REVIEW ARTICLE

A comprehensive review on biosensor-based diagnosis treatment of infectious disease

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Abstract

A biosensor is a device that measures biological or chemical reactions by generating signals proportional to the concentration of an analyte in the reaction. Its high precision and speed are advantages. Numerous biosensor kinds are employed in numerous fields. These biosensors are based on enzymes, nucleic acids, electrochemistry, and optics. Each of them may consist of several parts and functions. Biosensors are particularly useful in the pharmaceutical, food, defense, environmental, and agricultural industries, as well as in the early identification of diseases. Biosensors are widely used in industrial processing and monitoring, environmental pollution management, veterinary and agricultural applications, clinical analysis, and general health-care monitoring. Biosensor technology has promise for prompt and precise identification, trustworthy cancer cell imaging, monitoring of angiogenesis and cancer spread, and the capacity to determine the effectiveness of anticancer chemotherapy agents. Biosensors have increased worldwide and have attracted the attention of scientists. In this study, the classification of biosensors, application areas, characterization, studies on biosensors, and technologies developed and applied for the future are mentioned.

Key words: Biosensor, Commercial Biosensor, Electrochemical biosensor, Safety and Security

INTRODUCTION

The nano-chemistry research institute has carried out a scoping study and this report presents some of the initial outcomes. A search of the scientific literature (i.e., journal articles and conference proceedings) has provided most of the references [Figure 1]. This scoping study also contains information obtained from various companies, the patent literature, and personal communications with several world authorities on biosensors.

Pathogenic microorganisms, such as bacteria, viruses, fungi, and parasites, are the source of infectious diseases. Tuberculosis, meningococcal meningitis, malaria, acquired immunodeficiency syndrome, pneumonia, poliomyelitis, hepatitis, Ebola virus disease, dengue and chikungunya, American trypanosomiasis (Chiggers disease), leprosy, toxoplasmosis, and the disease are a few of the most common illnesses listed by the World Health Assembly of the World Health Organization.

The spread of infectious diseases is fueled by a combination of factors, including poor hygiene control, inadequate water management, high population density, and ecosystem disruption. Moreover, the rising prevalence of certain diseases, despite existing vaccination programs, underscores the impact of intentional under-vaccination and emphasizes the need for enhanced public health education, innovative immunization strategies, and alternative solutions to combat the growing health threats. Poor hygiene control,

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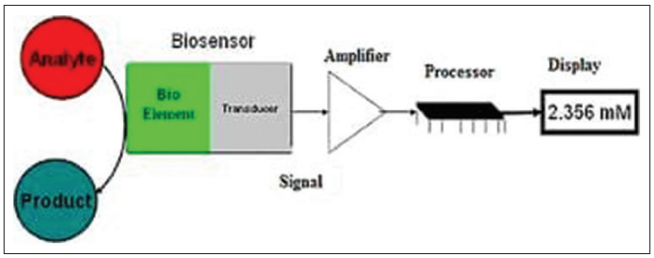

Figure 1: Basic concept of biosensors

inadequate water management, high population density, and ecosystem disruption collectively contribute to the spread of infectious diseases. The increasing prevalence of certain diseases, despite vaccination efforts, highlights the need for improved public health education, innovative immunization approaches, and alternative solutions to address the growing health concerns.

Objectives

The aims of this study are to:

(a) Provide an overview of the most common and widely used biosensor technologies, which have been reported recently in the literature
(b) Address the development of implantable and/or handheld biosensors to detect pathogens and diseases
(c) Highlight some recent advances in biosensor technology
(d) Identify market opportunities for existing biosensor technologies
(e) Determine the potential role of biosensor development.

