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BIOSENSORS A NEW ANALYTICAL TOOL: A REVIEW

G. Garg, D. Singh, M. Rawat, K. Dashora, Swarnlata Saraf and S. Saraf*

Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur - 492 001 (India)

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ABSTRACT

Biosensor is an analytical device, which converts a biological response into an electrical signal. This paper reviews the principal milestones in the history of biosensor development, classification, patterning, sensitivity, selectivity and applications. The current success of glucose biosensors is attributed to the extraordinary demands of diabetes and the ability of biosensors to offer a convenient, hygienic and compact method of personal monitoring. Biosensors offer enormous potential to detect a wide range of analytes in health care, the food industry and environmental monitoring. Biosensors represent a rapidly expanding field, at the present time, with an estimated 60% annual growth rate.

Key words: Biosensors, patterning, selectivity and medappli.

INTRODUCTION

The biological recognition systems are typically some enzymes, organelles, microbial, plant or animal cell, tissue slice or section and immune binding or receptor protein. The system is responsible for the specific recognition of the analyte and subsequent response with a change in some measurable parameters. Various types of detection systems can be used in biosensing, they are namely, electrochemical detection system, thermal and mass detection, photometric detection, surface plasmon systems and those based on signal processing. A biosensor is an analytical device, which converts a biological response into an electrical signal. The term 'biosensor' is often used to cover sensor devices used in order to determine the concentration of substances and other parameters of biological interest even where they do not utilize a biological system directly. The emphasis of this review concerns enzymes as the biologically responsive material, but it should be recognized that other biological systems may be utilized by biosensors, for example, whole cell metabolism, ligand binding and the antibody-antigen reaction.

The term biosensor has been variously applied to a number of devices either used to monitor living systems or incorporating biotic elements. A biosensor will be defined as a compact analytical device incorporating a biological or biologically derived sensing element either integrated within or intimately associated with a physicochemical transducer. The usual aim of a biosensor is to produce either discrete or continuous digital electronic signals, which are proportional to a single analyte or a related group of analytes[1].

History

The clarification of scope allows us to identify clearly Professor Leland C Clark Jnr. as the father of the biosensor concept. In 1956, Clark published his definitive paper on the oxygen electrode [2]. Based on this experience and addressing his desire to expand the range of analytes that could be measured in the body, he made a landmark address in 1962 at a New York Academy of Sciences symposium in which he described how "to make electrochemical sensors (pH, polarographic, potentiometric or conductometric) more intelligent" by adding "enzyme transducers as membrane enclosed

