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# Biosensors

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# Biosensors

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Biosensors are analytical devices that respond selectively to analytes in an appropriate sample and convert their concentration into an electrical signal via a combination of a biological recognition system and an electrochemical, optical or other transducer. Such devices will find application in medicine, agriculture, environmental monitoring and the bioprocessing industries. The last few years have seen great advances in the design of sensor architectures, the marriage of biological systems with monolithic silicon and optical technologies, the development of effective electron-transfer systems and the configuration of direct immunosensors. Recent progress in these areas has already led to the introduction of new-generation biosensors into the competitive diagnostics market place.

## The need for biosensors

It is now eight years since the Joint Working Party of the Advisory Council for Applied Research and Development, the Advisory Board for the Research Councils and the Royal Society chaired by the late Dr Alfred Spinks reported its conclusions and recommendations on the development of biotechnology in the United Kingdom. At that time, it was hardly appreciated that a newly emerging area of pleuridisciplinary technology, biosensors, which spanned biotechnology, materials science and electronics, had the potential for making a substantial impact in a plethora of lucrative markets (Lowe 1984, 1985; Foulds & Lowe 1985). It is not, however, difficult to understand why biosensor technology has since witnessed almost exponential growth. Most analytical measurements made today are concerned with the assay of chemical species in complex matrices. Commonly, such analyses involve complete separation of sample constituents followed by identification and quantification of the target analyte. However, if this information is required for a limited number of analytes in a complex sample matrix, this approach is difficult to justify on either temporal or financial bases and often precludes real-time analyses (Thompson & Krull 1984). Biosensors promise to provide an analytically powerful and inexpensive alternative to conventional technologies by being able to discriminate the target analyte from a host of inert and potentially interfering species (Lowe 1985). They do this task by combining the unique features of biomolecular recognition with appropriate electrochemical transducers to convert the concentration of the target analyte in the sample into an electrical signal.

The requirement for accurate analytical information is particularly marked in human health care and veterinary medicine, the agri-food, pharmaceutical and petrochemical industries, environmental monitoring, defence and security (Higgins & Lowe 1987). Currently, most of this chemical intelligence is acquired through the operation of well-equipped and well-serviced analytical laboratories. These centralized facilities are staffed by highly skilled personnel and contain reliable auto-analysers capable of processing up to 500 samples per hour on a low cost per sample basis. However, in recent years, there has been a marked movement away from centralized testing into a more devolved system of 'alternate-site' diagnosis. The emergence of





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diagnostic testing in the ward, outpatients, surgery, home, field or work place brings with it the requirement for rapid individual tests being done by unskilled personnel and the maintenance of quality testing in such dispersed environments. Thus to be practical, such technology needs to be simple to operate and require little or no sample preparation.

Biosensor technology is eminently suited to satisfy the needs of 'alternate-site' diagnostic testing. For example, among general practitioners working in local surgeries there is a growing demand for low-cost analysers to assist with diagnosis during consultation (Davis 1986). Similarly, in intensive care, patient-side testing with portable devices capable of continuous *in vivo* or *ex vivo* monitoring of key analytes is desirable. Finally, single-use diagnostic kits that permit qualitative or semi-quantitative estimation of analytes in the home are becoming increasingly popular, Not surprisingly, biosensors are most likely to have the greatest impact where there is advantage in obtaining an immediate result; for example, in checking for cancer markers in tissue surrounding an excised tumour within the operating theatre or in patients suspected of drug overdose. However, although the health care sector offers substantial market opportunities for biosensor products, the expansion of biosensors into the agricultural, veterinary and horticultural sectors is likely to gather pace (Lowe 1986). For example, it is anticipated that sensors of appropriate specificity could provide invaluable assistance to livestock management by routine monitoring and control of the environment and the feed, body condition and fertility of animals. Environmental monitoring and safety could also constitute a major use of biosensors as it could be possible to avoid the possibilities of contamination and other problems associated with batch sampling and to monitor fluctuations in pollutants over short-time excursions. Thus the testing of water for pollutants such as pesticide herbicide or fertilizer residues and the biological oxygen demand (BOD) are prerequisites for efficient management. Similarly, there is significant potential for rapid identification of drugs of abuse at points of entry and for strategic and tactical monitoring of chemical warfare. The principal applications in the bioprocess industries are in the fermentation industry where Japanese activity is particularly high.