TYPES OF BIOSENSORS

Resonant Biosensor

In this type of biosensor, an acoustic wave transducer is coupled with an antibody (bio-factor). The analyzed molecule (or antigen) gets added to the membrane and the mass of the membrane diversities. This leads to variations in the transducer's mass, resulting in a range of resonant frequencies. This frequency change is then measured.[3,29]

Optical Biosensor

Optical transducers represent another major family of biosensors that have been exploited commercially. Optical biosensors [Figure 2], which are sometimes called "optodes," have received considerable interest for disease/pathogen detection. The optical biosensor format may involve direct detection of the analyses of interest or indirect detection through optically labeled probes. In general, there are at least four types of biosensors using the principles of optical technology. These are as follows: Absorption/reflection, chemiluminescence, fluorescence, and phosphorescence.[4,5]

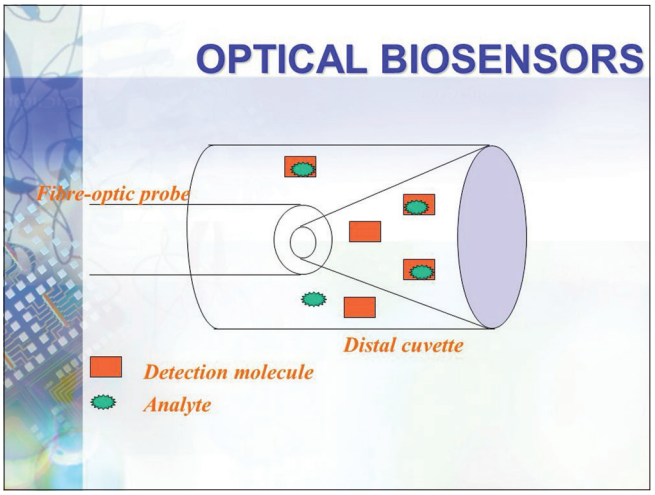

Figure 2: Optical biosensor

Optical-based Biosensors

Optical biosensors are devices that utilize the principle of optical measurements (absorbance, fluorescence, chemiluminescence, etc.). They employ the use of fiber optics and optoelectronic transducers. The output transducer signal that is measured is light.

THE PRINCIPLE OF OPERATION OF THE BIOSENSOR

Biosensors function through signal transduction, integrating a biorecognition component, biotransducer, and electronic setup (amplifier, processor, and display) to detect and measure biomolecules. Biosensors rely on signal transduction as their core operating principle, comprising key elements such as:

- A biorecognition component (e.g., antibodies, enzymes)
- A biotransducer (converting biological signals to electrical signals)
- An electronic setup, including:
- Amplifier (enhancing signal strength)
- Processor (interpreting and analyzing data)
- Display (presenting output).

These components work together to enable biosensors to detect and measure target biomolecules. It is possible for the bio-recognition element – basically a bioreceptor – to interact with a particular analyte. After measuring the interaction, the transducer outputs a signal [Figure 3]. The analyte concentration determines how strong the signal is at output. The electronic system then amplifies and processes the signal. On a surface, the biological component is rendered immobile. The transducer transforms the recognition event into a quantifiable signal that can be analyzed when a particular target analyte binds to the immobilized biomolecule.

A biosensor is a tool for analysis,

1. Essentially, the target analyte interacts with the bioreceptor, and the detecting component part uses a

reaction, particular adsorption, or another mechanism such as physical/chemical contact to uniquely identify the analyte

2. The digital detector module then measures the signal that the transducer converted the chemical changes into.[41] There are several ways to divide up the topic of transduction principles: Electrochemical, piezoelectric, optical, thermal, micromechanical, and magnetic
3. Biosensors have several advantages, such as outstanding performance, easy handling, quick reaction, high sensitivity and specificity, portability, small size, and real-time analysis.[39]

