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"Biosensors"

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ABSTRACT:-The development of biosensors has been the center of scientist's attention for recent decades. Biosensors can essentially serve as low-cost and highly efficient devices for this purpose in addition to being used in other day to day applications. Biosensor is a device that consists of two main parts:
A bioreceptor and a transducer.Bioreceptor is a biological component that recognizes the target analyte and transducer is a physicochemical detector component that converts the recognition event into a measurable signal. Biomolecules such as enzymes, antibodies, receptors, organelles and microorganisms as well as animal and plant cells or tissues have been used as biological sensing elements. In this paper, we review recent development in use of biosensors as a diagnostic tool, as well as some future applications of biosensor technology.Biosensors are nowadays ubiquitous in biomedical diagnosis as well as a wide range of other areas such as point-of-caremonitoring of treatment and disease progression, environmental monitoring, food control, drug discovery, forensics andbiomedical research.
A wide range of techniques can be used for the development of biosensors. Their coupling with highaffinity biomolecules allows the sensitive and selective detection of a range of analytes. We give a general introduction to biosensors and biosensing technologies, including a brief historical overview, introducing key developments in the field andillustrating the breadth of biomolecular sensing strategies and the expansion of nanotechnological approaches that are now available.

I. INTRODUCTION:-

A biosensor is a device that measures biological or chemical reactions by generating signals proportional to the concentration of an analyte in the reaction. Biosensors are employed in applications such as disease monitoring, drug discovery, anddetection of pollutants, disease-causing micro-organisms and markers that are indicators of a disease in bodily fluids (blood,urine, saliva, sweat).

HISTORY :-

The history of biosensors started in the year 1962 with the development of enzyme electrodes by the scientist Leland C. Clark. Since then, research communities from various fields such as VLSI, Physics, Chemistry, and Material Science have come together to develop more sophisticated, reliable and mature biosensing devices for applications in the fields of medicine, agriculture, biotechnology, as well as the military and bioterrorism detection and prevention. Biosensor is a device that consists of two main parts:

A bioreceptor and a transducer.Bioreceptor is a biological component (tissue, microorganisms, organelles, cell receptors, enzymes, antibodies, nucleic acids, etc) that recognizes the target analyte. Other part is transducer, a physicochemical detector component that converts the recognition event into a measurable signal. The function of a biosensor depends on the biochemical specificity of the biologically active material. The choice of the biological material will depend on a number of factors via the specificity, storage, operational and environmental stability. Biosensors can have a variety of biomedical, industry, and military applications. The major application so far is in blood glucose sensing because of its abundant market potential .

Biomolecules such as enzymes,

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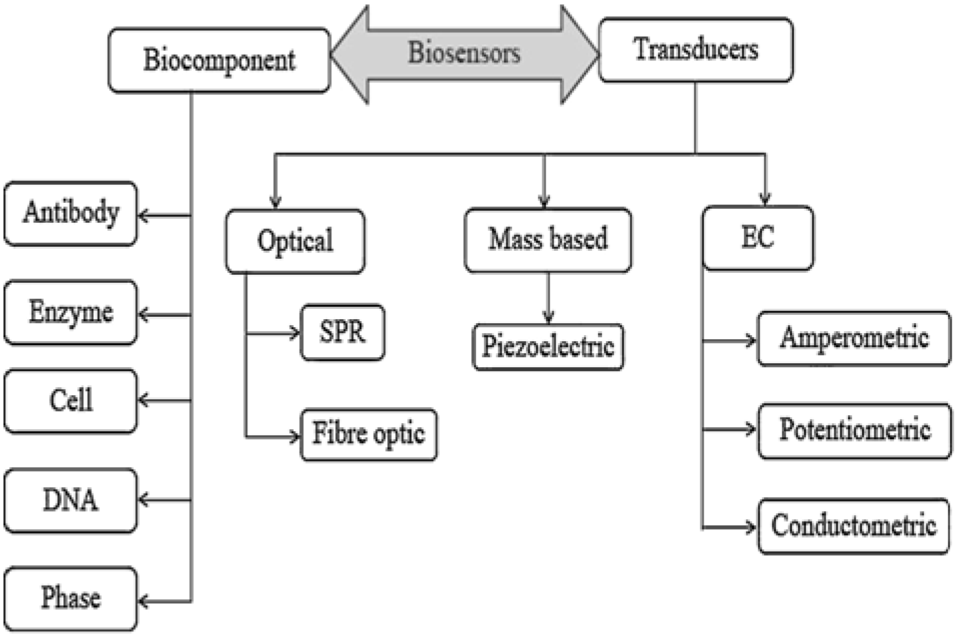
antibodies, receptors, organelles and microorganisms as well as animal and plant cells or tissues have been used as biological sensing elements . Microorganisms have been integrated with a variety of transducers such as amperometric, potentiometric, calorimetric, conductimetric, colorimetric, luminescence and fluorescence to construct biosensor devices. In this paper, we review recent development in use of biosensors as a diagnostic tool, as well as some future applications of biosensor technology.

