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# Biosensors trends, technologies, opportunities and challenges

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*Abstract :* Biosensors are useful analytical tools for environmental monitoring, capable of providing results in real time, simple to use, portable and cost-effective. The use of health and well-being monitoring technologies has been steadily increasing and such systems can now be found in smart homes, age-friendly workplaces, public spaces, and elsewhere. These monitoring technologies employ a wide variety of off-the-shelf smart sensors and medical devices to support functional, physiological, and behavioral monitoring and to address social interaction aspects of daily life. Biosensors and nanoscale analytical tools have shown huge growth in literature in the past 20 years, with a large number of reports on the topic of 'ultrasensitive', 'cost-effective', and 'early detection' tools with a potential of 'mass-production'. Yet none of these tools are commercially available in the market or practically viable for mass production and use in pandemic diseases such as coronavirus disease 2019 (COVID-19).

***IndexTerms* - Environmental monitoring, key trends, funding trends, technologies, need, opportunities, obstacles, challenges.**

## I. INTRODUCTION

The growing number of pollutants requires the development of innovative analytical devices that are precise, sensitive, specific, rapid, and easy-to-use to meet the increasing demand for legislative actions on environmental pollution control and early warning.To meet the increasing demand for legislative actions on the monitoring of a growing number of pollutants novel analytical devices featuring precision, sensitivity, specificity, speed, and usability are being developed. In the last decades, the use of biosensors for monitoring environmental health has gained much attention. To study the extent of chemical pollution and its consequences, biosensors that integrate exposure to pollutants in their environment are the useful tools. To estimate detrimental effects of metal pollution, different organisms serve as biosensors. Some examples of biosensors in advanced stage of development have been applied to real samples, as well as for commercial devices. Biosensors designed for measurement of either specific chemicals or their biological effects, such as toxicity biosensors and endocrine effect biosensors. Biosensors show the potential to complement laboratory-based analytical methods for environmental applications. Although biosensors for potential environmental-monitoring applications have been reported for a wide range of environmental pollutants, from a regulatory perspective the decision to develop a biosensor method for an environmental application should consider several interrelated issues. In the last decades the use of biosensors for monitoring environmental health has gained much attention. There is an urgent need to study the negative effects of xenobiotics, specifically chemical agents. To study the extent of chemical pollution and its consequences, biosensors are the useful tools. Among the most toxic elements heavy metals are the chemical pollutants to nearly all living organisms.