## Performance criteria

In order that a biosensor find application within these market sectors it must satisfy one of three criteria: it should have a performance/price ratio that is substantially above that of existing diagnostic tests; (ii) it should permit important new measurements to be made; and (iii) it should enable a measurement to be made rapidly in applications where time is an important factor (Smith 1987). However, the relative validity and importance of often-cited additional advantages of biosensors such as facile use by lay personnel, small size, ruggedness, inexpensiveness, fast response, ready interfacing with computer technology and biocompatability (Thomson & Krull 1984) will depend on the particular application area. For example, the absolute precision of a cancer marker, drug of abuse or pregnancy test could be quite low whereas for therapeutic drug monitoring, where the margin between therapeutic and toxic effects can be relatively narrow, the sensor must display high precision even at the expense of a longer time required for assay. Similarly, biosensors for monitoring glucose in the home by diabetics will be price sensitive, whereas devices for critical care units and industrial fermenters could be quite price insensitive. Thus the features required of biosensors will vary according to market area provided that in all cases the devices are specific, sensitive and reliable and that this performance is reproducible over the shelf life of the sensor (Smith 1987).



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## Sensor architectures

All biosensors exploit a basic union between a selective biorecognition site and a transducer, which is capable of translating a perturbation of physical chemistry associated with the biorecognition process into a usable signal (Lowe 1984, 1985). Generally, the action of these 'receptors' can be categorized into biocatalytic systems such as enzymes, organelles, whole cells or tissue slices where there is 'turnover' of the binding sites and thus capacity for continuous sensing, and 'irreversible' binding systems that exploit antibody and receptor systems where interactive sites can be consumed and thus become 'single-use' devices. Selective biosensors have now been developed in both systems, where recent advances in immobilization technology have provided improved stabilization, localization and activity of the sensing surfaces (Barker 1987).

### *Enzyme biosensors*

Most successful biosensors exploit enzymes as the biological recognition/response systems, as these are known to exchange transducible components such as protons, ions, heat, light, electrons and mass as part of their catalytic mechanism (Foulds & Lowe 1985). The simplest are those whose catalysis requires or releases protons or other ions that can be coupled to an appropriate potentiometric sensor. In this type of sensor a local equilibrium is established at the sensor surface, thereby generating a potential proportional to the logarithm of the analyte activity and which is measured under conditions of zero current flow relative to an inert reference electrode also in contact with the sample. Potentiometric sensors do not perturb the analyte concentration because there is no net consumption of analyte, but do require rapid electrode kinetics and are susceptible to noise. The most widely developed potentiometric biosensors are enzyme electrodes, where an enzyme is immobilized over an ion-selective electrode (Kuan & Guilbault 1987). For example, the enzyme urease has been immobilized at a glass pH electrode and used to detect urea in clinical samples (Nilsson *et al.* 1973) and in meat products. Enzyme electrodes for the determination of glucose, urea, L-amino acids, penicillin and many other substances of clinical importance have been developed (Kuan & Guilbault 1987). However, miniaturization of enzyme electrodes is often a prerequisite for medical application and considerable effort has been directed towards this goal over the last few years. This has been achieved by using monolithic silicon microfabrication technology combined with appropriate enzyme-immobilization techniques to produce highly selective microsensors (Karube 1987). Enzyme-sensitive field-effect transistors (ENFETS) have been fabricated from ion-selective field-effect transistors (ISFETS) by applying a thin overlayer of enzyme-loaded gel on the ion-selective membrane (figure 1). Danielsson *et al.* (1979) first reported a urea-sensitive ENFET based on an ammonia-sensitive FET. Subsequently, ENFETS sensitive to penicillin (Caras & Janata 1980, 1985), glucose (Caras *et al.* 1985), urea (Miyahara *et al.* 1983), acetylcholine (Miyahara *et al.* 1983) and ATP (Karube 1987) have been developed. In most cases the ENFET is fabricated by immobilizing the enzyme in a matrix of cross-linked albumin, polyacrylamide or triacetyl cellulose overlaid on a standard silicon nitride gate insulator. In practice, a dual-gate pH-ISFET chip is normally employed so that one of the FETS can act as a reference for the ENFET when its gate is coated with an enzyme-free membrane. If the difference between the two drain currents is monitored, the signal is insensitive to changes in the solution pH, temperature or electrical noise as the reference FET and ENFET respond almost equivalently to changes in sample potential and only enzymatically generated pH changes are measured. The penicillin-sensitive FET responded in less than 30 s to penicillin concentrations in the range $10^{-4}$ to



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$10^{-2}$ M and displayed a lifetime of approximately two months. However, the small size of the active gate region of these devices allows immobilization of only relatively small amounts of enzyme and thus creates problems with determining antibiotic in samples containing high buffering capacity. Theoretical considerations would suggest that at buffer concentrations around $10^{-2}$ M, sensitivity to substrate concentrations significantly below $10^{-3}$ M would not be expected (Eddowes 1985).