COMMERCIAL BIOSENSORS

There are well over 200 companies worldwide presently working in the area of biosensors and bioelectric.[6,7] Due to the comparatively significant number of commercial biosensors, this report will not be able to give due credit to all the products that are commercially available. Some of these companies are directly involved in biosensor fabrication/marketing (will be discussed afterward), whereas others play an important role in providing the necessary raw materials/reagents/instruments for biosensor production (e.g., Applied Enzyme Technologies, Biozyme Laboratories, Dupont Ltd., Eco Chime, Recon Incorporated, Gwent Electronic Materials Ltd., Palm Instruments, and Unison Instruments Ltd.,). Most of these companies are working on existing biosensor technologies that were developed over a decade ago.[6] Few of them are developing new technologies, although they appear to be improving existing technologies to move them into the commercial arena. Table 1 summarizes some of the biosensor instruments made by various companies for the detection of bacteria. It is obvious that the bioluminescence method appears promising; however, this method works on the fact that all microorganisms, except for viruses, contain ATP, suggesting that there may be some limitations in this technique for disease detection.

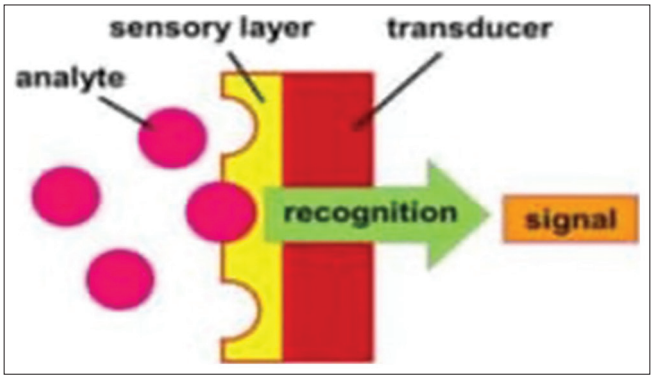

Figure 3: Principle of operation of the biosensor

IN VIVO AND IMPLANTABLE BIOSENSORS

A survey of the patent and scientific literature revealed that most of the work on implantable biosensor technologies has been directed toward developing a long-term glucose sensor.[10-13] The diagnosis and management of the worldwide health problem of diabetes have been the impetus behind the development of an implantable glucose biosensor.[10,14,15] Most of the implantable glucose biosensors presently available are mainly short term and have an effective lifetime in blood of less than several weeks.[12,13] Bio-fouling of the sensor membrane is still a major obstacle to the widespread application of implantable biosensors, noting that the sensor progressively loses function with time.[16] It has been shown that the accurate long-term usage of implanted sensors is limited by fibrosis formation that develops around the sensor and subsequently inhibits the influx of analyte to the detector.[16]

Table 1: Some manufactures of commercial biosensor instruments for bacteria detection (39)

Commercial instrument	Detection method	Detection limit (cells/ml)	Analysis time
Midas Pro (Biosensori SpA, Milan, Italy	Amperometry	10^6	20 min
PZ 106 Immuno-biosensor System (Universal Sensors, New Orleans, USA)	Piezoelectric	10^6	40 min
Bactometer (Bactomatic Inc.,Princeton, USA)	Impedimetry	10^5	3-8 h
Malthus 2000 (Malthus Inc.,stoke-on-Trent, UK)	Conductance	10^5	8-24 h
Unilite (biotrace, bridgend, UK)	Bioluminescence	10^3	15 min
Lumac Biocounter (Lumac b. v., Schesberg, Netherlands)	Bioluminescence	10^3	20 min
Coulter counter (Coulter Electronics, Canada)	Coulter counter	$5x10^4$	30 min
Thermal activity monitor (Thermometric, Northwich, Cheshire, UK)	Microcalorimetry	10^5	3 h
BIA-core (Pharmacia, Uppsala, Sweden)	Surface Plasmon Resonance	10^5	1 h
Vitek AutoMicrobic System (bioMerieux Vitek, Hazelwood, MO)	Optical	10^4	4 h