sandwiches". The concept was illustrated by an experiment in which glucose oxidase was entrapped at a Clark oxygen electrode using dialysis membrane. The decrease in measured oxygen concentration was proportional to glucose concentration. In the published paper [3], Clark and Lyons coined the term enzyme electrode, which many reviewers have mistakenly attributed to Updike and Hicks[4], who expanded on the experimental detail necessary to build functional enzyme electrodes for glucose. Guilbault and Montalvo [5] were the first to detail a potentiometric enzyme electrode. They described a urea sensor based on urease immobilised at an ammonium-selective liquid membrane electrode. Clark's ideas became commercial reality in 1975 with the successful re-launch (first launch 1973) of the Yellow Springs Instrument Company (Ohio) glucose analyzer based on the amperometric detection of hydrogen peroxide. This was the first of many biosensor-based laboratory analyzers to be built by companies around the world. The use of thermal transducers for biosensors was proposed in 1974 and the new devices were christened thermal enzyme probes[6] and enzyme thermistors (Mosbach)[7], respectively. The biosensor took a further fresh evolutionary route in 1975, when Divis[8] suggested that bacteria could be harnessed as the biological element in microbial electrodes for the measurement of alcohol. Lubbers and Opitz[9] coined the term *optode* in 1975 to describe a fiber-optic sensor with immobilized indicator to measure carbon dioxide or oxygen. They extended the concept to make an optical biosensor for alcohol by immobilizing alcohol oxidase on the end of a fiber-optic oxygen sensor[10]. Commercial optodes are now showing excellent performance for *in vivo* measurement of pH, pCO2 and pO2, but enzyme optodes are not yet widely available. In 1976, Clemens *et al.* incorporated an electrochemical glucose biosensor in a bedside artificial pancreas and this was later marketed by Miles (Elkhart) as the Biostator. A major advance in the *in vivo* application of glucose biosensors was reported by Shichiri *et al.*[11] who described the first needle-type enzyme electrode for subcutaneous implantation in 1982. Companies are still pursuing this possibility, but no device for general use is available yet. The idea of building direct immunosensors by fixing antibodies to a piezoelectric or potentiometric transducer had been explored since the early 70's, but it was a paper by Liedberg *et al.*[12] that was to pave the way for commercial success. They described the use of surface plasmon resonance to monitor affinity reactions in real time. The BIAcore (Pharmacia, Sweden) launched in 1990 is based on this technology. In 1984, published a much-cited paper on the use of ferrocene and its derivatives as an immobilized mediator for use with oxidoreductases[13] in the construction of inexpensive enzyme electrodes. In combination with electrochemical, optical, piezoelectric and thermometric transducers. Within each permutation lies a myriad of alternative transduction strategies and each approach can be applied to numerous analytical problems in health care [14], food and drink, the process industries, environmental monitoring [15], defense and security. Generic goals may be identified which underpin more applied biosensor programmes and tackle some of the principal hurdles to the more widespread adoption of biosensor technology for analysis. The design of integrated systems approaches to patterning sensitive elements and methods to improve the sensitivity, stability and selectivity of biosensors are key areas.

Classification of Biosensors

Biosensors can be classified by the method used to achieve signal transduction, the most common approaches are:

1. Electrochemical sensors: electrochemical sensors are subdivided into either amperometric, potentiometric or conductometric types.in the amperometric category, an enzyme is typically coupled to an amperometric electrode and as the enzyme reacts with the substrate, a current is produced that is correlated to the analyte concentration.
2. Potentiometric sensors: potentiometric sensors utilize either an immobilized enzyme on the surface of a glass pH electrode or they are based on the production or consumption of protons by the electrode. Measurements are usually done in the zero current modes for both liquid and gaseous configuration. One of the major limitations of the enzyme sensitive to pH, ammonia, carbon dioxide or other analytes

endogenous to the sample volume.

3. Thermal and mass colorimetric biosensors: The heat, which is generated during enzyme/substrate reactions, is used. Changes in solution temperature caused by the enzyme/substrate reactions are measured using a thermistor or transistor and compared to a sensor with no enzyme to determine the analyte concentration. Colorimetric microsensors have been manufactured for detection of cholesterol in blood serum based on the enzymatic ally produced heat of oxidation and decomposition.
4. Optical biosensors: This is another version of biosensor which is a small device along with its measuring instrument, uses optical; principles quantitatively to convert chemical or biochemical concentrations or activities into electrical signals. This type of sensor often incorporates biological molecules such as antibodies and enzymes as transducing elements.

There are two general approaches taken to implement optical biosensors:

(a) Measuring the change in light reflectance
(b) Measuring luminescence

5. Acoustic biosensors: The piezoelectric devices have been formed to exhibit sensitivity towards frequency of interactions, which pertain to surface mass. Principally, piezoelectric device based on acoustic principle that essentially relay on establishing vibrational wave in material i.e. under the influence of alternative current voltage apply through a electrode coated on its surface depending on the characteristics of acoustic waves which depend on the structure of device in terms they are known as quartz micro valence Saw (surface acoustic wave) lamb wave or acoustic plate based device. When antibodies are coated on the surfaces resulting constructs could selectively pick up the load of complementary antigens. The resultants increment in the surface mass loading decrease the vibrational frequency, which could be, quantify as and has found to be proportional to the mass.
6. Surface plasmon: surface plasmon is a quasi-free electron cloud which is prepared by coating the core with a thin layer of silver approximately 600Å thick. It used for kinetic analysis of low molecular weight compounds and by immobilizing receptors to the sensor surface.