- **Chemical Sensors:**

"A chemical sensor is a device that transforms chemcial information, ranging from the concentration of a specific sample component to total composition analysis, into an analytically useful signal"

- **Biosensors:**

Biosnesorsare analytical tools for the analysis of bio-material samples togain an understanding of their bio composition, structure and function byconverting a biological response into an electrical signal. The analytical devices composed of a biological recognition element directly interfaced to a signal transducer which together relate the concentration of an analyte (or group of related analytes) to a measurable response.



PARTS OF BIOSENSORS

- **Analyte**: A substance of interest that needs detection. For instance, glucose is an 'analyte' in a biosensor designed todetect glucose.
- **Bioreceptor**: A molecule that specifically recognises the analyte is known as a bioreceptor. Enzymes, cells, aptamers,deoxyribonucleic acid (DNA) and antibodies are some examples of bioreceptors. The process of signal generation (inthe form of light, heat, pH, charge or mass change, etc.) upon interaction of the bioreceptor with the analyte is termedbio-recognition.
- **Transducer**: The transducer is an element that converts one form of energy into another. In a biosensor the role of thetransducer is to convert the bio-recognition event into a measurable signal. This process of energy conversion isknown as signalisation. Most transducers produce either optical or electrical signals that are usually proportional tothe amount of analyte–bioreceptor interactions.
- **Electronics**: This is the part of a biosensor that processes the transduced signal and prepares it for display. It consists ofcomplex electronic circuitry that performs signal conditioning such as amplification and conversion of signals fromanalogue into the digital form. The processed signals are then quantified by the display unit of the biosensor.
- **Display**: The display consists of a user interpretation system such as the liquid crystal display of a computer or a direct
- printer that generates numbers or curves

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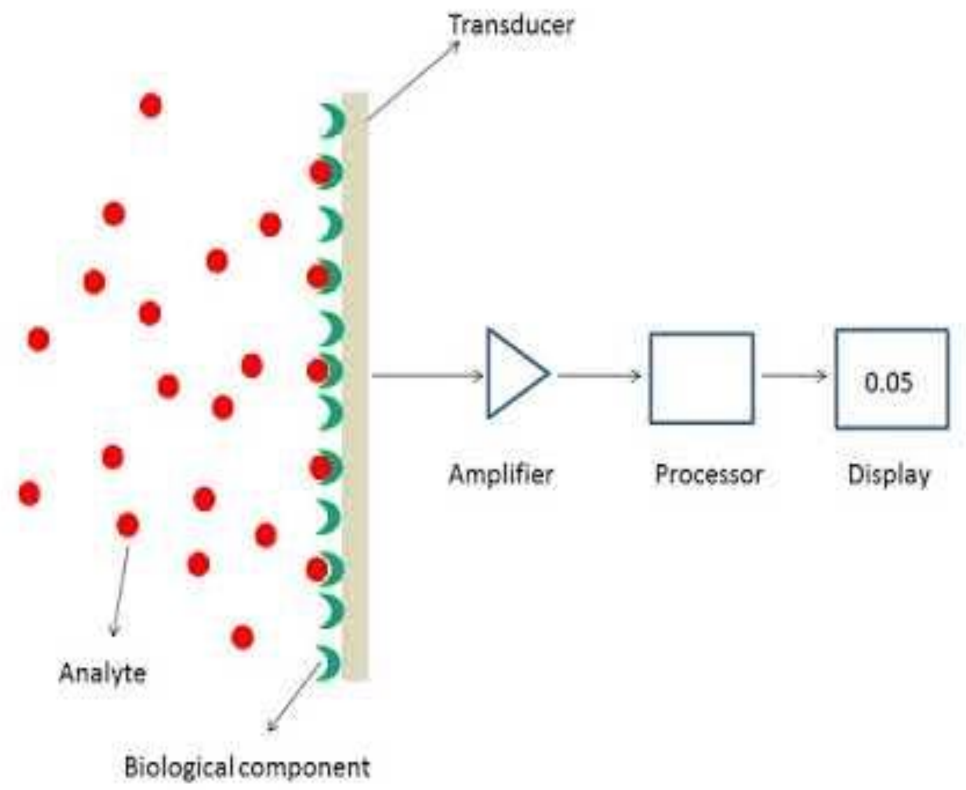
understandable by the user. This part often consists of a combination ofhardware and software that generates results of the biosensor in a user-friendly manner. The output signal on thedisplay can be numeric, graphic, tabular or an image, depending on the requirements of the end user.