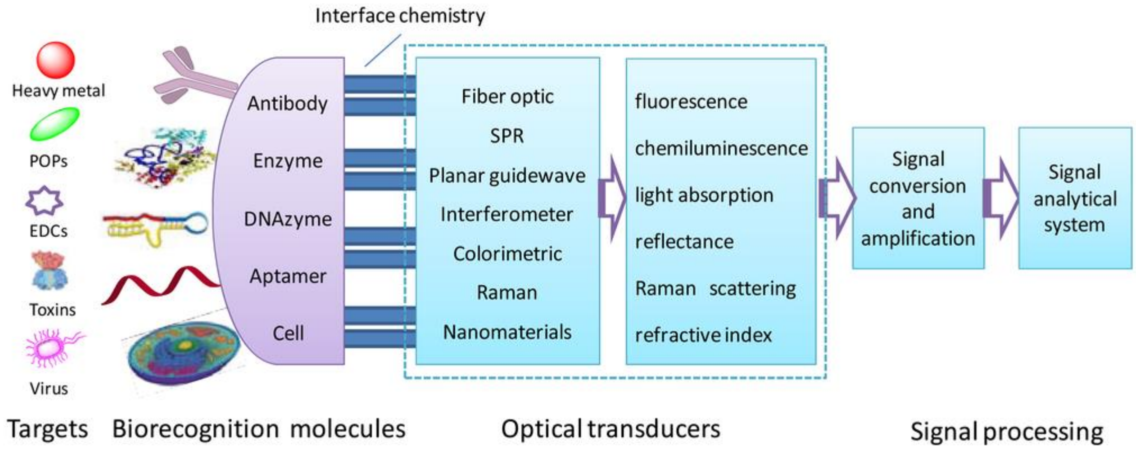
## ENVIRONMENTAL MONITORING

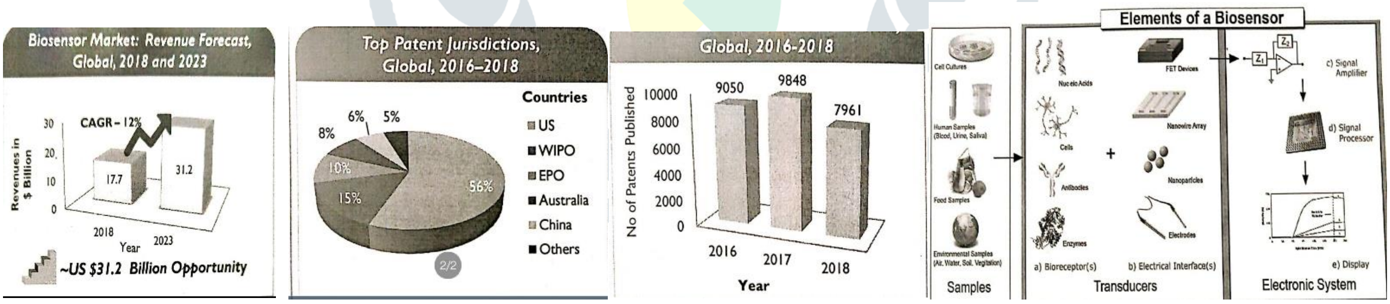
Environmental monitoring for the detection of pollutants is becoming increasingly important to regulatory agencies, the regulated community, and the general public. Many of the monitoring requirements of this environmental legislation might potentially be accomplished using biosensor applications. The Resource Conservation and Recovery Act (RCRA) primarily governs solid waste, hazardous waste, and underground storage tanks (such as those used for petroleum products). Given the number of these storage tanks now in use, this could be a sizable market. For example, it has been estimated that there are currently 295000 sites where leaking tanks have contaminated atleast 56 million cubic yards of soil (EPA, 1993a). There are at present, a number of commercially available chemical sensors, many of which have proven satisfactory for detecting petroleum product leaks. There are, however, applications which require lower levels of detection of specific constituents of petroleum products than is feasible using these chemical methods. For these cases, sensitive and specific immunochemical reagents have been developed primarily for use in test kits which could be employed. Biosensors developed as sentinels and placed at strategic locations could provide a cost effective means for screening large volumes of waste effluent for the presence of toxic compounds. This might be accomplished using immunochemically based biosensors for detection of specific compounds or using microbe-based devices to measure a wide variety of toxic compounds.

**Key Trends in Biosensors**

A biosensor incorporates a biological sensing element and picks up electrical signals generated by the interaction of a biological element and an analyte.

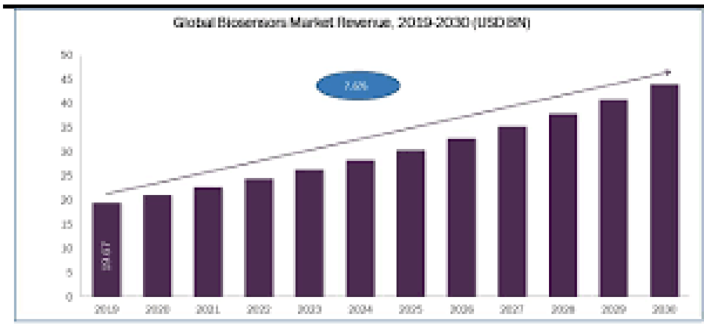
- ✓ Advances in manufacturing processes, and device integration are propelling developments in biosensors
- ✓ High Sensitivity and Selectivity: The ability to detect analytes at the molecular level boosts the adoption rate with continuous improvement in characteristics such as long-term stability, selectivity, and response time.
- ✓ According to Frost & Sullivan analysis, the global biosensor market is expected to grow at a 12%compound annual growth rate (CAGR) during 2018 -2023, from revenues of $17.7 billion in 2018,to reach $31.2 billion by the end of 2023.
- ✓ Key application segments include healthcare (e.g., point-of-care, home diagnostics), food, water quality, indoor/outdoor air monitoring, agriculture, security. Key opportunities await wearable biosensors to provide non-invasive monitoring of heart rate, breathing rate, glucose, disease diagnosis/detection.
- ✓ Opportunities will also more fully emerge for biometric sensors to monitor a driver's vital signs such as respiration, heart rate, temperature,skin conductance, to combat driver distraction or fatigue.
- ✓ Growth opportunities driven by miniaturization of sensors leading to ease of integration; increase in aging population; high demand for enhanced safety; and growth in real-time, and remote monitoring that reduces healthcare expenses.
- ✓ Development of implantable biosensor for long term usability is one of the key research and development (R&D) focus areas.
- ✓ Consumer electronics companies are increasingly involved in R&D activities, indicating the potential of integrating biosensors into products such as smartphones and wearables.
- ✓ According to the patent publication trends from 2016 to 2018, US leads the world with 56% of the total patents published in the region, followed by WIPO (15%), EPO (10%) and Australia (8%). This shows a strong focus on developing biosensor-based systems for varied applications in the United States and Asia-Pacific (APAC) region.