A successful biosensor must possess at least some of the following beneficial features:

1. The biocatalyst must be highly specific for the purpose of the analyses, be stable under normal storage conditions and, except in the case of colorimetric enzyme strips and dipsticks, show good stability over a large number of assays (i.e. much greater than 100).
2. The reaction should be as independent of such physical parameters as stirring, pH and temperature as is manageable. This would allow the analysis of samples with minimal pre-treatment. If the reaction involves cofactors or coenzymes these should, preferably, also be co-immobilized with the enzyme.
3. The response should be accurate, precise, reproducible and linear over the useful analytical range, without dilution or concentration. It should also be free from electrical noise.
4. If the biosensor is to be used for invasive monitoring in clinical situations, the probe must be tiny and biocompatible, having no toxic or antigenic effects. If it is to be used in fermenters it should be sterilisable. This is preferably performed by autoclaving but no biosensor enzymes can presently withstand such drastic wet-heat treatment. In either case, the biosensor should not be prone to fouling or proteolysis.
5. The complete biosensor should be cheap, small, portable and capable of being used by semi-skilled operators.

Biosensors: Integrated system

Biosensor technologists strive for the simplest possible solution to measurement in complex matrices. While notable success has been achieved with individual sensors, pragmatic solutions to many problems involve the construction

of a sensor system in which the carefully optimized performance of the sensor is supported by associated electronics, fluidics and separation technology. In process monitoring, for example, the process must remain inviolate while the sensor frequently requires protection from the process and its products. An integrated system comprising a rotary aseptic sampling system with flow-injection analysis incorporating a reusable, screen-printed electrode. The enzyme electrode utilized glucose oxidase immobilized in a hydrophilic gel and detected hydrogen peroxide at a catalytic electrode made of rhodinised carbon. While the enzyme electrode alone exhibited enhanced stability and interference characteristics, a complete solution of the monitoring problem demanded the optimization of the whole system. There are increasing demands for a systems orientated approach in other sectors; environmental monitoring places demands on sensor technology that in many cases are unlikely to be met by isolated sensors, and in clinical monitoring micro dialysis offers a useful way forward for measurement *in vivo*. The sensor/sampling system biointerface is a key target for further investigation and we are using evanescent wave techniques and atomic force microscopy to further our understanding of protein interactions [16]. Work on *in vivo* sensing systems for both glucose and lactate [17] has confirmed the effectiveness of phospholipid copolymers in improving haemocompatability. Immunosensors offer a further general example where micro separations, using for example immuno-chromatographic methods, can be coupled with electrochemical or optical detectors to yield simple dipstick style devices combining the speed and convenience of sensors with the specificity and sensitivity of immunoassays. The advent of micro machining makes these and other hyphenated techniques amenable to such a high degree of miniaturization that the distinction between sensor and analytical instrument becomes hazy.

Patterning

The success of single analyte sensors has been followed by the formulation of arrays of sensors to offer menus relevant to particular locations or situations. The most obvious example is in critical care where commercially available hand-held instruments provide clinicians with information on the concentration of six key analytes in blood samples and bench-top instruments on the ward can measure sixteen analytes. These instruments feature biosensors for glucose, lactate, urea and creatinine. The dual demands for increased range of analytes and decreased size are driving biosensors towards micro- or even nano-arrays. Thinking in this area is being stimulated by the demands of the pharmaceutical industry where high volume, high throughput drug screening is essential for survival. Newman *et.al.* already working with 12 channel Mach Zhender interferommeters[18] built on 1cm2 pieces of silicon and 244 individually addressable electrodes can be fabricated on a similar area. Advanced ink-jet printing technology[19] is being used to deposit fractions of a nanolitre on three-dimensional surfaces with a production line moving at 6 m/sec. In the longer term, however, arrays of a million sensors/cm2 are a realistic target. Photolithography, micro contact printing and/or self assembly techniques offer routes to high density arrays, but laser desorption is particularly promising and offers the ability to "write" proteins to surfaces with very high resolution.