Diagrammatic representation of a Biosensor

Characteristics of a biosensor

There are certain static and dynamic attributes that every biosensor possesses. The optimisation of these properties is reflected on the performance of the biosensor.

- **Selectivity**

Selectivity is perhaps the most important feature of a biosensor. Selectivity is the ability of a bioreceptor to detect a specific analyte in a sample containing other admixtures and contaminants. The best example of selectivity is depicted by the interaction of an antigen with the antibody. Classically, antibodies act as bioreceptors and are immobilised on the surface of the transducer. A solution (usually a buffer containing salts) containing the antigen is then exposed to the transducer where antibodies interact only with the antigens. To construct a biosensor, selectivity is the main consideration when choosing bioreceptors.

- Reproducibility

Reproducibility is the ability of the biosensor to generate identical responses for a duplicated experimental set-up. The reproducibility is characterised by the precision and accuracy of the transducer and electronics in a biosensor. Precision is the ability of the sensor to provide alike results every time a sample is measured and accuracy indicates the sensor's capacity to provide a mean value close to the true value when a sample is measured more than once. Reproducible signals provide high reliability and robustness to the inference made on the response of a biosensor.

- Stability

Stability is the degree of susceptibility to ambient disturbances in and around the biosensing system. These disturbances can cause a drift in the

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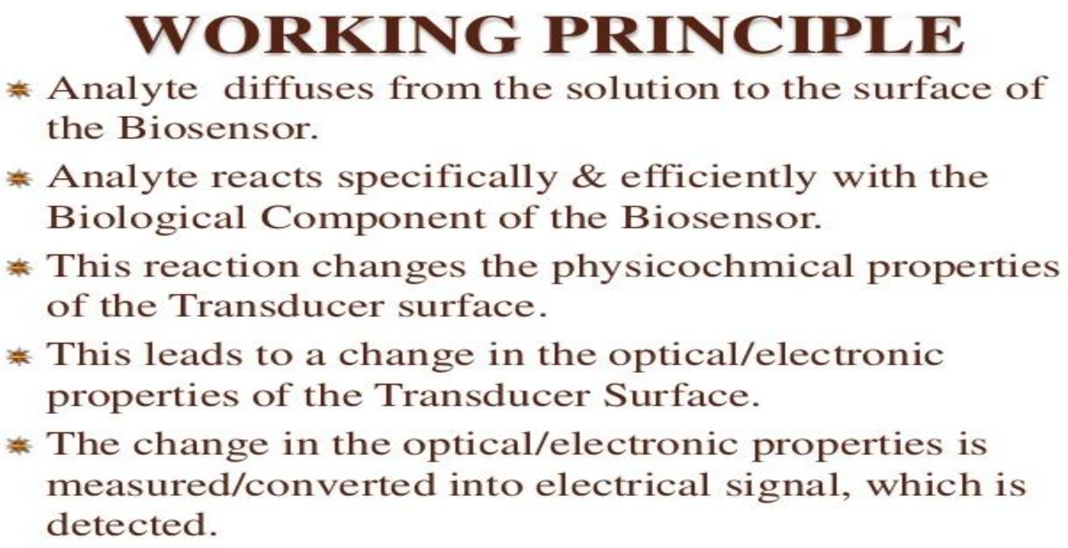
output signals of a biosensor under measurement. This can cause an error in the meas-ured concentration and can affect the precision and accuracy of the biosensor. Stability is the most crucial feature in applications where a biosensor requires long incubation steps or continuous monitoring. The response of transducers and electronics can be temperature-sensitive, which may influence the stability of a biosensor. Therefore, appropriate tuning of electronics is required to ensure a stable response of the sensor. Another factor that can influence the stability is the affinity of the bioreceptor, which is the degree to which the analyte binds to the bioreceptor. Bioreceptors with high affinities encourage either strong electrostatic bonding or covalent linkage of the analyte that fortifies the stability of a biosensor. Another factor that affects the stability of a measurement is the degradation of the bioreceptor over a period of time.