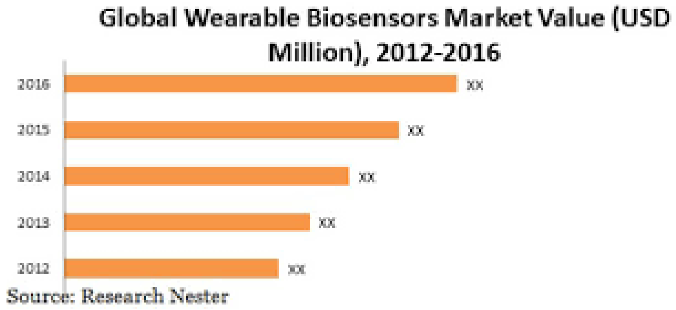



**Funding Trends**

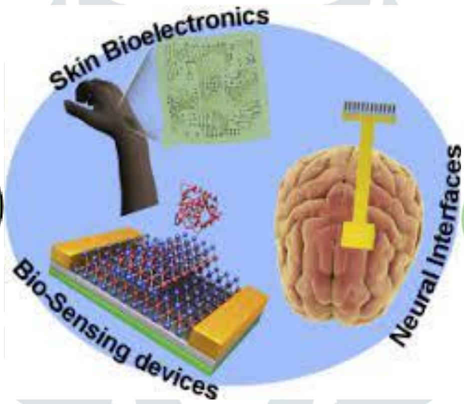
- ✓ Government agencies such as US National Institutes of Health (NIH) are bolstering biosensor research activities.
- ✓ For example, NIH funded research that used an antibody biosensor to discover that opioids used to treat pain, such as morphine or oxycodone, also bind to receptors inside neurons that are not a target for naturally occurring opioids. The medically used therapeutic opioids do not only act on the same surface receptors as the endogenous opioids produced naturally in the brain. The biosensor generates a fluorescent signal when a G protein coupled receptor (which opioids bind to) is activated. This knowledge could lead to designing pain relievers that do not produce addiction.

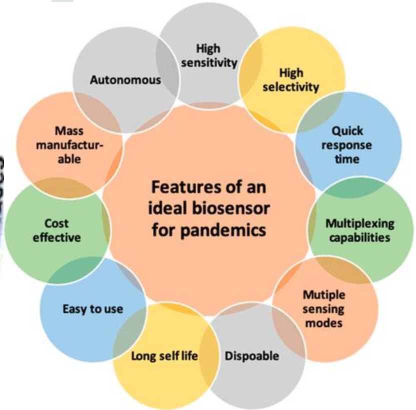



## Point of Care Diagnostics

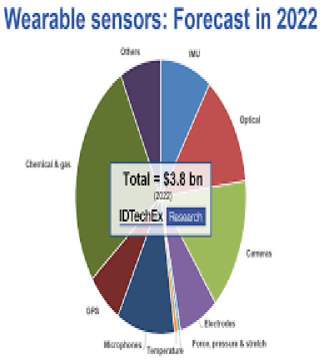
- ✓ A major growth area for biosensors is point-of-care (POC) testing and diagnostics to enable real-time, remote health monitoring. Biosensors provide more convenient, efficient, and sensitive detection of diseases or infections, such as diabetes, cardiovascular diseases, cancer, infectious disease. Microfabricated POC devices will be able to detect a range of pathogens. To be used as a complete diagnostic tool rather than just for initial screening of bioagents or pathogens, POC devices need to achieve sensitivity comparable to that of lab instruments. Paper-based biosensors, which further decrease the cost and increase the disposability of biosensors for POC will find expanding opportunities in underdeveloped or developing regions.
- ✓ Opportunities for biosensors will also be driven by the further proliferation of mobile phones for easier communication of health data.
- ✓ Historically, biomedical analysis has required collecting samples of, for example, blood, urine or genetic material and analyzing the sample at a laboratory away from the point-of-care. Biosensors possess the capabilities, such as high sensitivity, rapid detection, portability, and ability to provide non-invasive detection, to enable real-time diagnosis at the patient's location by non-professionally trained individuals.
- ✓ Drivers for biosensors for point-of-care diagnostics include the aging of the population, increasing need to decrease healthcare expenditures, the rise of cardiovascular diseases and cancer globally, and unhealthy lifestyles (e.g., lack of physical activity, obesity). Another driver is the rising demand for improved healthcare in emerging countries such as China and India