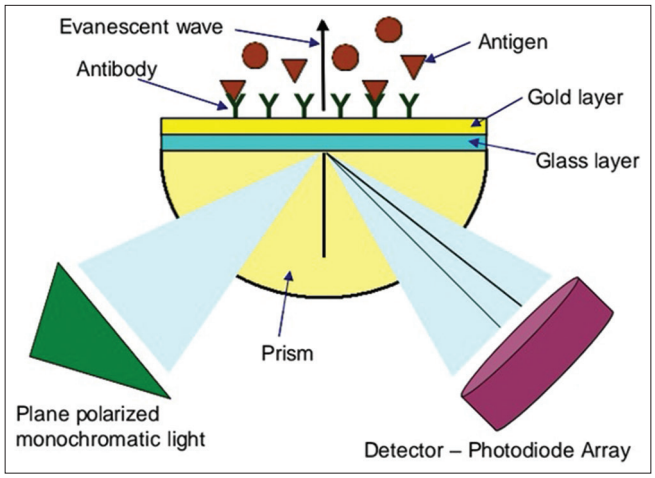

Figure 4: A surface plasmon resonance biosensor

BIOSENSORS BASED ON ELECTROCHEMISTRY

According to certain reports, electromechanical actuators form the cornerstone of nearly 50% of the biosensors published in the research.[38] According to a recent review of the literature, the most used and regularly quoted sensor platform in the literature is the electrochemical-based one.[10,18-20] Electrochemical immunosensors are becoming a growing trend in clinical analysis, according to research from Stefano *et al*. (2000), a trend that is primarily because of the better sensor they have selected design.[21] Similarly, compared to current laboratory-based immunochemical assays, Warsinke *et al*. (2000) indicated that an electrically charged immunosensor supplies an intriguing replacement.[22,42] According to Wang's (2002) overview of nucleic acid biosensors, the electrochemically based apparatus will be in charge.

Absorption and Reflectance Spectroscopy

When light (usually monochromatic) is passed through a sample, several things can transpire. The light can either be reflected back or it can be transmitted through the sample. The process that occurs will depend on the wavelength of light, the composition (i.e., the type and concentration of molecules, etc.), and the thickness of the sample. The energy from the electromagnetic spectrum can be used to provide information about the changes in the local environment surrounding the analysis. Absorption spectroscopy is one technique that can be used to monitor the transmitted light intensity according to the Beer–Lambert law. This is achieved using a spectrophotometer to collect the absorption spectrum of the sample [Figure 4]. The basic components of a spectrophotometer are as follows: Light source (i.e., deuterium laser, laser, etc.); wavelength selector; radiation transducer; and signal processor/readout device. The wavelength selector comprises various slits, lenses, mirrors, windows, gratings, or prisms to isolate the radiation of interest. The radiation transducer, which is usually a semiconductor material, converts the photon energy into an electrical signal. However, in the case of an infrared spectrometer, a dielectric material is sometimes employed to convert the heat energy into an electrical signal.

ELECTROCHEMICAL-BASED BIOSENSORS

It has been stated that more than half of the biosensors reported in the literature are based on electrochemical transducers.[17] A recent survey of the literature has revealed that the electrochemical-based sensor platform is the most common and in many cases, the most frequently cited in the literature.[10,18-20] A review by Stefan *et al*. (2000) has revealed that electrochemical immunosensors are gradually increasing in popularity in clinical analysis and this is partly due to improved sensor design[21,43] Similarly, Warsinke *et al*. (2000) demonstrated that the electrochemical immunosensor is a promising alternative compared to existing laboratory-based immunochemical assay.[22] Wang (2002) suggests in his review of nucleic acid biosensors that the electrochemical-based device will be responsible for achieving future large-scale genetic testing. This may not be surprising considering that electrochemical transduction possesses the following advantages: Low cost, high sensitivity, independence from solution turbidity, easily miniaturized/well suited to micro-fabrication, low-power requirements, and relatively simple instrumentation.[7,8,9,30,22]