- Sensitivity

The minimum amount of analyte that can be detected by a biosensor defines its limit of detection (LOD) or sensitivity. In a number of medical and environmental monitoring applications, a biosensor is required to detect analyte concentration of as low as ng/ml or even fg/ml to confirm the presence of traces of analytes in a sample. For instance, a prostate-specific antigen (PSA) concentration of 4 ng/ml in blood is associated with prostate cancer for which doctors suggest biopsy tests. Hence, sensitivity is considered to be an important property of a biosensor.

- Linearity

Linearity is the attribute that shows the accuracy of the measured response (for a set of measurements with different concentrations of analyte) to a straight line, mathematically represented as y=mc, where c is the concentration of the analyte, yis the output signal, and m is the sensitivity of the biosensor. Linearity of the biosensor can be associated with the resolution of the biosensor and range of analyte concentrations under test. The resolution of the biosensor is defined as the smallest change in the concentration of an analyte that is required to bring a change in the response of the biosensor. Depending on the application, a good resolution is required as most biosensor applications require not only analyte detection but also measurement of concentrations of analyte over a wide working range. Another term associated with linearity is linear range, which is defined as the range of analyte concentrations for which the biosensor response changes linearly with the concentration.



Types of Biosensors

- **Resonant Biosensor**

In this type of biosensor, an acoustic wave transducer is coupled with an antibody (bio-element). When the analyte molecule (or antigen) gets attached to the membrane, the mass of the

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membrane changes. The resulting change in the mass subsequently changes the resonant frequency of the transducer. This frequency change is then measured .

- **Optical biosensors**

The output transduced signal that is measured is light for this type of biosensor. The biosensor can be made based on optical diffraction or electrochemiluminescence. Optical transducers are particularly attractive for application to direct (label-free) detection of bacteria. These sensors are able to detect minute changes in the refractive index or thickness which occur when cells bind to receptors immobilized on the transducer surface. They correlate changes in concentration, mass or number of molecules to direct changes in characteristics of light. Several optical techniques have been reported for detection of bacterial pathogens including: monomode dielectric waveguides, surface plasmon resonance (SPR), ellipsometry, the resonant mirror and the interferometer .

- **Surface plasmon resonance (SPR) biosensor**

This is an evanescent field based optical sensors using thin gold film for sensing applications. The interaction between analyte flowing over immobilized interactant on gold surface is probed through the detection of reflection minima on photo-detector array sensors. SPR has successfully been applied to the detection of pathogen bacteria by means of immunoreactions .

- **Piezoelectric biosensors**

Piezoelectric (PZ) biosensor offers a real-time output, simplicity of use and cost effectiveness. The general idea is based on coating the surface of the PZ sensor with a selectively binding substance, for example, antibodies to bacteria, and then placing it in a solution containing bacteria. The bacteria will bind to the antibodies and the mass of the crystal will increase while the resonance frequency of oscillation will decrease proportionally .

- **Thermal Biosensors**

This type of biosensor is exploiting one of the fundamental properties of biological reactions, namely absorption or production of heat, which in turn changes the temperature of the medium in which the reaction takes place. They are constructed by combining immobilized enzyme molecules with temperature sensors. When the analyte comes in contact with the enzyme, the heat reaction of the enzyme is measured and is calibrated against the analyte concentration. Common applications of this type of biosensor include the detection of pesticides and pathogenic bacteria .