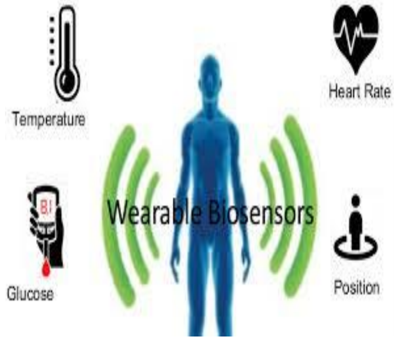



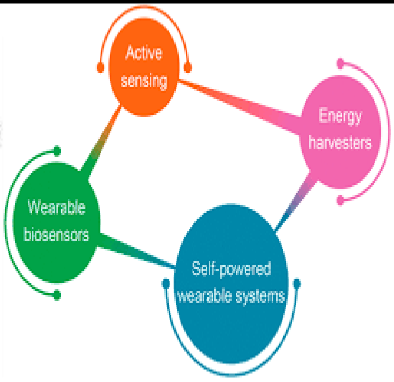




## Wearable Biosensors

- ✓ Wearable biosensors find increasing opportunities for continuous monitoring of vital signs of patients, premature infants, children, athletes or fitness buffs, and individuals in remote areas far from medical and health services.
- ✓ Wearable biosensors can alleviate the burden on the healthcare system by facilitating selfmonitoring to control one's health and prevent disease. Wearable, connected biosensors enable remote monitoring to allow patients to avoid hospitalization or leave earlier. By enabling telemedicine (monitoring and transmitting physiological data from outside the hospital), wearable biosensors can ease the burden on healthcare personnel and free up hospital space for more responsive care. Smart textiles with sensors in the fabric can provide a simple, more convenient system to monitor vital signs . Biosensor patches or tattoos, leverage conformal, printed electronics, can better enable physicians to collect data on a patient for long periods of time. Such sensors dovetail with the quantified self trend to track one's biological data to optimize one's health. Moreover, disposable patches can allow analyzing key biomarkers such as sodium, potassium, glucose, in sweat or other substances (e.g.,saliva).
- ✓ There is also potential for wearable biochemical sensors that monitor alcohol consumption through detection of ethyl glucuronide (EtG) in human sweat.
- ✓ Non invasive monitoring of glucose has been a holy grail in diabetes monitoring. Measuring blood glucose is challenging, as sugar is colorless and present in minute concentrations. Measurement of glucose is subject to noise, due to interferences from water, cells, circulating metabolites. Devices that measure glucose directly in blood or other fluids try to work around the interference using, for example, glucose oxidase to trigger a measurable reaction.
- ✓ A noninvasive technique that could replace finger pricks would significantly transform monitoring and care of diabetics. It has been elusive to produce a needle-free technique with sufficient precision for diabetes monitoring and care.
- ✓ Varied techniques have been, and continue to be investigated, such as infrared spectroscopy to measure glucose level through the skin, electrical current to draw sugar from interstitial fluid, monitoring glucose in sweat, smart contact lenses to measure glucose, electrochemical biosensors that use graphene and magnetic nanoparticles, etc.