Sensitivity

Clinicians, food technologists and environmentalists all have an interest in generally increased sensitivity and limits of detection for a range of analytes. While the precise demands to meet today's requirements may be modest in these respects, few would contest the longer-term benefits of reliable detection of trace amounts of various indicators, additives or contaminants. With the advent of atomic force microscopy we can consider single molecule detection in the research laboratory, but great strides have also been made with conventional sensors. Enzyme electrodes have been designed which preconcentrate the analyte of interest[20]. Danison *et.al*. reported a gas-phase micro biosensor for phenol, for example, in which polyphenol oxidase was immobilized in a glycerol gel on an interdigitated microelectrode array[21]. Phenol vapour partitioned directly into the gel where it was oxidised to quinone. Signal amplification was enhanced by redox recycling of the quinone/catechol couple resulting in a sensor able to measure 30 ppb phenol. Detection limits of parts per trillion volatile organic carbons are

feasible with this approach. Ultra-low detection limits are achievable with affinity sensors and electrochemical detection may be readily integrated with chromatographic techniques to yield user-friendly devices [22]. In an alternative approach, double-stranded DNA may be used as a receptor element. "Sandwich"-type biosensors based on liquid-crystalline dispersions formed from DNA-polycation complexes may find application in the determination of a range of compounds and physical factors that affect the ability of a given polycation molecule to maintain intermolecular cross links between neighboring DNA molecules [23]. In the case of liquid-crystalline dispersions formed from DNA-protamine complexes, the lowest concentration detectable of the hydrolytic enzyme trypsin was 10-14M. Elimination of the cross links caused an increase in the distance between the DNA molecules, which resulted in the appearance of an intense band in the circular dichroism spectrum, and a "fingerprint" (cholesteric) texture. Work is in progress to develop mass-producible films and inexpensive instrumentation.

Stability

Arguably the most obvious disadvantage in exploiting the exquisite specificity and sensitivity of complex biological molecules is their inherent instability. Many strategies may be employed to restrain or modify the structure of biological receptors to enhance their longevity. Psoma *et.al.* recently confirmed the effectiveness of sol gels as an immobilization matrix in an optode for glucose using simultaneous fluorescence quenching of two indicators, (2,2'-bipyridyl)ruthenium(II) chloride hex hydrate and 1-hydroxypyrene-3,6,8-trisulphonic acid. In addition to the excellent optical properties of the gel, enhanced stability of the glucose oxidase catalyst was clearly evident[24]. Some desirable activities, however, remain beyond the reach of current technology. Methane monooxygenase is one such case where, despite reports of enhanced stability in the literature, the demands of hydrocarbon detection require stability far beyond that exhibited by the enzyme. In these cases it is valuable to resort to biomimicry to retain the essence of the biocatalytic activity, but to house this within a smaller and more robust structure. For example, we have developed a simple and rapid method for quantifying a range of toxic organohalides based on their electro catalytic reaction with a metalloporphyrin catalyst. This approach can be used to measure Lindane and carbon tetrachloride (representative of haloalkane compounds) perchloroethylene (a typical haloalkene) 2,4D and pentachlorophenol (aromatics) and the insecticide DDT[25].