- **Electrochemical Biosensors**

Electrochemical biosensors are mainly used for the detection of hybridized DNA, DNA-binding drugs, glucose concentration, etc. Electrochemical biosensors can be classified based on the measuring electrical parameters as: (i) conductimetric, (ii) amperometric and (iii) potentiometric. Compared to optical methods, electrochemistry allows the analyst to work with turbid samples, and the capital cost of equipment is much lower. On the other hand, electrochemical methods present slightly more limited selectivity and sensitivity than their optical counterparts .

- **Conductimetric Biosensors**

The measured parameter is the electrical conductance/resistance of the solution. When electrochemical reactions produce ions or electrons, the overall conductivity or resistivity of the solution changes. This change is measured and calibrated to a proper scale. Conductance measurements have relatively low sensitivity .

- **Amperometric Biosensors**

This is perhaps the most common electrochemical detection method used in biosensors. This high sensitivity biosensor can detect electroactive species present in biological test samples. substance to be detected. The most common amperometric biosensors use the Clark Oxygen electrode .

- **Potentiometric Biosensors**

These are the least common of all biosensors, but different strategies may be found nonetheless in this type of sensor the measured parameter is oxidation or reduction potential of an electrochemical reaction. The working principle relies on the fact that when a voltage is applied to an electrode in solution, a current flow occurs because of electrochemical reactions. The voltage at which these reactions occur indicates a particular reaction and particular species .

- **Bioluminescence sensors**

Recent advances in bioanalytical sensors have led to the utilization of the ability of certain enzymes to emit photons as a byproduct of their reactions. This phenomenon is known as bioluminescence. The potential applications of bioluminescence for bacterial detection were initiated by the development of luciferase reporter phages. The bacterial luminescence lux gene has been widely applied as a reporter either in an inducible or constitutive manner. In the inducible manner, the reporter lux gene is fused to a promoter regulated by the concentration of a compound of interest. As a result, the concentration of the compound can be quantitatively analyzed by detecting the bioluminescence intensity. Bioluminescence systems have been used for detection of a wide range of microorganisms [2 and 11].

- **Nucleic Acid-based Biosensors**

A nucleic acid biosensor is an analytical device that integrates an oligonucleotide with a signal transducer. The nucleic acid probe is immobilized on the transducer and acts as the bio-recognition molecule to detect DNA/RNA fragments .

- **Nanobiosensors**

Nanosensors can be defined as sensors based on nanotechnology. Development of nanobiosensor is one of the most recent advancement in the field of Nanotechnology. The silver and certain other noble metal nanoparticles have many important applications in the field of biolabelling, drug delivery system, filters and also antimicrobial drugs, sensors .

- **Microbial Biosensors**

Microbes have a number of advantages as biological sensing materials in the fabrication of biosensors. They are present ubiquitously and are able to metabolize a wide range of chemical compounds. Microorganisms have a great capacity to adapt to adverse conditions and to develop the ability to degrade new molecules with time. Microbes are also amenable for genetic modifications through mutation or through recombinant DNA technology and serve as an economical source of intracellular enzymesas high analytical specificity. Over 90% of the enzymes known to date are intracellular. In this respect, the utilization of whole cells as a source of intracellular enzymes has been shown to be a better alternative to purified enzymes in various industrial processes. Whole cells have been used either in a viable or non-viable form. Viable cells are gaining considerable importance in the fabrication of biosensors. Viable microbes metabolize various organic compounds either anaerobically or aerobically resulting in various end products like ammonia, carbon dioxide, acids etc that can be monitored using a variety of transducers. Viable cells are mainly used when the overall substrate assimilation capacity of microorganisms is taken as an index of respiratory metabolic activity, as in the case of estimation of biological oxygen demand (BOD) or utilization of other growth or metabolically related nutrients like vitamins, sugars, organic acids and nitrogenous compounds. Another mechanism used for the viable microbial biosensor involves the inhibition of microbial respiration by the analyte of interest, like environmental pollutants.