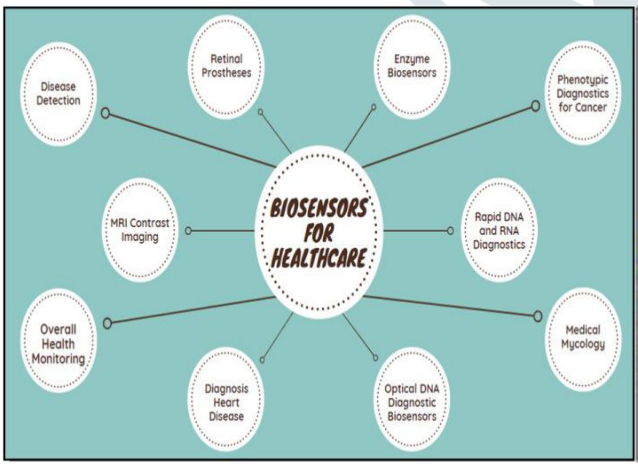



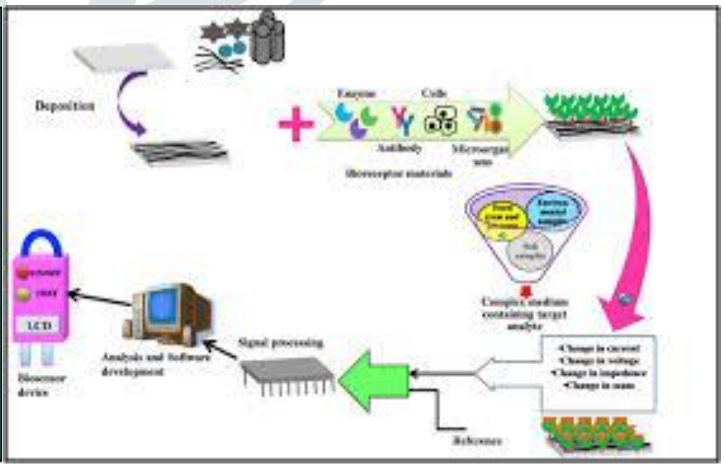




- ✓ Cygnus had a promising technology, the GlucoWatch Biographer, which uses electric current to draw glucose from interstitial fluid under the skin's surface into a sensor where the sugar was oxidized by an enzyme to produce hydrogen peroxide detected by a biosensor. The device was approved by the US FDA in 2002 and intended to complement rather than replace the finger prick method. Although the technology generated great fanfare, it had problems such as generating rashes in the skin from the irritating electric currents, a long (3 hour) warm up time, and too many false alarms for low glucose levels.
- ✓ Biometric sensors or biosensors are poised for use in vehicles to monitor driver vital signs, stress and emotion levels. Such sensors can be placed in seats, seatbelts or on the steering wheel. Biosensors for driver health monitoring have increasing opportunities as self-driving vehicles gain adoption. For example, non-contact ECG monitors in the driver's seat record signal through the driver's clothes. Capacitive plates register the electric charges between the plates and the driver's body, which vary with each heartbeat. There are also opportunities for glucose monitors in the vehicle (e.g., using the in-car communications system to track a driver's blood glucose), and for non-contact heart rate and respiration monitors.
- ✓ In addition, biosensors are finding opportunities in vehicles for applications such as alcohol detection.

**Biosensor Technologies Driving Growth Opportunities**

- ✓ Nanobisensors, composed of materials with one of their dimensions between 1 and 100 nanometers, can enable faster, more intelligent and precise, less costly and more user-friendly biological detection. Key types of nanomaterials used to improve biosensors include carbon nanotubes (CNTs), nanoparticles, quantum dots, nanowires, nanorods.
- ✓ Nanobiosensors have promise in a range of applications such as biomedical and diagnostics, environmental monitoring,(e.g., detection of nitrates, inorganic phosphates, biological oxygen demand, remediation), industrial (e.g., separation of impurities in metallurgical applications), food production, crop protection, pathogen and toxic detection, water/waste water treatment. Nanobiosensors improve the specificity, sensitivity, and detection limit of chemical analysis of food and beverages.
- ✓ Minimizing the biosensor's dimensions to the nanoscale addresses the functional requirements of point-of-care and wearable applications; and improves the biosensor's signal-to-noise ratio.
- ✓ However, minimization can lengthen the biosensor's response time (it takes longer to collect target analytes on the sensor's surface). Researchers fabricated a bioinspired nanobiosensor, comprised of CNTs, that uses electronic-based taste receptors for diagnosing glucose (glucose oxidase). The electrochemical (amperometric) biosensor with taste bud-inspired circuits provided an increase in the frequency of the output pulse based on glucose concentration.




- ✓ Opportunities also exist for Giant Magneto Resistance (GMR) biosensors that provide faster, streamlined detection of diseases or drugs. Laboratory testing health diagnostics techniques tend to be complicated, to require sophisticated and expensive equipment, trained operators and have a slow turn around time. Such techniques are not suitable for point-of-care use or applications in remote areas or non-clinical areas such as homes, offices, or schools. MagArray (Milpitas, CA), formed in 2005, licensed GMR nanobiosensor is targeting providing lab services to physicians, focusing on lung detection. The company's REVEAL lung characterization blood test non-invasively measures unique biomarkers associated with lung caner. The test indicates the risk of nodule malignancy in patients with pulmonary nodules in the range of 6 mm-3 cm). REVEAL helps pulmonologists identify lung nodules with a high probability of being benign or malignant. Currently, lung nodules are detected using a CT scan, which may not enable the physician to distinguish benign from malignant nodules. Patients tend to be diagnosed at an advanced stage of lung cancer which is the leading cause of death.