DNA/Nucleic Acid Sensors

Traditional techniques for DNA sequencing are based on the coupling of electrophoretic separations and radio-isotopic (32P) detection.[38] These methods are known to be labor intensive, time-consuming, high cost, hazardous, have disposal problems associated with radioactive waste, and are not well suited for routine and rapid environmental analysis.[35,36] Subsequently, various promising alternative methods of DNA detection, which use a non-radioactive labeled probe, have been developed. The detection of specific DNA sequences provides the fundamental basis for detecting a wide variety of microbial and viral pathogens.[28] Several reviews have been published on the development and application of DNA sensors for the testing of virus infections,[7,29-38] noting that viruses appear to be almost uniquely DNA or RNA composed within an outer coat or capsid of protein.[30] In essence, the technology relies on the immobilization of a short (20−40 mer) synthetic oligomer (the single-stranded DNA [ssDNA]), whose sequence is complementary to the target of interest.[38] Exposure of the sensor to a sample containing the target results in the formation of the hybrid on the surface, and various transduction methods (i.e., optical, electrochemical, and piezoelectric) have been used to detect duplex formation.[38,42] J.J. Gooding (2002) revealed that

relatively few DNA biosensor studies have been carried out in real complex biological samples.[7,26,27,38]

SAMPLING PROCESS: SPATIAL AND TEMPORAL REPRESENTATIVENESS

The representativeness of a wastewater-based epidemiology (WBE) study is directly affected by the spatial and temporal aspects of the sampling process.[30,42] The particularities of the sewage systems must be considered when establishing a WBE protocol. In addition, models of viral decay and wastewater flow rates throughout the sewage system should be considered to accurately estimate viral concentration within the catchment population. Furthermore, the time of sampling is also another important factor; for example, in some sewage systems, there may be a specific period of time that takes for water to travel from the households to the centralized wastewater treatment plants. Autosamplers can be used to obtain more representative samples over specific periods of time.[30] Nonetheless, this may not be economically feasible for many low- or middle-income Countries and other resource-constrained regions.

Sample Concentration and Pre-treatment Processes

The detection of viral pathogens requires the concentration of the samples into smaller volumes to improve detection limits.[30] At present, membrane filtration is the most common primary sample concentration and virus recovery method for water matrices; e.g., virus adsorption-elution and cross-flow ultrafiltration. Even though these recovery techniques have been useful for viral detection in water samples, the variability and complexity of sewage composition usually result in low and poorly reproducible recoveries. Different types of molecules that are suspended or dissolved in wastewater are likely to foul the filters, limit recovery yields, and potentially interfere with downstream assays. Moreover, some filters may require pre-conditioning steps to facilitate adsorption; this is time-consuming and can limit the final sample volume, which is disadvantageous, especially if collected samples need to be transported for their processing. Preconditioning processes may also have a negative impact on the integrity of the target pathogen, hindering the accurate assessment of the sample.[23,25,37,50]

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.[35]

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[39-41] which have 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 communicates only with the analyte of interest.[38,39]

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.[28] 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.[29] 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.[28] 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,[7,12] for example, glucose oxidase-based sensors have a response time between 5 and 30s.[38]

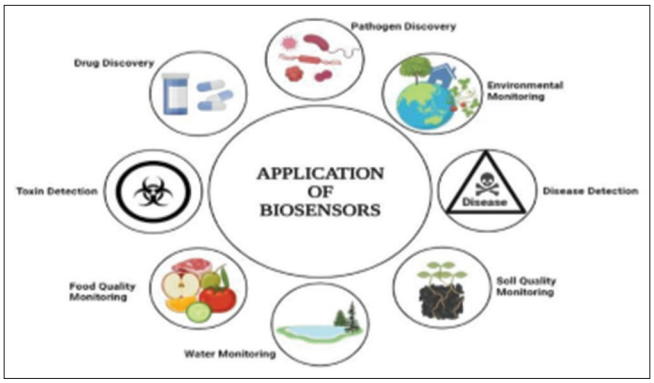

Figure 5: Application areas of biosensor[31]

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.[28,29] For mass production, it is important that the biosensing parameters are quantitatively validated.[30,39] The analytic hierarchy process was used, to perform a quantitative analysis of the signal produced by a carbon nanotube 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.[1]

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.

