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Biosensors: Future Analytical Tools

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Abstract: Biosensors offer considerable promises for attaining the analytic information in a faster, simpler and cheaper manner compared to conventional assays. Biosensing approach is rapidly advancing and applications ranging from metabolite, biological/ chemical warfare agent, food pathogens and adulterant detection to genetic screening and programmed drug delivery have been demonstrated. Innovative efforts, coupling micromachining and nanofabrication may lead to even more powerful devices that would accelerate the realization of large-scale and routine screening. With gradual increase in commercialization a wide range of new biosensors are thus expected to reach the market in the coming years.

Keywords: Electrode, transducers, genetic screening, food analysis, bioterrorism, environment monitoring

1. Introduction

Modern economy is technology driven, promising revenues that are mind-boggling. Biosensor is one such product of biotechnology that is becoming increasingly popular in fields like environmental monitoring [1-2], bioterrorism [2-3], food analyses [4] and most importantly in the area of health care and diagnostics [5]. This rapidly expanding field has an annual growth rate of 60 %, with major impetus from the health-care industry (30% of the world's total analytical market) supported with other analytical areas of food & environmental monitoring including defense needs [6]. There is clearly a vast market exponential potential as less than .1% of this market is currently using biosensors. Research & Development in this field is wide and at the forefront of multidisciplinary science that involves the collaboration of physics, chemistry, biology, nanotechnology, electronics and software engineering. The concept of biosensors is just four decades old and the feasibility of biosensing was first demonstrated by an American scientist Leland C. Clark in 1962. He described how to make electrochemical sensors more intelligent by adding "enzyme transducers as membrane enclosed sandwiches"[7]. This idea was commercially exploited in 1975 with the successful launch of the Yellow Springs Instrument Company's glucose analyzer based on the amperometric detection of hydrogen peroxide (H_2O_2). Since then, many biosensors have been developed to detect a wide range of biochemical parameters, using a number of approaches, each having a different degree of complexity and efficiency. Recently, the most fascinating and prospective sensors includes Immunosensors [8-9] and Nucleic acid sensors [10-11], based on affinity reactions between Ab-Ag & hybridization reaction of complimentary ssDNA oligonucleotides respectively.

In general, a biosensor is an analytical device, which detects, transmit and record the information regarding the physiological, biochemical change or the presence of a specific analyte (a chemical or biological substance that needs to be measured) by producing a signal proportional to the concentration of the target analyte. A basic biosensors assembly includes a receptor, transducer and processor (amplification and display) as shown in Figure 1.

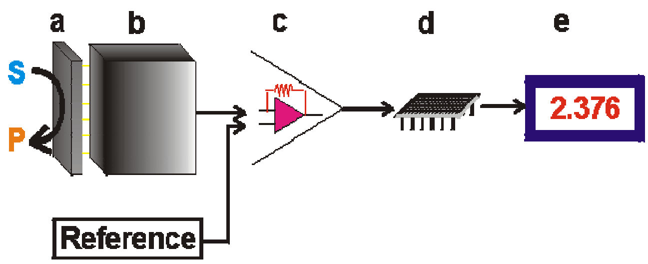

Fig. 1. Schematic diagram showing the main components of a biosensor. The biocatalyst (a) converts the substrate to product. This reaction is determined by the transducer (b) which converts it to a signal. The output from the transducer is amplified (c), processed (d) and displayed (e).
(Reproduced with permission from ref. 6).

Technically, it is a probe which incorporates a biological/ biologically derived sensing element (e.g. whole cells/ antibodies/ enzymes/ nucleic acids) forming a recognition layer, that is either integrated within or intimately associated to the second major component of biosensors that is a transducer via immobilization, adsorption, cross-linking and covalent bonding so that the close proximity of the biological component to the transducer is achieved. This is necessary so that the transducer can rapidly and easily generate the specific signals in response to the undergoing biochemical interactions, secondly the transmittance should be proportional to the reaction rate of biocatalyst with the measured analyte for a high range of linearity. The transducer critically acts like a translator, recognizes the biological/chemical event from the biological component and transforms it into another signal for interpretation by the processor that converts it in to a readable/ measurable out put. The transducer can take many forms depending upon the type of parameters being measured. They may be a) *Amperometric:* detect changes in current at constant potential [12], b) *Potentiometer:* detect changes in potential at constant current [13], c) *Piezoelectric:* detect the changes in mass [14], *d) Thermal:* measures changes in temperature [15], e) *Optical:* detects change in light transmission [16].