- ✓ Researchers have fabricated a highly sensitive and label-free disposable fiber optic surface plasmon resonance (SPR) biosensor for specific detection of C-reactive protein. Dopamine is used a cross-linking agent to immobilize the antiCRP monoclonal antibody, which is an efficient and simple method for specific modification of the fiber optic SPR sensor. The researchers noted that CRP is considered one of the most important inflammation markers in the human body. Methods developed for CRP detection, such as enzyme linked immunosorbent assay (ELISA), immunofluorescence assay and latex agglutination, have the limitations of being time-consuming, semi-quantitative, and lack of miniaturization, and the requirement of on-site analysis. 13 D7C2-TV
- ✓ Graphene, which consists of 2D hexogonally arranged carbon atoms, enables very sensitive biosensors, due to its physical and chemical properties. Graphene is extremely strong and light, offers good electrical conductivity, excellent thermal conductivity, good optical transparency. It is also conducive for fast, multiparameter sensors. However, there are challenges in integrating delicate graphene into standard high-volume production processes. The steps in producing a graphene biosensor include electrode pattering, graphene growth, patterning and deposition, and wafer passivation with a dielectric.The process should be free of contamination. Rogue Valley Microdevices (RVM, Medford, OR), a MEMS foundry, designed the process to manufacture the graphene biosensors. To enable production of the graphene biosensors, RVM optimized the resist to minimize graphene contamination, optimized oxide adhesion to the graphene, and guarded against over- or under-etching.
- ✓ Microelectromechanical systems (MEMS) technology allows miniaturization of biosensors, which enables previously inaccessible signals to be obtained from inside the patient. MEMS biosensors (BioMEMS) enable a very small footprint, which minimizes power consumption and difficulties of implantation along with the transport time for chemical analytes. MEMS fabrication reduces the biosensor's response time and enables mass production and ease of scale-up without sacrificing the high reproducibility and reliability of MEMS fabrication.MEMS technology is conductive to incorporating organic materials. MEMS biosensors that use flexible materials (such as flexible microcantilevers and flexible organic substrates, can detect very small elements such as chemical molecules, bacteria, or mycotoxin in low concentrations

## Need for Biosensor Research and Development

In applications such as point-of-care and wearables, there are opportunities to ensure that minimizing the biosensor's dimensions to the nanoscale does not unduly lengthen the biosensor's response time. In POC testing, a need exists for POC assays for rapid determination of biomarkers to detect a stroke.

