

# Electrochemical Sensors

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The last fundamental review on this general topic was entitled *Dynamic Electrochemistry* and diverted significantly from the earlier series on chemical sensors by Janata in scope and content. The last chemical sensors review, which appeared in 1998, had made it already clear that modern electronic searching and abstracting tools were becoming so powerful and widespread that it no longer made sense to write comprehensive reviews on a large topic. Indeed, the electrochemical sensors section of that review alone covered already some 1000 references, which made it nearly impossible for the authors to write a truly critical review. It was therefore decided that future fundamental reviews in this series should be drastically more selective. This is a difficult task, as any authors of this series will invariably report on papers that caught their eye and that no longer represent a near-complete coverage of the literature.

We were asked to limit the number of references to about 200 and to write a review on electrochemical sensors and detectors. The topic is technically a subset of the last review, *Dynamic Electrochemistry*, which covered a great deal of fundamental electrochemistry (now a separate review) in addition to the sensor part. However, it also omitted the entire field of ion-selective electrodes, which to this day still comprises the largest field of electrochemical sensors. That field is now covered here.

It must also be noted that the entire area of chemical sensors is much larger than the electrochemical sensors discussed here. Optical, thermal, and surface acoustic wave sensors, for example, are all exciting areas of research that complement the field of electrochemical sensors and each other. We apologize, therefore, for any omissions that this drastic selection must have caused. There is excellent work on chemical sensors research going on that is not reported here.

It seems that much has changed in chemical sensors research in the past years. In many ways, it is one of the most fruitful, exciting, and interdisciplinary areas of research in analytical chemistry. Moreover, it appears that it is today also one of the most free-spirited fields, where new approaches and concepts are much more easily embraced and explored than just a few years ago. A good example for this change of mind can be seen in a list of titles of recent Gordon conferences on chemical sensors, where nearly everything but traditional chemical sensors research was presented. The embracement of new concepts and approaches certainly draws new blood and new ideas into an established field that welcomes renewal. However, one must not forget that chemical sensors are, at the end of the day, supposed to be useful devices that have to perform a near-automated chemical analysis task in a relatively complex sample. Perhaps too many researchers are quick to point out that some new concept could be used as a sensor, without taking the time to think it through. Organic chemists are today used to calling simple host molecules “sensors”, and bioanalytical chemists sometimes describe as sensors what used to be chemical assays. The concepts of selectivity, reversibility, detection limits, and ruggedness remain extremely important characteristics of any chemical sensor and should not be forgotten.

There are many directions in electrochemical sensor research that can be observed. Of course, the all-important trend in the physical sciences to go smaller is very evident with chemical sensors. Micro- and nanoelectrodes, and microtechnological approaches to manufacturing sensors, demonstrate the strong link between chemistry, physics, and engineering in this field. Integration into microfluidic platforms is just the latest, logical step in the miniaturization direction. On the other hand, the field of electrochemical sensors effectively interfaces with materials and polymer research, with organic chemistry and biological chemistry

for chemical recognition development, and with fundamental electrochemistry for answering mechanistic questions. All these developments are important and occur in parallel. Unfortunately, this extreme diversity makes it often difficult to find a common language between researchers that are involved in sensor research.

We searched the chemical abstracts and the science citation index databases as well as the table of contents of various journals to compile a library with a few thousand references. The patent literature, non-English articles, and simple conference proceedings were not included in that library. The final selection for this review was mainly done by hand, by selecting papers that are representative of a particular chosen subtopic. Therefore, as stated above, this review cannot have the claim of being comprehensive. It merely tries to offer some guidance in identifying interesting directions in modern electrochemical sensors research. We apologize if the reader finds that an important paper is not listed here. This review is structured into five sections: potentiometric sensors, voltammetric sensors, electrochemical biosensors, electrochemical sensors and detectors in fluidic systems, and electrochemical gas sensors.