Selectivity

Improvement in the selectivity of biosensors may be sought at two levels; the interface between the transducer and the biological receptor may be made more exclusive thus reducing interference, and new receptors can be developed with improved or new affinities. The use of mediators as a strategy to improve performance in amperometric biosensors has proved extremely popular. A recent publication [26] describes the use of pyrroloquinoline quinone as a "natural" mediator, but used with glucose oxidase in an enzyme electrode for the measurement of sugar in drinks. Alternatively, electro catalytic detection of the products of enzymatic reactions may be enhanced by the use of chemically modified electrodes such as rhodinised[27] or hexacyanoferrate-modified[28] carbons. The latter method results in a Prussian Blue coating on the electrode which may then be used for amperometric detection of hydrogen peroxide at both oxidative and reductive potentials in enzyme electrodes for lactate and glucose[29]. Arguably a more elegant solution is to seek connection of the redox centre of an enzyme to an electrode via a molecular wire. Much has been published about so called "wired" enzymes, but these papers have generally been concerned with immobilized mediators on various polymer backbones. Use of molecular wires in their pure sense for long distance electron transfer affected via a single molecule with delocalised electrons. Novel heteroarene oligomers, consisting of two pyridinium groups, linked by thiophene units of variable length (thienoviologens) are promising candidates for such conducting molecular wires and may be used in conjunction with self-assembly techniques to produce an insulated electrode which transfers electrons specifically along predetermined molecular paths. This design should produce enzyme electrodes free from electrochemical interference. Advances in computational techniques now allow us to model

both electron transfer reactions and receptor binding interactions with increasing accuracy. This not only enhances our understanding of the receptor/transducer interface, but also allows us to consider designing new receptors based on biological molecules. To obtain improved binding ligands for use in an optical sensor for glycohemoglogin (HbA1c), a novel synthetic peptide library composed of one million L-amino acid hexapeptides was constructed from ten amino acids using combinatorial chemistry[30]. The hex peptide library was screened against HbA1c, HbA1b, HbAF and HbA0, and selected ligands sequenced. Individual ligands or arrays of ligands in conjunction with pattern recognition techniques will be used to design a sensor with improved selectivity.

Applications

Biosensors have the potential to affect many areas. Field application areas including medicine, physical therapy, music, and the video game industry, can all benefit from the introduction of biosensors? Although biosensors are not limited to any group of people, they are particularly useful for the handicapped. Even completely paralyzed individuals have electrical activity in their bodies that can be detected.

1. One biosensor application developed for the handicapped is an electronic instrument that produces music from bioelectric signals[31,32]. Signal inputs such as eye movements, muscle tensions, and muscle relaxations are converted to MIDI (Musical Instrument Data Interface) and output to a synthesizer. Before being mapped to MIDI, the signals are analyzed for specific intensity and spectral characteristics for the particular individual. For dysfunctional or weak muscles the signals can be amplified according the level of tension and relaxation. These signal inputs are then interpreted to control volume, pitch, tempo, and other aspects of musical composition.
2. Medical applications are presently seen in the diagnosis and correction of eye disorders. Strabismus is conditions in which an individual's eyes are not aligned properly, and thus do not move in conjunction with one another. This can be corrected by surgery but the current use of prisms to determine the degree of correction necessary is not very accurate. Biosensors tracking the eye movements can determine with high accuracy the number of degrees in both the X and Y planes that the eyes need to be adjusted.

   Just as biosensors can be used to determine amounts of eye correction, they can also be used to train the eye, as they can be an input device to video game exercises to realign eye tracking. This same method of muscle training through a video game could be used for rehabilitation of potentially any muscle group, as biosensors can be individually customized to detect levels of muscle activity for most muscle groups. In the same way that patients undergoing rehabilitation could use biosensors as an input device for their video exercises, the video game industry could use biosensors as yet another powerful input device for entertainment.
3. Biosensors contributing in physical therapy, biosensors can help to create custom exercise programs for injured patients and athletes, can be used by athletes to check muscle condition, and can be connected to a multitude of external monitoring devices.
4. Optical Biosensors for Neurotransmitters and Other Intercellular Signals Enzymes, encapsulated in the pores of the sol-gel derived glass, retain their spectroscopic properties and their biological activities. We have used one such encapsulated enzyme, glutamate dehydrogenase (GDH), to measure concentrations of glutamate, the major excitatory. Neurotransmitter in the central nervous system, with the goal of monitoring glutamate release with a temporal resolution of milliseconds and a spatial resolution of tens of micrometers. GDH catalyzes the oxidative deamination of glutamate to á-ketoglutarate, with NAD+ serving as electron acceptor. To allow continuous monitoring, we have adopted a photochemical means of regenerating NAD+ from NADH. The technology we have developed can be extended to other dehydrogenases, the largest class of redox enzymes, for one-time or real-time

monitoring of other analytes.