In wearables, there is a need for biosensors to more conveniently, non-invasively, selectively measure multi-parameters, such as lactose, glucose, sodium, potassium, in sweat in a wearable configuration (such as a headband). There also needs for the next generation of wearable biosensors that, rather than monitoring wellness and fitness, can provide long-term, continuous monitoring of chronic diseases, such as COPD, diabetes, or peripheral artery disease.
Needs exist for biosensors with improved sensitivity and selectivity that can provide faster, less expensive food testing (for example, E. coli).
In environmental monitoring, there are requirements for more sensitive, selective, less expensive and rapid portable biosensing devices to monitor pollutants in the field such as pesticides. Nanomaterials and nanocomposites have promise to enable improved sensitivity and detection limit.
In passive in-vehicle driver breath alcohol detection, based on infrared spectroscopy detection of $CO_2$ and alcohol, improvements in sensor resolution and system ruggedness are required.Touch-based in-vehicle sensors that would use infrared spectroscopy (IR light) to measure blood alcohol content in the capillaries under the skin need improvements in size, durability, and cost.
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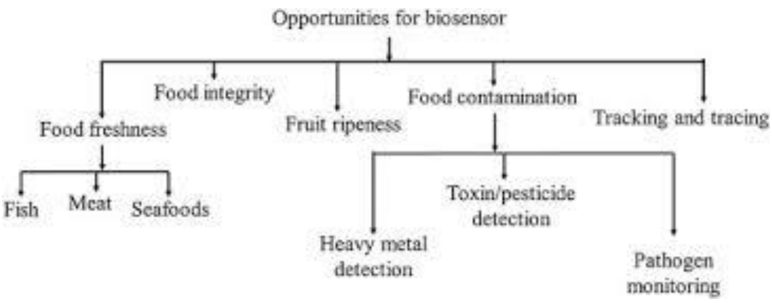
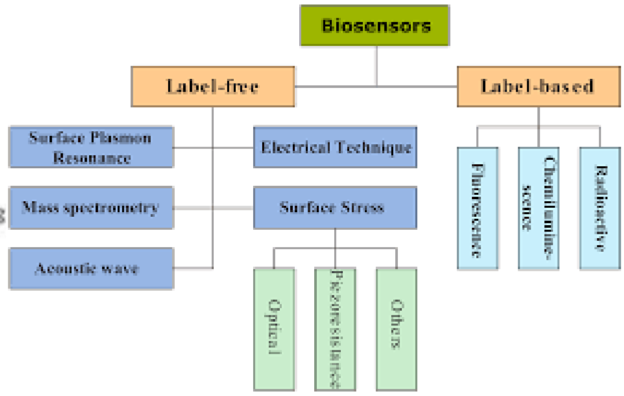
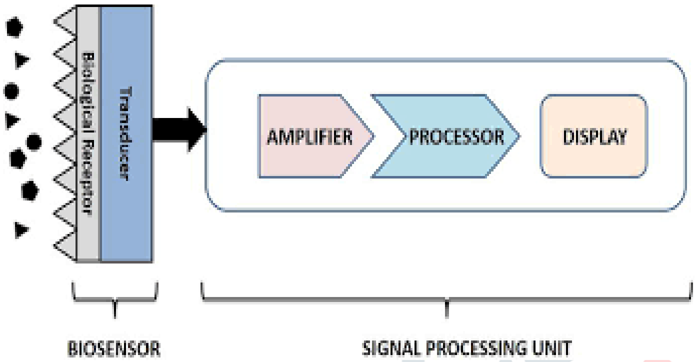
## OPPORTUNITIES FOR BIOSENSORS

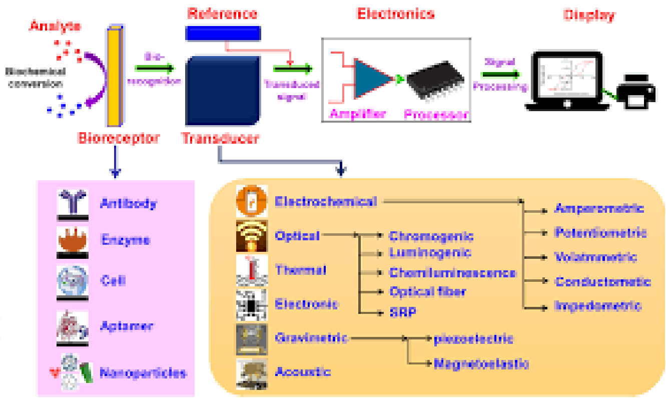
Driven by the need for faster and more costeffective methods for environmental monitoring, a variety of environmental field analytical methods are commercially available or currently being developed .These methods can be classified as miniaturized laboratory methods, field test kits, or chemical (bio)sensors. Although the chemical (bio)sensors have not been extensively developed, they show unique potential for continuous and remote field monitoring applications. Because, in many cases, the physical signal transducers for chemical sensors are similar to those for biosensors, the characteristics of biosensors relative to these technologies depend primarily on the properties of the biological recognition element as compared with the chemically selective coating used in chemical sensors. For example, a specific polymer coating may adsorb a number of different organics from aqueous solution, whereas an immunochemical coating will bind to a specific compound or closely related group of compounds. Further, although chemical sensors are relatively rugged as compared with biosensors, their limited selectivity can be a problem for a number of applications. By contrast, biosensors can be highly sensitive and selective, and biological macromolecules are not particularly rugged, especially for use in environmental settings. Because biological recognition elements show a wide range of affinities for a variety of analytes, these bioselective coatings may complement the range of applications currently available to chemical sensors.

Many biosensors reported for environmental applications show the potential to be developed for either single-sample formats for field screening applications or continous formats for field monitoring applications.