### POTENTIOMETRIC SENSORS

The field of potentiometric sensors, or ion-selective electrodes (ISEs), has reinvented itself in recent years. It is a classical field of chemical sensors, which bridges fundamental host-guest chemistry (see ref *P1* for a review on calixarenes in sensors), fundamental membrane science, engineering (see ref *P2* for a review on microfabricated ISEs), and the specific application it targets. Recent retrospective reviews from researchers that have been active in this field for many years include that of Thomas (*P3*), Buck (*P4*), and Janata (*P5*). While previously regarded as a mature field where all important contributions had been made, it has recently been realized that there are a significant number of emerging directions that make research in this field quite exciting. A recent review summarizes sensor configurations with various nonclassical response mechanisms (*P6*), and another describes the recent breakthrough of lowering detection limits to ultratrace levels (*P7*). Recommendations were published on accurately reporting membrane selectivities of ISEs in order to avoid the large biases so often encountered in the past (*P8*). In addition, specific nomenclature, definitions, and conventions in the use of ISEs for blood electrolyte analysis were recommended (*P9*).

**Mechanistic Studies.** The reemergence of ion-selective electrodes as a strong research direction in the field of chemical sensors is due to a large part to their improved mechanistic understanding. This has made the field less empirical, and more effort is being spent on rationally predicting scientific results rather than on trial-and-error-based research. Most of the nonequilibrium models are mentioned in the section Low Detection Limits, so that mainly equilibrium response models and experimental studies of interest are discussed here. Unfortunately, advances in discovering selective host molecules (ionophores) are not discussed in this review. Their number would be too large to be adequately covered here.

The application of electrically charged ionophores has received significantly renewed attention in recent years. It was pointed out that the addition of ion exchanger of the same charge as the

primary ion, as often required for membranes with electrically charged ionophores, is not always beneficial for membranes containing a simple nonspecific ion exchanger (*P10*). On the other hand, an expanded equilibrium model was presented that offers a detailed look at the required concentration of anionic or cationic lipophilic ion exchanger in the membrane with respect to the charged ionophore concentration in order to achieve optimal membrane selectivity (*P11*). Such studies had been presented before for other, simpler systems, but this paper offers an increased level of detail and emphasizes the sometimes extreme complexity of the different equilibria that can exist in a hydrophobic ion-selective membrane. This general theoretical framework has been very useful in finally explaining why anion-selective membranes containing metalloporphyrins often show apparent super-Nernstian response slopes (*P12*), which was a long-standing problem in the field. The higher electrode slopes could be fully explained with the existence of an additional hydroxy-bridged dimerization equilibrium of the porphyrin. Indeed, picket fence-style porphyrins, where such dimerization is not possible for steric reasons, induced a Nernstian response slope. Similar studies were performed in different membrane matrixes, with analogous results (*P13*). Other authors described an interfacial study of ion-selective membranes containing metalloporphyrins by optical second-harmonic generation, with the purpose of correlating the protonation of the porphyrin in acidic samples to the potentiometric response to sample anions (*P14*). See ref *P15* for a review of this technique for ISEs.

In different work, the dimerization reaction of the neutral surfactant dodecyltrimethylamine oxide was used to explain an apparently double Nernstian response slope at certain sample pH values (*P16*). Other authors performed an X-ray spectrometric analysis of ISE membranes containing a mercury(II) ionophore to confirm the occurrence of  $\text{HgOH}^+$  in the membrane after contact with pH 7 samples, which was used to explain the apparent double Nernstian response slope of the membrane (*P17*). These mechanisms involved equilibrium reactions of the analyte, not of the ionophore as discussed above.

As an extension of earlier work on the lipophilicity of lipophilic ion exchangers, the lifetime of ISEs based on electrically charged ionophores was predicted (*P18*). The leaching rate was stated to be dependent on the ionophore lipophilicity, the complex formation constant, and the nature of the coextracting counterion.

A detailed study of ionophore-free ISEs in urine samples, with the original goal of measuring creatinine, revealed that a number of natural, electrically neutral lipids exist in such samples that easily extract into the membrane and interact with the analyte in an ionophore-like fashion, thus causing large potential drifts (*P19*). Such effects are only reduced if an ionophore is present in the membrane.