5. Sensors in Modern Medicine: Technology in biomedical sensors must be developed in concert with the clinicians and biologists who understand how these sensors can be used. The primary barriers to successful transfer of technology have to do with highly specialized knowledge and vocabularies; technologists lack a clear understanding of the clinical problems they are trying to solve, while clinicians lack knowledge about technical options for meeting their needs. These two groups of people rarely come in contact with each other naturally, and when they do, they can lack a shared vocabulary to discuss and develop technological solutions to medical problems.

   CIMIT, The Center for Integration of Medicine and Innovative Technology at MIT and Harvard, attempts to solve this basic problem by bringing together people from a "problem-rich environment" (Harvard Medical School and the Boston area hospitals) and a "solution-rich environment" (MIT and the Draper Laboratories). Besides the need for an appropriate team work on biomedical.

6. Biosensors: disease management

   Sensors will be increasingly important for medicine as we attempt to tailor therapies to the individual, as better treatments turn lethal diseases into chronic diseases, and as we move toward home care. Need smaller, cheaper, more portable sensors that can be used easily by the patient or are indwelling. These sensors must be very reliable, fast, and have a well-defined failure mode. In addition, they must have adequate data storage, computing and communication ability. An example of a sensor application is the operating room where a large number of sensors are used, and medical personnel must evaluate the readings from each individually and mentally integrate these readings to follow a patient's physiology. An integrated processing system is needed that can acquire and process several signals into a coherent picture that can be quickly understood and used to make medical decisions.

   A "wish list" of desired sensors and their capabilities includes "smart forceps" to improve surgery, the ability to predict total organ failure, a "deployable" ICU, a device to track skin lesions, a closed loop 'dosing system', such as that needed to deliver insulin in response to changes in blood glucose, and wireless technology for sensors. Collaboration of specialists with different expertise will be essential to attain this "wish list" as well as other applications.

7. Biosensors: Microsystems - Based Technologies for Medicine

   The rapidly emerging field of Micro Electro Mechanical Systems (MEMS), also known as micro systems technology, has penetrated a wide array of applications, in areas as diverse as automotives, inertial guidance and navigation, micro optics, and chemical and biological sensing. Commercial success has already been realized in automotive and industrial sensing applications; however, the most significant opportunity for micro systems lies in the domain of biomedical technology, most specifically in the field of biosensing. Advantages of MEMS sensors in this arena include the unprecedented level of precision realized by micro fabrication, the equivalence of size scales with cells, the potential for multifunctional integration, low cost, and small size, which enables small sample volumes and implantable devices. Two Microsystems-based technologies with applications in clinical diagnostics presented; a miniaturized ion mobility spectrometer, and a transducer array with functional zed surface chemistry.

The micro machined Planar High Field Asymmetric Waveform Ion Mobility Spectrometer (PFAIMS) developed at Draper Laboratory is a novel detector for chemical and biological sensing applications. The FAIMS method uses the non-linear mobility dependence of ions on high strength RF electric fields for ion filtering, and has a detection limit in the part-per-trillion regime. The FAIMS scales down without a loss in sensitivity, unlike conventional time-of-flight ion mobility spectrometers. Gas samples are introduced into the spectrometer and then ionized, and the ions are

transported through a filter towards a detector by a carrier gas. The ion filter is electronically tunable and the ion species allowed to pass through the filter are selected by adjusting the RF and compensation electric fields applied between the ion filter electrodes. Preliminary work with the PFAIMS spectrometer has been conducted for many promising biomedical applications. It is widely known that the presence of biogenic amines in human body fluids such as urine, saliva, and blood may reveal or suggest pathological conditions such as cancer. Chemical changes and degradation processes of cells after death are accompanied by the formation of molecular byproducts. For example, decarboxylation of ornithine and lysine produces putrescine and cadaverine respectively.