Since, these devices offer an excellent combination of the selective biology with the processing power of nano-electronics to generate rapid, simple and sensitive signal proportional to the target analyte; they are regarded as potent substitutes to conventional analytical techniques. These low complexity devices are suited for use at the point of care by healthcare workers with minimal training. By eliminating a number of steps and much labor, the instrumentation may save a lot of money & time for laboratories and hospitals. It would therefore in the near future be possible to measure group of biochemical parameters simultaneously from a single finger prick blood sample. Besides, they allow the clinical analysis to be performed at the bedside, in the critical care units and doctor's clinic rather than in the centralized laboratories.

2. Biosensors in Health Care and Diagnostics

With rising healthcare costs and to improve patient care, diagnostic laboratories have been challenged to develop new tests that are reliable, cost–effective and accurate and to optimize existing protocols by making them faster and more economical. Although there are number of commercial successes, but most successful to date is the glucose biosensor [17] for routine monitoring of glucose in blood by individuals suffering from diabetes. The basic principle is that glucose is recognized by the bioreceptor layer i.e. the glucose oxidase enzyme to yield the redox active species like hydrogen peroxide (H_2O_2) and gluconic acid. Out of these H_2O_2 passes through a series of membranes and is finally detected at the working electrode. The resulting electrical current is amplified and recorded. Other compounds, which may give an artificial signal or foul the electrode, are excluded by the membrane system. Companies are fabricating implantable biosensors that can trace blood glucose levels and simultaneously deliver insulin. For example "Microchips" is testing a chip implant that offers long term, time-controlled drug delivery [18]. Compatibility with microfabrication and ability to store and release drugs on demand would have potential applications in medical diagnostics, industrial process monitoring and control, combinatorial chemistry, microbiology, and fragrance delivery[19]. More importantly, it may provide new treatment options to clinicians in their fight against disease. The next step is to develop a manually, wirelessly controlled biosensor that detects and treats an acute condition, and then a biosensor that will approximate an artificial organ. This will permit sensing a condition and responding automatically without user intervention.

Biosensors also offer enormous potential in detecting wide range of analytes that are regularly needed to show a patient's metabolic state especially for those who are hospitalized, more so if they are in intensive care. Critical care is one of the most challenging (and stressful) areas of medicine, in the sense that the decision makers (primarily doctors, nurses and ambulance staff) must take their decisions quickly. At the moment of first examination, the patient's clinical state is usually unknown, and once known, it is prone to rapid change. The earlier these fundamental clinical data are provided; a reasoned therapeutic decision can be taken instantly for enhancing success rate. Biosensors that facilitate the measurement of calcium[20], lithium[21], lactate[22], cholesterol[23], urea[24], uric acid[25], oxalate[26], triglycerides[27], ascorbic acid[28] and creatinine[29] have been demonstrated and needs refinement for commercial viability. External biosensors are used in emergency rooms as point-of-care diagnostic units – such as I-Stat's "lab on a chip", which can reveal almost immediately whether a patient is under cardiac arrest by testing blood chemistry[30]. Similarly, it will be extremely helpful to have instantaneous on-site determinations for creatinine, sodium, potassium, chloride, and CO_2 levels of patients in the dialysis unit of a hospital or at a hemodialysis center.

Several variants of the classical biosensors are already thriving in the medical field. A new biosensor technology based on magneto-resistive sensors is introduced by Philips [31]. This biosensor measures the magnetic field created by magnetic nano-particles that bind to target molecules in a biological assay. Compared with optical sensing methods, the use of magnetic nano-particles eliminates the additional steps required to bind optical labels to the target molecules and improves sensitivity.