A simple method to determine complex formation constants and other important membrane processes directly in the membrane phase, originally described by others, was critically evaluated (*P20*). This so-called sandwich membrane technique fuses two membranes with different, known compositions together in order to obtain a concentration polarized ion-selective membrane. The resulting potential is dependent on the ion activity ratio at both membrane interfaces and was used to assess the extent of ion pairing in the membrane (*P20*), the complex formation

constants of 18 different ionophores in two different membrane materials (P21), and the ionic impurities of PVC membranes containing no added ion exchanger (P22). The complex formation constants compared well with data obtained earlier with other methods reported recently. This and other methods make it finally possible to quantitatively assess binding constants of novel ionophores in actual sensing membranes.

A chronoamperometric method, whose principle had been described earlier, was used to predict changes in the membrane composition of ISEs (P23). A large potential was imposed over the membrane, and the time upon which the current starts to decrease drastically was recorded. This method was reported to be useful to estimate residual lifetimes of ISEs utilized in routine analysis.

An impedance analysis was performed on ISE membranes before and after first contact with a primary ion solution (P24). This method of conditioning in an interfering ion solution was proposed earlier to measure unbiased selectivity coefficients. The results suggested that the interfacial transfer reactions are reversible for both the primary and the interfering ions and that the contamination of the sample solution with primary ions is the only reason for the lack of Nernstian response in interfering electrolytes, as originally proposed.

**Low Detection Limits.** The perhaps most surprising and innovative research direction in potentiometric sensors continues to be the dramatic improvement of the lower detection limit. It was now shown by scanning electrochemical microscopy that concentration polarizations indeed occur near ion-selective membranes measured under zero-current conditions (P25). In optimized membranes, such transmembrane ion fluxes are thought to originate primarily from counterdiffusion processes. Some ions are displaced from the sample side of the membrane by interfering ions, which leads to small concentration gradients across the membrane (for a review, see ref P7). These processes have been described theoretically for the steady-state case in a compact form and were used to accurately predict experimental detection limits of lead (P26) and cadmium-selective electrodes down to 10 parts per trillion (P27). The first paper also established for the first time that ion-selective electrodes can be used to assess lead concentrations in actual environmental samples at levels sufficiently below the action limit, and the results were compared quantitatively with concentrations obtained by ICPMS (P26). The knowledge from this research was utilized to demonstrate that detection limits of potentiometric titrations can also be significantly improved (P28). A surprising finding of that paper was that seemingly nonideal ISEs with super-Nernstian response slopes showed end points that were much larger and sharper than predicted classically.

It was shown that ISEs with low detection limits can also be fabricated for alkali metals by adding an ion-exchange resin to the inner solution of the membrane (P29). Ordinarily, low detection limit ISEs required a water-soluble chelator in the inner solution, which limited the types of ions for which the detection limit could be improved. Ion-selective membranes that showed apparent super-Nernstian response slopes because of strong ion fluxes in the direction of the inner solution were shown to be useful (P30). ISEs with step responses were fabricated without the need for reference electrodes, and the potential was found to change drastically only at critical sample activities.

Research continued to focus on the fine-tuning of low detection limit ISEs by applying a small current across the ion-selective membrane. Such constant-current (galvanostatic) systems were shown to yield detection limits down to the picomolar range (P31). These phenomenal detection limits were achieved by serial dilution experiments only, and it remains to be seen whether this method is sufficiently robust for the assessment of low concentrations in actual samples. In other work, it was recognized that rotating electrodes can be very useful in potentiometry if concentration polarizations near the membrane are relevant. The measuring range and detection limit of potentiometric polyion sensors was shifted to lower concentrations with increasing rotational speeds in complete agreement with established rotating disk theory and the response theory for polyion sensors (P32). It is expected that the use of a rotator will also decrease the detection limit of other ISEs, as demonstrated with ISEs using a wall jet configuration (P31).

Low detection limits were also reported to be drastically lowered in the case of chalcogenide glass membranes for the measurement of iron(III) in seawater (P33). However, that paper was disputed (P34), and it remains to be seen whether solid membrane materials will achieve the desired performance.