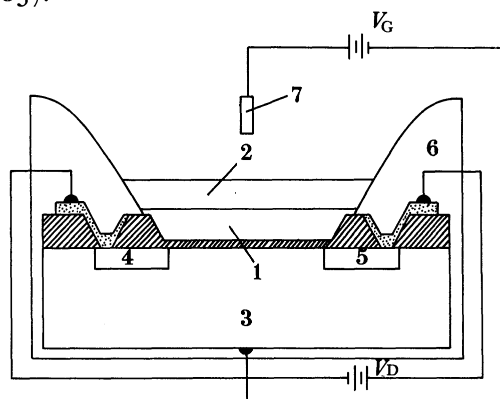


FIGURE 1. Diagram of a typical enzyme-sensitized field-effect transistor (ENFET) with (1) ion-selective membrane, (2) immobilized enzyme layer, (3) silicon substrate (*p*-type), (4) source (*n*-type), (5) drain (*n*-type), (6) insulating encapsulant and (7) reference electrode. $V_G$ and $V_D$ represent the gate and drain voltages respectively.

An alternative enzyme transistor configuration in which enzymes were immobilized in close proximity to a palladium-gated metal-oxide semiconductor field-effect transistor (Pd–MOSFET) has also been reported (Danielsson *et al.* 1979). When the device is exposed to hydrogen or gases such as $NH_3$ or $H_2S$, the gas is dissociated on the catalytically active palladium surface to generate hydrogen atoms which diffuse out to form a dipole layer at the Pd–$SiO_2$ interface. The response time of the device is in the order of seconds with a working sensitivity better than 1 p.p.m. $H_2$ or 10 p.p.m. $NH_3$ in air. The Pd–MOSFET has been exploited as a proximal sensor for the detection of $NH_3$ generated enzymically by urease, asparaginase, aspartase, glutamate dehydrogenase, adenosine deaminase and creatinine iminohydrolase on response to their respective substrates (Danielsson & Winquist 1987).

A major advantage of chemically-sensitized FETs is their small size and amenability to low production costs and multiplexing with microlithographic techniques. For example, recent work has shown the feasibility of producing monolithic multi-analyte ENFET biosensors with photolithographically patterned, enzyme-loaded polyvinylalcohol films, on a triple—function, silicon-on-sapphire (SOS) electrode array with an 'on-chip' pseudo-reference electrode for the simultaneous monitoring of $K^+$, urea and glucose (Karube 1987). Other approaches exploiting photoactivatable p-nitrophenylazides, photosensitized polyvinylalcohol and piezoelectric ink-jet devices have all been developed to fabricate active small-area enzyme membranes (Lowe & Earley 1984). However, despite these advances in technology, attempts to commercialize the enzyme-modified FET biosensors have been plagued by poor device sensitivity and response times and by prohibitively high encapsulation and fabrication costs. Present predictions of a $2 manufacturing cost per unit, even in high volume, may necessitate some creative marketing of this technology.

An alternative approach to enzyme biosensors exploits the oxidation or reduction of an electroactive species at an electrode surface. These current measuring or amperometric devices

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involve electron transfer from an enzyme substrate or product, coenzyme or the enzyme itself to the electrode surface. Amperometric techniques offer a wider scope of applications than potentiometric techniques and give a current response which is linearly dependent on analyte concentration, a normal dynamic range and a normal response to errors in the measurement of current (Albery *et al.* 1986). First-generation amperometric devices (figure 2) measured

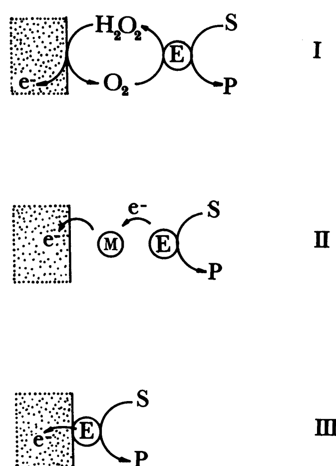


FIGURE 2. Evolution of amperometric electrodes. E is the enzyme, S and P its substrate and product respectively, and M is an electron-transfer mediator.