Oak Ridge National laboratory (ORNL) has developed "*Medical Telesensor*" chip (Fig-2) which can measure and transmit data related to body temperature [32]. Similar chips are being developed as a defense need for military personals to transmit data essential data to the remote monitor. This monitor alerts the medical team in critical circumstances.

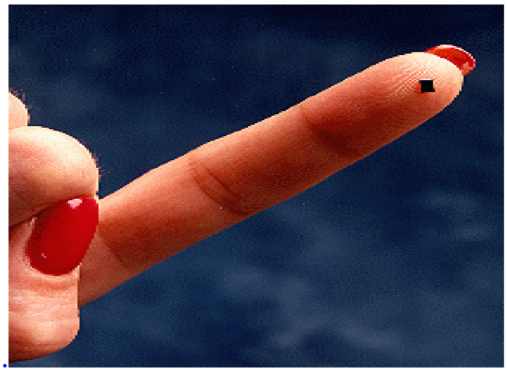

Fig. 2. This "medical telesensor" chip on a fingertip can measure and transmit body temperature (Courtesy: Oak Ridge National Laboratory, ref. 32).

3. Biosensing and Nucleic Acid Analyses

Over the past two decades, the practice of DNA sequence detection has become more ubiquitous and will continue to increase exponentially in genetics (primary patient diagnosis, carrier detection and prenatal diagnosis), pathology, criminology, food safety and biological warfare agents. This has been driven partly by the quantity of DNA sequence information that we have collected on humans and other organisms and partly by the increasing technological advances that provides us with the tools needed to develop new techniques to monitor biorecognition and interaction events. Current methods[33] for the identification of a particular DNA base sequence in a biological sample begin with the isolation of intact, double-stranded DNA and employ the polymerase chain reaction (PCR) to amplify the region of interest. The PCR product can then be subjected to electrophoresis or adsorbed directly onto a membrane, which is then exposed to a solution containing a DNA probe which has been chemically or enzymatically labeled with a radioactive material, chemiluminophore or hapten / ligand such as biotin to provide detectable signal for DNA hybridization. Radioactive materials are extremely sensitive, but have the obvious disadvantage of short self-life & high cost. Radioactive assay can not be done in open or ordinary labs which are not well equipped for handling, storage & dumping of radioactive materials. Fluorescent dye labels are expensive, they photobleach rapidly & are less sensitive. Most recently, Luminescent semiconductor nanocrystals (or “quantum dots”, QD) have been used as labels for bioanalytical applications [34-35]. Thermoquenching and extremely high cost are potent disadvantages of Quantum dots and hence generally limited to use in sensitive research experiments. There fore, large-scale, routine clinical screening based on gene diagnostics is limited by the current available technologies. Remarkably, DNA Biosensor technology can provide rapid, simple and low-cost on field detection of specific DNA sequence (pathogenic, virulent, transgenic) or point mutations that are responsible for, or linked to, inherited diseases. Diseases such as cystic fibrosis, muscular dystrophy, sickle-cell anemia, phenylketonuria, β-thalassemia and hemophilia A are known to be associated with specific changes in normal DNA base sequence. The list of known genetic abnormalities that cause, or are associated with, disease states will continue to expand as the sequencing of the human genome continues. During sensing of nucleic acids, single-stranded (ss) oligonucleotide probe are immobilized onto transducer surface forming a recognition layer that binds its complementary (target) DNA sequence to form a hybrid. The hybridization reaction is recognized and analytical signal (light, current, frequency) is passed by the transducer to the processor to provide a readable output. The measurement system (transducer and read out device or signal processor) can be gravimetric [36], electrochemical [37], optical [38], electrical [39], surface plasma resonance [40] based. Electrochemical DNA biosensor based detection show superior results over the other existing measurement systems. Basic principle of DNA biosensor is based on the properties that 1) DNA is double helical and has strong stacking interaction between bases along axis of double-helix and the base-pairing interactions between complimentary sequences are both specific and robust. 2) Double stranded DNA shows long- range electron transfer through π stacks of aromatic rings of base pairs [41-42]. The first example of a DNA chip, called the eSensorTM, was produced by Motorola Life Sciences Inc. [43]. eSensor^{TM} bioelectric chips also successfully detected 86% of the HPV types contained in clinical samples[44]. Toshiba's electrochemical DNA hybridization detection system is called the Genelyzer^{TM} [45]. It contains an electrochemical DNA chip that is able to analyze and type single-nucleotide polymorphisms (SNPs) and common DNA sequence variations by using the redox-active dye Hoechst33258 [46].