**New Materials and Concepts.** It is very well known that plasticized poly(vinyl chloride), used so often as membrane material in ion-selective electrodes, has a number of disadvantages, and research has intensified to obtain alternatives. Different methacrylic-acrylic copolymers were synthesized by free-radical solution polymerization and photopolymerization to provide glass transition temperatures well below room temperature (P35). Such polymers required no plasticizer and were shown to be fully functional. They present a viable platform for the covalent immobilization of ionophores, as demonstrated by the incorporation of different acrylic crown ethers (P36). In a parallel approach, a methacrylic sodium-selective calix[4]arene ionophore was synthesized and covalently immobilized onto a methyl methacrylate-isodecyl acrylate polymer matrix requiring no plasticizer (P37). The sensor characteristics were essentially identical to that of plasticized PVC containing the dissolved ionophore but the lifetime was significantly increased.

Ion-selective electrodes based on sol-gel membranes were developed with encapsulated valinomycin or bis(crown ether) derivatives (P38). The size of these membranes could be increased by using solid-state filter materials as membrane support. The study also showed that the sol-gel could be chemically functionalized with alkoxysilylated bis(crown ether) derivatives as covalently immobilized ionophores.

Liquid crystalline materials were evaluated for the fabrication of ion-selective membranes. A liquid crystal ionophore for ammonium showed superior potentiometric properties with a non-ionophoric liquid crystal material as plasticizer, suggesting that a liquid crystalline phase is retained at room temperature (P39). Such materials have promise because of the way liquid crystals can be manipulated and switched, as also suggested by a different study incorporating ionophores into liquid crystalline materials (P40). Another report described that semiconductor materials such as InAs, InSb, and GaAs may be useful as indicator electrode materials in the determination of chlorides and sulfates by potentiometric titration (P41).



The concept of molecular imprinting appears to be difficult to implement in potentiometric sensors. One paper reported the use of imprinted titanium oxide thin films to detect chloroaromatic acids with ISFETs (*P42*). While the reported selectivities appeared to be impressive, the detection limits were poor, the response times slow, and the electrode slopes severely sub-Nernstian.

The development of ion-selective electrodes with reduced thrombogenicity continued to receive significant attention, since a truly biocompatible material is essential for reliable in vivo applications (for a review, see ref *P43*). One report described a layering strategy, by coating ion-selective membranes with a known biocompatible phosphorylcholine polymer (*P44*). The coating appeared to leave the original sensor properties intact. In another study, a commercially available silicone-modified segmented polyurethane was evaluated as membrane material of improved biocompatibility, with promising results (*P45*). One should note the innovative approach of using nitric oxide-releasing materials in the development of sensors with improved biocompatibility. While potentiometric sensors based on this technology had been presented earlier, an excellent study with an amperometric oxygen sensor was reported recently (see *Voltammetric Sensors*) (*V28*).

An improved dissolved CO<sub>2</sub> gas sensor was proposed by the groups of Cha and Nam (*P46*). The sensor principle was related to the well-known Severinghaus-type electrode, where the pH change of an inner electrolyte separate from the sample by a CO<sub>2</sub> gas-permeable membrane is measured. Here, however, the gas-permeable membrane was pH sensitive by itself, a concept originally introduced by Meyerhoff for the design of a dual lumen catheter that could simultaneously measure pH and pCO<sub>2</sub>. This paper further improved the CO<sub>2</sub> response characteristics by introducing an enzyme into the inner solution that enhanced the CO<sub>2</sub> rehydration after membrane transport. These chemical principles were combined into a microfabricated electrode configuration, with good results.

**Solid Contact.** The development of ion-selective electrodes with a solid inner contact instead of an aqueous electrolyte has been a topic of research for many years. Historically, so-called coated wire electrodes with a simple metal–membrane interface without any well-designed potential stability were known to exhibit potential drifts. A mechanism for this apparent instability has now been proposed to come from changes in the electrolyte composition of a water layer between the metal and the membrane (*P47*). Indeed, potential–time profiles were in good agreement with theoretical expectations, and the potentials became stable if a hydrophobic monolayer was deposited onto the metal, which suppressed the water film. In a different study, the carbon dioxide interference of solid contact electrodes was reexamined (*P48*). The CO<sub>2</sub> interference was found to be largest with pH-sensitive membranes backside contacted with a pH-insensitive metal (Ag/AgCl) or with pH-insensitive membranes backside contacted with a pH-sensitive metal such as Pt. These findings are again in agreement with the formation of an intermediate water layer that can change its pH upon exposure to CO<sub>2</sub>. Only if both materials are pH sensitive or insensitive, is the net effect small.