- **Biosensors and cancer**

Cancer diagnosis and treatment are of great interest due to the widespread occurrence of the diseases, high death rate, and recurrence after treatment. According to the National Vital Statistics Reports, from 2002 to 2006 the rate of incidence (per 100,000 persons) of cancer in White people was 470.6, in Black people 493.6, in Asians 311.1, indicating that cancer is wide- spread among all races. Cancer can take over 200 distinct forms, including lung, prostate, breast, ovarian, hematologic, skin, and colon cancer, and leukemia, and both environmental factors, and genetic factors are associated with an increased risk of developing cancer.Bacterial and viral infections are also strongly associated with some types of cancer . In medicine, biosensors can be used to monitor blood glucose levels in diabetics, detect pathogens, and diagnose and monitor cancer .The use of emerging biosensor technology could be instrumental in early cancer detection and more effective treatments, particularly for those cancers that are typically diagnosed at late stages and respond poorly to treatment, resulting in improvements in patient quality of life and overall chance of survival . By measuring levels of certain proteins expressed and/or secreted by tumor cells, biosensors can detect whether a tumor is present, whether it is benign or cancerous, and whether treatment has been effective in reducing or eliminating cancerous cells.

- **Biosensors and Pathogen detection**

Bacteria, viruses and other microorganisms are found widely in nature and environment. Microbial diseases constitute the major cause of deaths in developing countries .Pathogen detection is of the utmost importance primarily for health and safety reasons. Polymerase chain reaction (PCR), culture and colony counting methods as well as immunology-based methods are the most common tools used for pathogen detection. They involve DNA analysis, counting of

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bacteria and antigen–antibody interactions, respectively. In spite of disadvantages such as the time required for the analysis or the complexity of their use, they still represent a field where progress is possible. Biosensors have recently been defined as analytical devices incorporating a biological material intimately associated with or integrated within a physicochemical transducer or transducing microsystem, which may be optical, electrochemical, thermometric, piezoelectric, magnetic or micromechanical These are enzymes, antibodies and, nucleic acids. In the detection of pathogenic bacteria, however, enzymes tend to function as labels rather than actual bacterial recognition elements. Enzymes can be used to label either antibodies or DNA probes much in the same fashion as in an ELISA assay. In the case of amperometric biosensors enzymatic labels are critical.

Working of Biosensors

The combination of biological sensitive element and a transducer will convert the biological material into a corresponding electrical signal. Depending on the type of enzyme, the output of the transducer will be either current or voltage.If the output is voltage, then well and good. But if the output is current, then this current should be converted into equivalent voltage (using an Op-Amp based current to voltage converter) before proceeding further.

The output voltage signal is usually very low in amplitude and superimposed on a high frequency noise signal. So, the signal is amplified (using an Op-Amp based Amplifier) and then passed through a Low Pass RC Filter.

This process of amplifying and filtering the signal is the job of a Signal Processing Unit or a Signal Conditioning Unit. The output of the signal processing unit is an analog signal that is equivalent to the biological quantity being measured.

The analog signal can be displayed directly on an LCD display but usually, this analog signal is passed to a Microcontroller, where the analog signal is converted into digital signal, since it is easy to analyze, process or store a digital signal.

Advantages of biosensor

- Specific in response to analyte
- Rapid response
- Simple to operate
- Require no pretreatment of sample
- Ease of miniaturization
- Economical
- Amenability for continuous operation
- Can be easily interfaced withmicroprocessor

Applications of Biosensors

- **Biosensors for Clinical Diagnostics**

The diagnosis and monitoring of various diseases require intensiveroutine examination of blood samples and other associated tests.Appropriate times, trained manpower and sophisticated analyticaltechniques are required for undertaking clinical trials. Several ofthe detected analytes are specific for a given disease, and can behelpful to monitor its progress .Further, the importance ofthese clinical tests is determined by their sensitivity, specificityand response time. In this context, biosensors may be a boon formonitoring clinically important parameters such as blood glucose,urea, lactate, cholesterol and uric acid. These biosensors offer anadvantage to additional laboratory analyses of relevant substances for clinical analyses .In the next section, we discuss some recentexamples of biosensors being used for the detection of severalclinically relevant metabolites.