4. Applications in Food Analyses and Quality Assurance

Safety monitoring and quality control of foods are essential for food industry and the use of biosensors allows the assessment of food safety in real time. Hence biosensors have been developed for automated process control and provide a good alternative to other methods which are tedious, time & energy consuming and may require expensive instruments and reagents in addition to considerable technical skills[4]. The importance of on-line measurement compared to a laboratory measurement in terms of process control is firstly its response time. Sampling and subsequent analysis in a laboratory involves a time delay which can be sometimes several days. Although laboratory instruments have some inherent advantages, on-line biosensor describes the real time state of the process. Data generated from the biosensor provide rapid and/or continuous feedback information which can help the food processor both reduce wastage and increase productivity by incorporating microbiological and quality control into processing line. Because foods are highly unstable materials and can quickly undergo rapid and often detrimental changes, process control is an uncertain and doubtful strategy. Because of this, food industry needs instruments which will simultaneously monitor the parameters of production lines and report data to the computer for feedback control.

Most of the electrodes used in biosensors are often based on the measurement of O_2 consumption because there are at least 50 known oxidases acting on fatty acids, hydroxy acids, sugars, amino acids, aldehydes, etc. Using this concept ethanol, methanol, lactose, lactic and acetic acid, glucose and galactose on line biosensors have been developed by different researchers.

Beer, wine, bread and dairy industry suffer from lack of monitoring the growth conditions of microorganisms which must be kept at certain limits. On-line biosensors offer these industries feedback control of both the component and microbial levels of these and similar processes by continual on-line monitoring.

A unique situation that recently has come to light in India is the adulteration of milk with materials that are toxic or production of synthetic milk using ingredients such as urea. Biosensors have already been developed to check this menace. For example, urea is detected in milk samples by employing the enzyme unease. Urea and water are converted to ammonium and bicarbonate ions in the aqueous medium. Bicarbonate ions are weak ions so contribute less to the pH change but the alkaline ions due to their high alkaline nature contributes maximally to the pH change which is detected by the potentiometric transducer.

5. Biosensors for Environmental Monitoring

With several countries on the path to acquiring chemical and biological weapons there is now a need to develop biosensors for the early detection of these agents in accidental release during production and deliberate use by terrorists. Defense applications have become very prominent, particularly since the atrocities of September 11th 2002 and the subsequent anthrax attacks. To circumvent this latest threat to human health, efforts are underway to develop biosensors that could be used under these situations.

Biological and chemical warfare agents have broad threat spectrum, ranging from relatively simple chemical agents to complex bioengineered microorganisms. Traditional chemical agents (nerve, vesicant, and blood agents) have acute toxicities in the range of 10^{-3} g/person and are relatively easy to detect. Emerging chemical agents (toxic chemicals and aerosols) and bioregulators (neuropeptides and psychoactive compounds) are more varied in their chemical structure, requiring more sophisticated analytical methods for identification and detection. The most difficult chemical agents to detect are the cytotoxins and neurotoxins with chronic toxicities as low as 10^{-10} g/person. To identify and detect this complex array of chemicals, the ideal instrument would respond within min, cover the 15 to 200,000 dalton threat beside field portability. Despite the public's anticipation that biosensors with real-time detection will be able to monitor biological and chemical weapons, the technology hasn't caught up with expectations. Presently, biosensors in environmental monitoring stations, worldwide can detect compounds like anthrax – but detection can take 12 to 24 hours. Sandia National Laboratories, USA is developing the µChemLab, a system that detects biotoxins in 5 minutes [2]. Currently they are trying to upgrade the µChemLab to integrate both gas-based and liquid-based analysis into one handheld device. This type of biosensor could be incorporated into military uniforms and eventually into high security buildings.