The most commonly used stable solid contact materials are conducting polymeric materials such as poly(pyrrole) (*P49*) or

poly(thiophene) (*P50*) that act as ion-to-electron transducers. An interesting low-frequency current-reversal chronopotentiometric experiment revealed that such layered membranes can be adequately simulated with a RC equivalent circuit by using the resistance of the ion-selective membrane and the capacitance of the redox polymer (*P51*). Other groups utilized a single redox membrane material, poly(pyrrole), that may act as the ion-selective membrane and the solid contact at the same time (*P52*). The polymer was doped with a calcium ionophore and exhibited useful response in potentiometric calcium titrations. This research could have important implications, as such polymers can be easily fabricated on metal electrodes by simple electropolymerization. Consequently, some authors have a profound interest in studying the ion- and electron-conducting characteristics of the redox polymer itself (*P53*), since the resulting sensors may exhibit redox-sensing characteristics as well. In this context, the evaluation of an all-solid-state electrode array deserves mention (*P54*). The authors used a polyurethane-based reference element, together with a number of indicator membranes, cast onto a patterned array of metal electrodes. While the reason for the apparent functioning of the reference electrode remains unknown, the array appeared to give functional responses to five different electrolytes commonly found in blood.

## VOLTAMMETRIC SENSORS

Dynamic electrochemistry is a well-explored, very versatile transduction principle for chemical sensors. Most biosensors and flow detectors, discussed below separately, also belong to this group. Some reviews on this topic include a general voltammetry retrospective (8 references) (*V1*), voltammetric detection without added electrolyte (48 references) (*V2*), stochastic sensors (54 references) (*V3*), sol–gels for electroanalysis (48 references) (*V4*), ultramicroelectrodes for environmental analysis (53 references) (*V5*), remote sensing in environmental analysis (20 references) (*V6*) and aqueous metal ion analysis (269 references) (*V7*), general scanning probe microscopy (130 references) (*V8*), scanning electrochemical microscopy (128 references) (*V9*), ion conducting polymer based sensors (46 references) (*V10*), silicate materials for electroanalysis (246 references) (*V11*), and the microfabrication of electrochemical sensors (171 references) (*V12*).

**New Concepts.** Most chemical sensor research in the past has focused on the accurate assessment of concentration or activities of analytes. Janata has recently proposed an entire different approach, by showing that the oscillating concentrations of an analyte in a flowing stream originating from a point source can provide valuable information (*V13*). This principle is thought to play a major role in how aquatic animals find food, such as sharks circling about or crabs possessing multiple sensoric elements on their moving legs. This “chemical plume tracking” research analyses the frequency response of chemical sensors. It appears that higher harmonics in the coherence spectra depend on the distance from the plume source (*V14*). A virtual plume instrument was constructed to mimic the flow conditions in a real chemical plume. This research approach fundamentally challenges the way we think of chemical sensor applications, and it can be expected that more work continues in this interesting direction.

A multianalyte detection concept for electrochemically silent analytes was recently proposed on the basis of the underpotential

deposition and stripping of halides onto gold electrodes containing a silver adlayer (V15). Each halide possesses a characteristic, sharp, underpotential deposition potential onto the Ag adlayer, and the current–potential relationship could be used to identify the type of halide and its concentration. Consequently, this technique allows one to perform multianalyte analysis as long as the electrode surface is unsaturated (submonolayer coverage). While this method is interesting, one must note that the measuring range is very limited (no calibration curve was shown) and that the method will fail in the presence of a high concentration of any of the halides.

