the principle of mass-based production of mechanical force produced due to the interaction of analyte-bioreceptor interaction.