APPLICATIONS OF BIOSENSOR

Biosensors have many uses in clinical analysis, general health-care monitoring, veterinary and agricultural applications, industrial processing and monitoring, and environmental pollution control. The advantages are likely to include low cost, small size, quick and easy use, as well as a sensitivity and selectivity greater than the current instruments. The advent of cheap, user-friendly biosensors will revolutionize the practice of health-care monitoring and enable more in-depth diagnosis on a metabolic basis. The introduction of suitable biosensors would have a considerable impact in the following areas.

The first biosensor is L.C. It was used by Clark in 1950 to measure the amount of glucose in the blood. Today, studies on biosensors continue to gain importance considering the results obtained in recent years.[31] Because the working discipline of biosensors has a wide range. In general, the amount of glucose is used for the detection of drugs, viruses, diseases, etc. Its use continues to be widespread in many application areas.[29] In addition to these, it also operates in areas such as medicine, food, pharmacy, quality control, industry, animal husbandry, environmental pollution, waste control, and military applications.[28] In addition to these, the possible application areas of biosensors are as follows: Bacterial and viral diagnosis, process control, industrial wastewater control, toxic gas analysis in mines and enterprises, biomedical, field agriculture, vineyard-garden agriculture, veterinary, etc. Although 25 biosensors have been used commercially so far, biosensors have been prepared for many more different substances. Although this number is not clear, it is known as more than 180.[39] From these applications, biosensors have been used by utilizing silver nanoparticles in bacterial viral diagnosis.[38] Figure 5 shows the application areas of biosensors.[24,28,31,33]

SAFETY AND SECURITY

Researchers must be mindful that infecting animals can add a new dimension to the risks, whether intentionally or unintentionally. All necessary permissible regulations and measures, including infectious agents, must be followed both before and after the experiment during an investigation. The safety and security measures for infectious agent experimentation must be approved by government policies or an in-house formed authority.[32,34]

Take the necessary precautions and safety measures when working with biohazards, such as limiting access to the area to listed personnel only, decontaminating all surfaces and waste after each day of experimentation, not pipetting or spitting during an investigation, wearing personal protective equipment (including an eye mask and face shield), being familiar with the written instructions and documentation of the working area or experimentation, and adhering to the waste disposal procedures.[36]

CONCLUSIONS

(a) There appears to be very little worldwide drive/interest for the development of an implantable biosensor for the detection of infectious diseases. The reasons for this are the extremely difficult nature of the problem at hand and the significant resources/time required to develop a reliable device. The technical challenges facing an implantable device are too many to list here; however, the main obstacle is still the issue of biocompatibility
(b) Biosensors have played an important role in disease

monitoring. Although many challenges still lie between the laboratory and the market, there is some evidence that commercial immunosensors are just beginning to emerge in the marketplace

(c) Biosensors have been applied primarily in two major areas, medical/health and pharmaceutical monitoring. Consequently, there still is huge market potential for biosensors in areas such as food/agricultural and environmental monitoring

(d) It was revealed that relatively few studies have been undertaken using biosensors to directly measure an analyte (i.e., antigen) in a real complex biological sample such as blood. Most reports so far have shown that biosensors work reliably only in simple clean buffer solutions

(e) It has been shown that there is substantial interest in the development of biosensors for the detection of DNA. At this stage, there is no commercially available handheld DNA biosensor. However, a great deal of work has been directed toward developing DNA chips for addressing multiple analytes in molecular diagnostic assays.

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