An unusual chemical sensors method reminding one of the early work of Rechnitz is the so-called electrochemical cell–substrate impedance sensing method introduced a few years ago that was further developed for the monitoring of live insect cells (V16). Insect cells were cultured in tissue culture wells, which contained small, optimally coated gold electrodes on the well bottom. An impedance analysis of the electrodes showed important changes as a function of the motion and metabolic activity of the attached insect cells. An inhibition assay for host toxins (explosives) was successfully performed with this principle, suggesting that this method could also be used for the screening of such compounds.

**Stochastic Sensing.** Stochastic sensors are an emerging direction based on single-molecule counting events. Typically, a steady current originating from ion transport across a single nanotube (single-channel current recording) incorporated in an otherwise nonpermeable membrane is perturbed by blocking events coming from large molecules. The frequency of these measured events can be related to the concentration of the blocker, and sometimes the signature of each event can reveal its identity. Few, if any reports have attempted experiments in real biological samples, but this research is exciting and interesting applications will surely emerge soon.

An innovative approach to selective stochastic sensing utilized polymers containing molecular recognition elements that can interact with single pores (V17). The rate of threading of the polymer through the pore was dependent on its free solution concentration, which in turn changed with the analyte concentration. The utility of this technique was demonstrated with two different proteins that could be simultaneously detected. While this work utilized polymers dissolved in solution, it can be expected that the sensitivity of the method could be greatly increased with polymers that are covalently attached at or near the pore. Perhaps as a precursor to such a system, seven staphylococcal  $\alpha$ -hemolysin subunits were combined to a stable heptamer, and a 500-Da poly(ethylene glycol) chain was covalently attached within the channel lumen before assembling it into a lipid membrane (V18). Rather unexpected long-lived negative current spikes were observed in that work, however.

A related direction by the group of Martin utilizes chemically modified nanotubular membranes. These are not stochastic sensing devices because of the large number of tubules, but the membranes show molecular size and shape selectivity. One work described the deposition of gold nanotubules within the pores of a polycarbonate template membrane (V19). Coating of the gold surface with L-cysteine by simple chemisorption rendered the

membrane permselective. At low pH, anion transport was observed, while at high pH, the membrane became cation permeable. Owing to the small inside diameters of the pores, the selectivity of the membrane also depended on the molecular size of the ions.

**Miniaturization.** A gold-coated microelectrode array integrated into a portable field instrument was developed and characterized for on-site arsenic detection in well water (V20). Arsenic detection remains indeed a very important problem in a number of countries, where millions of people are subjected to arsenic poisoning from drinking water wells. This sensor array was operated with square wave anodic stripping voltammetry and was only sensitive to As(III), one of the more abundant arsenic species. It showed a number of interferences from heavy metal ions, especially at levels that exceeded the arsenic concentration. Actual arsenic measurements in water samples produced data that were in good correspondence with established techniques.

A new method for the fabrication of carbon fiber nano- and microelectrodes was reported (V21). It involved flame etching of the tip to yield a smooth glass/fiber interface, thereby increasing signal to noise in the resulting cyclic voltammograms. On the other hand, advanced photolithography was used to make interdigitated microelectrode arrays that can pass higher currents and exhibit faster response times (V22). This was achieved with a small interelectrode distance and a large active surface area.

Silicon-based microelectrodes are potentially very attractive because of the ease of fabrication with existing microfabrication technology. Unfortunately, their long-term stability has not proven useful thus far. A paper reports on the systematic study of microelectrode arrays with varying electrode shapes, sizes, and coatings and discusses the optimal configurations to achieve acceptable lifetimes (V23).

**In Vivo Sensing.** In continuation of earlier excellent work in this area, carbon fiber microelectrodes were used to measure dopamine release from individual neurons (V24). Identification of the target cells was possible by the coexpression of a detectable marker protein, alkaline phosphatase. The discrete dopamine quantities from the transient concentration spikes at the cell surface, believed to originate from small vesicles, were quantified at about 52 zmol/spike in average. In other work, carbon fiber electrodes were coated with overoxidized poly(1,2-phenylenediamine) for the simultaneous detection of nanomolar concentrations of dopamine and millimolar levels of ascorbate (V25). A number of potentially interfering species were tested, without any effect on the response.