Breath analysis has been utilized for centuries in the diagnosis and management of disease, with a wide spectrum of volatile organic compounds associated with particular conditions. These include ketones in ketoacidosis, feculent amines in bowel obstruction, and bacterial byproducts in anaerobic infections. Radioactive labeled metabolites are used in gastroenterology tests. Breath pentane, produced by peroxidation within cell membranes, has been found to be elevated in proportion to ischemia and inflammation in heart disease, and is a promising marker for reperfusion injury. Preliminary experiments with the PFAIMS indicate the potential for a simplified non-invasive breath analysis system. In these experiments, sample collection involved collecting a breath sample directly onto a solid phase micro-extraction (SPME) fiber assembly. The SPME assembly was inserted into a GC injector port and desorbed the sample from the fiber into the GC column.

Future goals

There are future applications that make biosensors ideal input devices. Eye tracking devices that can focus and select objects in 3D virtual environments would couple sight and limb 3D selection creating powerful immersive environments. Users in a virtual environment could realize the laser abilities from the eyes of 'Superman'.

Possible use of prosthetic limbs where just the bioelectric activity to the nerve endings of a missing limb could be used to control an artificial limb. In cases of paralysis, the nerves, prior to loss of transport ability, or brainwaves might be electrically monitored for instructions to control/ move a mechanical device attached to the paralyzed limb.

When brainwaves can be reliably monitored, we can study relationships between EEG (brain activity) and specific cognitive activities such as sleep behaviors and sleep states. Simple brain wave detection has been successful in early research stages, but breaking through the use of sub vocal commands would be perhaps the most powerful input controller we have yet seen. Just picture monitoring brain activity so that when you think, "draw a circle", a circle appears on your monitor or in your virtual environment.

Biosensors potentially have a number of uses in the emerging field of Virtual Reality, particularly in the areas of user interaction and the development of these interaction devices. Biosensors could be used as powerful input devices for immerse environments. Imagine a virtual environment in which your entire body was immersed. This environment could react to hand or arm gestures, eye movements, or any muscle or nerve as input. These forms of input are attractive as they are somewhat more natural and intuitive to the user, as the user is accustomed to manipulating the "real" world with such movements. These natural forms of input are successfully being researched with input devices such as gloves and body suits. Biosensors strategically placed on the body could provide an alternative way to provide this interface, and may be less encumbering than full body suits or gloves. Handicapped people who may not be able to use a glove or body suit also could utilize them. Currently, researchers are developing a biosensor wristband to detect electrical activity in the hand. Primitive gesture recognition has been successful, providing a possible alternative to a glove in the future[33,34]. Another possible, natural input to a virtual environment is muscle tension. This could be quite useful if utilized in the design of a glove. In this way input can be given to indicate if the user is touching or smashing an object in a virtual environment. Eye movement also has

important interaction implications in virtual reality. Wherever the user's eyes look, the virtual environment could be displayed appropriately. Furthermore, convergence of the eyes on a specific object in the environment could be detected. This could be used to select and object in the virtual environment. With the methods of head movement tracking currently used, the scene can be rendered, but it is difficult to tell if the user is focusing on a specific object.

Biosensors could also be used to measure and analyze muscle activity and patterns, and in that way, aid in the development of VR hardware such as gloves, body suits, or robotic arms used in telepresence environments.

Conclusion

The indications are that analytical chemistry, and sensor technology in particular, could follow the same trends as microelectronics. As chemical analysis becomes simpler and more widely available, we can expect to see a proliferation of uses in conjunction with microprocessors and telecommunications equipment. Equipment capable of acquiring data as well as processing it could find wide application in monitoring personal health, the food we eat and our environment. In order to facilitate this analytical revolution, biosensor technologists must resolve the remaining problems hindering the exploitation of biological molecules and their analogues in conjunction with microelectronics. With continued progress, we can expect the limiting factors to be shifted from technological problems to the identification of sensible exploitation of an immense analytical capability.

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