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GLUCOSE MONITORING IN BLOOD

- Glucose monitoring , pregnancy test in diabetes patients ←**historical market driver**
- Environmental applications e.g. the detection of pesticides and river water contaminants such as heavy metal ions
- Remote sensing of airborne bacteria e.g. in counter-bioterrorist activities
- Remote sensing of water quality in coastal waters by describing online different aspects of clam ethology (biological rhythms, growth rates, spawning or death records) in groups of abandoned bivalves around the world
- Determining levels of toxic substances before and after bioremediation
- Routine analytical measurement of folic acid, biotin, vitamin B12 and pantothenic acid as an alternative to microbiological assay
- Drug discovery and evaluation of biological activity of new compounds
- Detection of toxic metabolites such as mycotoxins

- **Environmental Monitoring**

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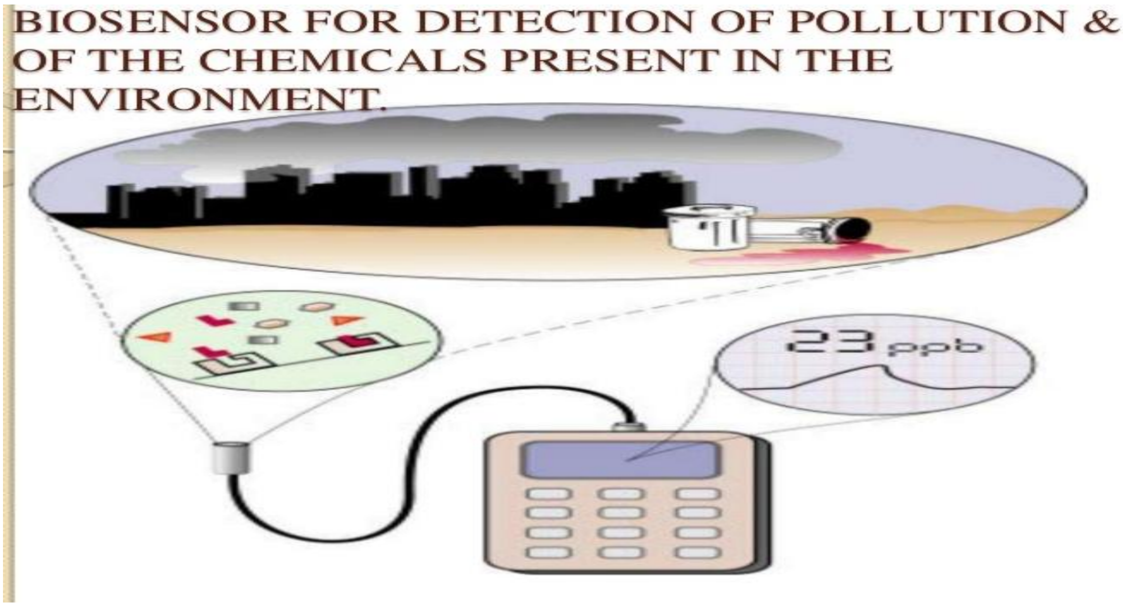

One of the major application of Biosensor is in the field of Environmental Pollution Monitoring. Especially, water pollution monitoring is an area where Biosensors have substantial advantage. There are numbering pollutants that are contaminating ground water and as a result the quality drinking water is getting worse.

Biosensors with sensing elements for nitrates and phosphates are becoming common for battling water pollutants.

Another important application is for the military to detect chemicals and hazardous biological specimens that can be used a bio-weapons.

- **Industrial Applications**

Fermentation is a large industrial operation used in dairy, alcohol and other similar products. Large scale Bacteria and cell culture must be maintained for this purpose. In order to minimize the cost of production and risk free fermentation, it is essential to monitor these delicate yet expensive processes.
Biosensors are designed to monitor and measure the generation of a fermented product.

- **Food Industry**

Commercial Biosensors that can measure carbohydrates, acids, alcohol, etc. are already available in the market. Biosensors are used in food industry for food quality control for measurement of amino acids, carbohydrates, alcohols, gases, etc.

Some of the common food industries are Wine, Beer, Yogurt, soft drinks etc.

II. CONCLUSION

Biosensors have been miniaturised extensively in the recent years. Keeping in line with such Developments, microbial cells with high enzyme behaviors may be needed. This is chief definitely when microbial cells are applied as replacements to enzyme based sensors. Microorganisms, due to their low cost, long lifetime and wide range of suitable pH and temperature, have been widely employed as the biosensing element in the construction of biosensors.

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