Nitric oxide continues to excite electrochemists. A microelectrode for the in vivo determination of NO was developed with a modified Clark-type electrode design with a 10- $\mu$ m tip diameter (V26). For ease of miniaturization, the reference electrode was placed coaxially around the working electrode tip, and a thin double membrane layer was used to eliminate interferences from ionic species. The utility of this electrode was demonstrated in vitro and in vivo by acetylcholine stimulation of endothelial cell NO release. A similar design was proposed by the group of Gratzl (V27). In that work, a simple Clark-type NO sensor with a cellulose acetate coating was characterized for in vivo NO sensing. To improve selectivity and stability, a differential amperometry protocol was adopted. Nitric oxide release rates of activated macrophages were subsequently determined. On the other hand,

the group of Meyerhoff showed that nitric oxide-releasing compounds embedded in the gas-permeable polymeric coatings of oxygen-sensing catheters rendered the sensing much more thromboresistant (V28). While the sensor performance was shown to be unaltered by the presence of the NO-releasing compound, a much superior analytical accuracy was demonstrated in vivo, followed by reduction of thrombus formation on the sensor surface. This elegant method of using the in vivo characteristics of nitric oxide has the potential of finally solving the long-standing biocompatibility problem of in vivo chemical sensing.

In view of the development of an improved insulin sensor, the catalytic properties of iridium(IV) were studied and used to fabricate an insulin-selective electrode by plating a glassy carbon electrode with an iridium oxide surface film (V29). The catalytic activity was ascribed to a combination of electron- and oxygen-transfer mediation by the film. Detection limits were found to be 20 nM in flow injection analysis. A combination dual needle-type sensor for the simultaneous detection of glucose and insulin was described that was based on modified carbon-paste working electrodes (V30). The glucose-sensing carbon paste contained glucose oxidase as catalyst, while the insulin probe contained ruthenium oxide. No cross-talk between the two sensor signals was observed in mixed solutions, and the configuration appears to be very promising for the detection of insulin/glucose ratios in diabetes patients. This paper is one example on how the selectivity of carbon paste electrodes can be chemically tuned by adding suitable biological and chemical catalysts to the paste material.

**Environmental Analysis.** Stripping voltammetry has been very successful for trace metal analysis in seawater samples, partly because of the high ionic strength of this medium. An excellent example of careful work in this area reports on the catalytic cathodic stripping voltammetry of iron in seawater, which yielded picomolar detection limits in situ (V31). While the experimental setup utilized a mercury drop electrode, which is fairly standard, the work stands out from the uses of a ligand, 2,3-dihydroxynaphthalene and a catalyst, bromate, in the sample. The ligand brought the reduction wave of adsorbed iron(III) to iron(II) into a range where sample interferences were no longer a problem, and the catalyst continuously reoxidized the iron(II) at the electrode surface. This yielded 300-fold larger currents than uncatalyzed stripping voltammetric analysis. Electrode deposition times could therefore be kept to just 60 s.

The group of Buffle has characterized mercury-plated iridium-based microelectrode arrays covered with a gel layer for speciation measurements in natural waters (V32). While the detection mode was the established anodic stripping voltammetry, the gel layer on the electrode surface was used to distinguish freely dissolved metal species from colloidal particles. The same array design was also used in a clever way to assess concentration profiles of Pb(II) and Tl(I) at liquid/liquid and liquid/solid interfaces, in one measurement without repositioning the sensor array (V33). The spatial resolution was as small as 200  $\mu\text{m}$ . Traditional profiling measurements had to be done by continuously changing the position of one single microelectrode, leading to long reequilibration times and possible perturbations after each translation.

A less toxic alternative to mercury thin-film electrodes, which are so widely used in stripping voltammetry, was presented with

bismuth film electrodes (V34). The bismuth layer was deposited on glassy carbon electrodes, and stripping voltammetry of cadmium, lead, thallium, and zinc was performed in nondeaerated solutions, giving well-defined stripping peaks with nanomolar detection limits. These early results suggest that this may be an environmentally attractive alternative to mercury film electrodes.