oxygen consumption or hydrogen peroxide production associated with the oxidation of substrates by their complementary oxidases. For example, the peroxide formed by the enzymatic oxidation of glucose by the flavoprotein glucose oxidase is normally detected by its electrochemical oxidation at a platinum electrode (Davis 1985). Unfortunately, first-generation devices based on natural oxidase substrates or products suffer from dependence on ambient oxygen concentrations and interference by contaminating electroactive species found in the sample at the high electrode potentials required for electron exchange. Second-generation devices have circumvented these problems by substituting for oxygen an artificial electron mediator that shuttles electrons from the biological component to the electrode. Such mediators should readily participate in enzymic redox reactions, exhibit rapid electron-transfer rates, be stable and non-toxic, be amenable to immobilization and exhibit appropriate redox potentials sufficiently removed from other electroactive species present in samples to avoid interference (Cardosi & Turner 1987). Ferrocene analogues largely satisfy these criteria and are able to shuttle electrons between glucose oxidase and a graphite electrode (Cass *et al.* 1984). The sensor requires less than 30 s to reach 95% of the steady-state current and exhibits a linear response over the concentration range 0.5–35 mM glucose. The electrode is relatively insensitive to interferants such as uric acid, L-cysteine, reduced glutathione and ascorbic acid likely to be present in undiluted whole-blood samples. This technology has now been developed into single-use disposable strips comprising printed carbon electrodes on a polyvinyl chloride support containing glucose oxidase, the mediator and a pen-like mini-potentiostat that gives a digital reading of the glucose concentration within 30 s. However, despite the effective commercialization of mediated-enzyme sensors, biosensor technology is developing so rapidly that third-generation devices capable of encouraging reduced enzymes to react 'directly' with

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the electrode itself are being researched. For example, conducting organic salts such as $NMP^+$ $TCNQ^-$ appear to be particularly suitable electrode materials for electron exchange with enzymes (Albery *et al.* 1986). However, concerns over the leakage of toxic mediators and electrode materials may limit the applicability of these devices for clinical applications. More recently, the entrapment of redox enzymes in electrically conducting organic polymers has been suggested as a means of promoting interaction between the enzyme and the electrode surface (Foulds & Lowe 1986). This technique of incorporating enzymes into electro-depositable-conducting polymer films also permits the localization of biologically active molecules on defined electrodes of any size or geometry. Initial studies have provided evidence that glucose oxidase may be incorporated into polypyrrole (Foulds & Lowe 1986) films electrochemically deposited on printed platinum electrodes, with the enzyme-catalysed oxidation of glucose being monitored by the oxidation of $H_2O_2$ at the electrode surface. The electrodes responded rapidly reaching a steady state within 20–40 s, and exhibit a current-limited enzymic response. Recent extensions of this approach have included the co-entrapment of mediators into the polypyrrole films by electrochemical deposition of polypyrrole co-polymers with pendant redox functionalities with glucose oxidase. *N*-Pyrrole ferrocene analogues were synthesized and electrochemically co-polymerized with pyrrole monomers at the electrode surface in the presence of enzyme (Foulds & Lowe 1988). This technique of enzyme deposition within redox-modified polymers provides an elegant means of producing reagentless enzyme electrodes that is particularly amenable to the fabrication of micro-amperometric devices. Alternatively, electron transfer from the redox centres of enzymes to electrodes may be promoted by chemical modification of enzyme with mediator analogues (Bartlett & Whitaker 1987; Degani & Heller 1987) or by covalent attachment of the flavin cofactor of an oxidase to an electron-conducting support such that the cofactor becomes an integral part of the electronic communication between the enzyme and electrode (Wingard & Narasimhan 1988). However, despite developments in the design, fabrication and operation of fully integrated amperometric biosensors, this approach is not universally applicable to analytes of interest as in many cases suitable redox enzymes are not available.