A discussion concerning the cleanup of a Superfund site may provide examples of the scope and kinds of environmental screening and monitoring problems for which biosensors could provide unique solutions. After preliminary screening and ranking, the cleanup of a hazardous waste site typically proceeds through three major steps: characterization, remediation, and postclosure. Different analytical tasks are required during each of these steps 535biosensor methods. Many biosensors reported for environmental applications show the potential to be developed for either single-sample formats for field screening applications or continous formats for field monitoring applications Biosensor research over the last decade has focused primarily on clinical applications. Only recently, driven by the need for better methods for environmental surveillance, have reports of biosensors for these applications become more prevalent in the literature. Biosensors reported for environmental applications measure a fairly broad range of compound classes. These biosensors use a variety of biological recognition elements, including enzymes, immunochemicals, and microbes, which are interfaced to electrochemical, optical, and acoustic-wave transducers. Nevertheless, in spite of the impressive array of devices reported by investigators from academia, government, and industry, biosensors have yet to be commercialized for the environmental market. There are a variety of possible reasons.
These fall into two broad areas:
(1) technical issues associated with measurement of pollutants in environmental samples, (2) practical issues associated with development and marketing within the highly regulated and diverse environmental monitoring area.

**Technical obstacles**

One of the technical obstacles to the commercialization of biosensors for environmental applications is the broad number and class range of environmental pollutants. Environmental contaminants range over a variety of chemical classes. Many of these compounds are considered to be hazardous substances due to their potential deleterious effects on human health or ecosystems. The Agency for Toxic Substances and Disease Registry has compiled a list of 275 priority hazardous substances based on their potential for human exposure and associated potential health risks. For example, over 600 chemical compounds have been identified at hazardous waste sites alone, and there are as yet thousands of unidentified pollutants (ATSDR, 1992). This diversity of environmental pollutants has a direct consequence on the monitoring tasks and challenges associated with the market for field analytical methods. Because the market associated with detection of any single environmental pollutant is small, the most competitive biosensor systems will be designed to either interchange a variety of biological recognition elements to measure a suite of related compounds, or be generic enough to detect the presence of a variety of compounds.

**Practical challenges**

In addition to the previously discussed technical obstacles involving the wide variety of pollutants, co-contaminants, and matrices, there exist a number of practical challenges as well. These practical obstacles include:

i. the requirement for a substantial operational or cost-benefit over other existing or merging field analytical methods; • the lack of well-established expectations (i.e. Data Quality Objectives (DQOs)) by the potential market for field analytical methods;
ii. the presence of a sufficient market (for any particular application or group of related applications) to offset the expense of moving a laboratory prototype to the market;
iii. the field testing, evaluation, and validation required by regulatory agencies for methods approval for specific applications in specific media;
iv. the time required to move a new method (and associated technology) through the regulatory approval process. In order for emerging technologies

**CONCLUSIONS**

There currently exists a clear and increasing need for environmental field analytical methods which are fast, portable, and cost-effective. Biosensors, because of their versatility, may find a number of specific niche applications among the variety of other methods and technologies currently competing for this expanding market. In fact, a variety of enzymes, antibodies, and microbial-based biosensors using optical, electrochemical, and acoustic-signal transducers have been reported to measure a significant number of environmental pollutants from a variety of compound classes. Nevertheless, there are a considerable number of technical challenges and practical obstacles which must be met before any of these field analytical methods find widespread acceptance and use. During the development of biosensors for environmental monitoring applications, it is important that there exists a free flow of creative ideas concerning the use of diverse biological recognition elements, alternative operating formats, and innovative signal transducers.Although developing biosensors for environmental applications is not a trivial task, there appears to be sufficient evidence that biosensors can be configured to be selective, sensitive, and inexpensive to manufacture. It is further likely that with appropriate development, testing and commercialization,biosensors can have a significant impact on reducing costs and increasing the efficiency of certain environmental monitoring applications

Biosensors are equally effective for analysis of chemical components from vegetarian and non vegetarian foods. Selection and use of bioreceptor (eg:enzyme)is of key importance of identification of particular compounds. Biosensors are equally effective in estimation of food constituents as electronic gazettes in practice. It is faster, reliable and cheaper tool for determination of food constituents. Electrochemical biosensor has existed for nearly fifty years and seems to possess great potential for the future. This technology gains practical usefulness from the from the combination of selective biochemical recognition with the high sensitivity of electrochemical detection. Thanks to current technological progress, such biosensors profit from miniaturized electrochemical instrumentation and are the very advantages for some sophisticated application requiring portability, rapid measurement and use with a small volume of samples. Numerous commercial applications confirm the attractive advantages of electrochemical biosensor. The research is going on to increase the sensitivity of the biosensor for the effective application.

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