6. Future Prospects and Popularization of Biosensors

Simplicity, quick results and economic advantages are enabling new procedures in hospitals while increasing the possibilities for self-care. For the biosensor to be of optimal use, it must be at least as precise and standardized as other available technology. Personnel with minimum training should be able to use these devices. Collecting and analyzing specimen at the bedside or in the clinic will enhance the superior turnaround time of biosensors. Reducing blood specimen volumes to micro (µ) level may permit continuous on-line monitoring of critical blood chemistries and has the advantage of creating less blood to clean up hence reducing the potential for infectious contamination from patient blood. It is anticipated that the health care worker at the bedside of a hospital patient µl aliquot of whole blood directly into the chip, and insert the chip into a portable biosensor instrument. In addition, a single chip insert may measure multiple parameters. This multi-specialty in itself will save considerable time and effort over the specimen processing that constitutes a substantial part of today's laboratory workload. In addition, mass-produced disposable biosensors will make medical diagnosis cheaper. The world total analytical market is approx ₤12000, 000, 000/ year and less than .1% of this market is currently using biosensors. Despite huge market potential & except for few commercial successes, many of the prototypes of biosensors in our laboratories are not commercially viable. The gap between research and the market place still remains wide and commercialization of biosensor technology has continued to lag behind the research by several years. Some of the many reasons includes: cost considerations, stability and sensitivity issues, quality assurance and competitive technologies. Until all these issues are addressed it would be difficult to move these devices from the research lab to market place. Biosensors undisputedly have got tremendous applications in healthcare, but the level of sophistication, reliability, awareness, cost, availability and marketing of these devices are important for deciding whether biosensors will be popular in the near future.

7. Conclusion

Biosensors are analytical devices which can transform biological recognition into a measurable signal. Our fascination with biosensor world is due to its exponential potential in analytical market. This multidisciplinary field offers potential applications in clinical diagnostics, defense, food and beverage industry, pollution control. In addition to sensitivity, simplicity and fast processing power, micro fabrication technology enhances biosensors with desired specifications. There is a great need to bring synergy among R&D institutions and Government, Industrial houses that leads to smooth transmission of technology. The level of sophistication, awareness, cost, reliability, availability and marketing are all factors involved in deciding, whether biosensors would become popular in near future.

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Guide for Contributors

Aims and Scope

Sensors & Transducers Journal (ISSN 1726- 5479) provides an advanced forum for the science and technology of physical, chemical sensors and biosensors. It publishes state-of-the-art reviews, regular research and application specific papers, short notes, letters to Editor and sensors related books reviews as well as academic, practical and commercial information of interest to its readership. Because it is an open access, peer review international journal, papers rapidly published in *Sensors & Transducers Journal* will receive a very high publicity. The journal is published monthly as twelve issues per annual by International Frequency Association (IFSA). In additional, some special sponsored and conference issues published annually.

Topics Covered

Contributions are invited on all aspects of research, development and application of the science and technology of sensors, transducers and sensor instrumentations. Topics include, but are not restricted to:

- Physical, chemical and biosensors;
- Digital, frequency, period, duty-cycle, time interval, PWM, pulse number output sensors and transducers;
- Theory, principles, effects, design, standardization and modeling;
- Smart sensors and systems;
- Sensor instrumentation;
- Virtual instruments;
- Sensors interfaces, buses and networks;
- Signal processing;
- Frequency (period, duty-cycle)-to-digital converters, ADC;
- Technologies and materials;
- Nanosensors;
- Microsystems;
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