Two alternative measuring principles that are widely applicable to biological systems are the exploitation of changes in heat evolved or ionic conductivity produced by enzymic reactions. For example, many enzymic reactions produce or consume ionic species and thereby alter the overall electrical conductivity of the solution. The development and operation of an inexpensive, rapid and accurate micro-conductance biosensor that exploits the change in conductance by the catalytic action of enzymes immobilized proximal to a planar microelectronic conductance cell of defined geometry has been described (Watson *et al.* 1987). With a planar micro-conductance cell comprising serpentined and interdigitated metal tracks overlaid with immobilized urease, the device responds to any given urea concentration in buffer and serum samples with a typical accuracy of $\pm 1\%$. This approach is applicable to measuring substrates catalytically degraded by hydrolases, amidases, decarboxylases, dehydratases, esterases, proteases, kinases, phosphatases, sulphatases and various types of nucleases. Like conductimetric techniques, thermometric principles are applicable to a plethora of biological reactions, are largely independent of the optical or rheological properties of the sample and obviate any requirement for auxiliary enzymic reactions often required to generate a measurable end product. The enzyme thermistor is a relatively simple device for measuring the heat output when a sample solution is passed through a small immobilized



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enzyme reactor surrounding a thermistor (Mosbach & Danielsson 1981). The general detection principle offers flexibility in the choice of biological component and can be exploited for the measurement of metabolites, enzyme activities, immunological analytes, heavy metal and other pollutants and microbial activity. The commercial development of these latter devices has been limited to date, although their appeal as 'universal transducers' for a wide range of analytes should not be underestimated and research activity in this area, particularly with miniaturised devices, could lay the foundation for some exciting new products.

### *Immunosensors*

Enzyme-based sensors display inherent weaknesses associated with poor stability, selectively towards some key analytes and sensitivity when the analyte is present at suboptimal or very low concentrations. Under these conditions, highly selective and sensitive devices based on immunological recognition systems can be devised. Unfortunately, recognition and binding of antigens by antibodies is accompanied by few tangible changes in physico-chemical parameters and thus 'direct' sensing has proved difficult to resolve. In most cases, therefore, near-term devices comprising various enzyme-labelled immunoassays associated with end-product detection on appropriate transducers have been proposed (Lowe 1984, 1985; Aizawa 1987). Thus amplified enzyme-immunosensors based on potentiometric, amperometric, conductimetric, thermometric and optical detection of enzymic end-products have all shown promise for the detection of a range of analytes at concentrations as low as $10^{-15}$ M. However, although labelled immunosensor devices can currently achieve the desired sensitivity they are often cumbersome devices requiring several incubation and washing steps, although such criticisms can be overcome to some extent by careful configuration of the devices (Bradley *et al.* 1987).

The development of 'direct' immunosensors, which require only the addition of the sample to elicit a response, represents a challenging longer-term goal for single-use immunoassay. Early attempts at constructing an immunologically sensitized field-effect transistor (IMMUNOFET), where the surface charge generated by the interaction of the antigen with an appropriate antibody immobilized over the gate region of an FET is measured by the transistor, have not proved wholly promising (Blackburn 1987) despite the use of a number of novel membrane materials. Indeed, it is thought highly improbable that an immunochemically sensitive potentiometric sensor will ever be created in view of difficulties encountered in realising an ideally polarized interface at which measurements could be made.

In principle, direct immunosensing could be achieved by exploiting sensitive mass to frequency transducers based on piezoelectric materials. Piezoelectric crystals coated with thin films of selective adsorbent have found application as conventional gas and vapour detectors for several years. Similar principles have been exploited in attempts to develop a piezoelectric immunosensor in which ST-cut surface acoustic wave (SAW) crystals comprising interdigitated transducers between which was deposited goat (anti-human) IGg by covalent attachment to the silanized surface (Roederer & Baastians 1983). Significant changes in resonant frequency were noted on immersion in aqueous solutions and difficulties associated with non-specific protein adsorption and sensitivity were also experienced. Damping of crystal resonance in fluid media has been circumvented by the simple expedient of allowing adsorption to ensue in aqueous media and then air-drying the device before measurement of the resonant frequency, although such *ex situ* methods can be compromised by retention of solvent. However, although sensitivity may present problems in clinical diagnosis, these devices may offer promise in non-



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clinical markets, where sensitivity is far less critical. For example, the simplicity of SAW devices may be appropriate in the food industry for meat speciation, i.e. discrimination between meats from various animal sources.

Optical biosensors are receiving considerable attention in a number of research laboratories worldwide. Light-emitting diodes and photodetectors have been used to detect absorption, fluorescence or luminescence generated by a biological system (Lowe & Goldfinch 1988). However, such systems display limited sensitivity because the signal is proportional to the amount of biological material present. Optical sensors based on total internal reflectance offer a means of overcoming these limitations in sensitivity by increasing the measurement volume 'swept' by the interrogating light beam. For example, when light is reflected within a light guide, such as an optical fibre or planar wave guide, an electromagnetic wave, the evanescent wave, is generated in the optically rarer medium outside the guide. The evanescent wave penetrates only a fraction of a wavelength beyond the optical surface and can be used to interrogate immunological or enzymic reactions occurring at, or proximal to, this surface (Badley *et al.* 1987; Sutherland & Dahne 1987). However, although results so far warrant further exploration, difficulties associated with non-specific adsorption of proteins to the optical surface remain to be resolved.

Surface plasmon resonance (SPR) in a thin metallic film deposited on an optical carrier can be induced by an evanescent wave and is highly sensitive to variations in the refractive index of the medium immediately proximal to the metal surface. Excitation of surface plasmons in the metal film may be achieved either by coupling light through prisms (Liedberg *et al.* 1983; Flanagan & Pantell 1984 or via metallized diffraction gratings (Cullen *et al.* 1988) and can be used to detect immunological reactions at the surface of the metal.

## Perspectives and conclusions

It is now generally recognized that biosensors are likely to form a vital and necessary part of any future chemical-control system. This review has described sensor technologies being developed for a wide range of analytes of significance in the clinical, agricultural, fermentation, environment and defence industries. A clearer appreciation of the problems facing the development of biosensors and of future trends is now apparent. For example, the lability of biological systems and the uncertainty of measurements over extended time regimes is a matter of great concern for all types of biosensor, whether for *in vitro*, *ex vitro*, or *in vivo* application (Thompson & Krull 1984). The ubiquitous 'drift' in calibration results in unacceptable variations that cannot be tolerated in applications such as implantable systems. One solution to this problem would be to develop more stable biorecognition systems exploiting the fruits of chemical or genetic manipulation (Villafranca *et al.* 1983) or of developments in the synthesis of artificial enzymes (Ho & Rechnitz 1987). Alternatively, intelligent interfaces could be exploited to offset some of the current limitations of biosensors. The interface could perform data acquisition and control, implement intelligent algorithms and communicate via a network to the central controller (Thompson & Krull 1984). This system could be designed to recognize the performance characteristics of specific sensors, correlate, reject signals, compensate for interference and perform auto-calibration. The possibilities of fabricating a digital voter that will detect and eliminate a faulty sensor in an array of identical devices has already been reported (Flanagan *et al.* 1987).



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The concept of the 'intelligent' sensor acknowledges the fact that the majority of current sensors are insufficiently selective for effective use for certain analytes, but that judicious use of arrays coupled to analytical chemimetrics could provide pattern recognition and, thereby, a more precise analysis. Multiplexed multisensor devices could provide sufficient 'back-up' to provide reliable chemical intelligence *in vivo* or in fermenter. Finally, multi-analyte devices capable of monitoring a number of key metabolites simultaneously could provide complete diagnostic systems. A multifunction chip comprising an array of biologically sensitive electrodes on a monolithic silicon device a few square millimetres in size could, in principle, incorporate sufficient signal-processing capability to address each sensor in turn and assess the concentration of the analyte by comparing it with a calibration standard and then output the reading, date, batch code and operator code. Unfortunately, modern silicon microelectronics and optoelectronics is considerably in advance of the developments in biological recognition and surface chemistry required for the execution of these concepts. Thus recent advances in receptor technology employing membrane-embedded proteinaceous receptors could be exploited if the correct orientation of these systems could be achieved at the transducer surface. Interaction between the receptor and its complementary stimulant can generate a sudden and measurable ion flux across the membrane (Krull & Thompson 1985). Chemical amplification through the operation of ion-flux triggers is potentially a powerful sensing principle if it can be harnessed to a suitable transducer in a rugged and reproducible manner. Both these and direct immunosensors require orientation of biological systems in defined locations on appropriate transducers which are amenable to the manufacture of relatively low-cost, mass-produced devices. The production of such 'simple-to-use' devices inherently incurs high development costs, which in turn specifies the need for high volume markets. Nevertheless, given suitable time to mature, biosensor technology is eminently suited to satisfy the needs of 'alternate-site' testing.

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