The quest of introducing additional chemical selectivity to voltammetric heavy metal analysis is well described by the group of Mandler (V35). This paper critically compares two different approaches to host-guest recognition at electrode surfaces, one based on selective monolayers on the electrode surface, the other on a ion-exchange polymer containing molecular host compounds. While the sensitivity of monolayers was better, the ruggedness of polymeric coatings made it a superior choice for routine use.

**Host-Guest-Based Sensing.** Ferrocene-derivatized calix[4]-arene ligands were synthesized and characterized in view of lanthanide ion sensing (V36). The sensing principle relied on the anodic perturbation of the ferrocene-ferrocenium redox couple upon binding to the metal ions. The studies remained fundamental, however, with no immobilization or actual sensor application reported. A similar principle was exploited by the introduction of redox active monolayers composed of calix[4]arene-disulfide-diquinone units (V37). The calixarene was found to be highly selective for barium ions, with a 500-fold preference over calcium in separate solution experiments. The voltammetric behavior of the modified electrode was found to be dependent on the barium concentration in the sample. The sensor is expected to be sensitive to barium concentration changes only at low concentrations, where the surface coverage of barium on the monolayer remains unsaturated.

Aromatic ureas were detected by modulation of the redox behavior of phenanthrenequinone electropolymerized as a pyrrole derivative onto a metal electrode (V38). The selective detection of the urea compounds was explained by a strong hydrogen bond formation with the redox-dependent receptor. While significant loss of material was reported, the urea-dependent half-wave potential shift was found to be independent of electrode coverage. Polythiophene polymers incorporating cone and partial cone bridged calix[4]crown ethers were prepared on platinum electrodes and characterized for the redox-mediated sensing of alkali metals (V39). The films showed high sodium ion selectivity in acetonitrile solutions, demonstrating that the redox behavior of the film could be altered by selective recognition of sodium ions by the calixarene units. In a related approach, metal(III) deuteroporphyrins functionalized with pyrrole groups were electropolymerized and found to electrocatalyze dioxygen and benzoic anhydride (V40). Feasibility of using such systems as molecular recognition-based sensors was demonstrated with cyanide ions that interacted with Fe(III) porphyrins and changed the redox behavior of the film.

**Electrocatalysis.** A chemically modified electrode for the detection of L-methionine and insulin was reported (V41). The analytes were detected anodically, mediated by a ruthenium(II) dendrimer incorporated in a multilayer assembly on a glassy carbon electrode. The sensitivity was found to be linearly dependent on the number of ruthenium dendrimer layers, and the detection limit for insulin detection was found to be 2 nM.



Microelectrodes coated with a Nafion-entrapped  $\text{SiO}_2$  composite were shown to be useful in the speciation of the  $\text{Re(I)}/\text{Re(II)}$  redox couple in solution (V42). While faster scan rates were possible at unmodified carbon fiber electrodes, the detection limits were found to be 4 orders of magnitude smaller with the coating, owing to the preconcentration of the  $\text{Re(I)}$  complex by the composite material.

It was demonstrated that electrochemically anodized diamond film electrodes can be used for the selective measurement of uric acid in the presence of up to a 20-fold excess of ascorbic acid (V43). The oxidation peaks of the two species were found to be about 0.5 V apart with this electrode material, and the detection limit was  $\sim 10^{-8}$  M.

**Ion-Transfer Voltammetry.** More researchers find interest in exploring electrochemical sensors based on ion-transfer voltammetry, also called electrochemistry at the interface of two immiscible electrolyte solutions (ITIES). In this system, the transfer of an ion from an aqueous to an organic phase is induced by the application of an external potential. The current associated with the ion-transfer process is often proportional to the sample concentration and can be mediated by the presence of a selective complexing agent (ionophore) in the organic phase. The beauty of this method is that nonelectroactive analytes can be measured directly, without having to undergo a redox reaction. This is an established method since the days of Koryta, and current research aims at making organic materials more rugged for routine use and introduce microchannels for higher sensitivity, in complete analogy to the advances of metallic microelectrodes.

One approach in view of the mass production of precalibrated ion-transfer voltammetric sensors used an internal solid contact of high surface area to avoid concentration polarizations at the inner side (V44). The sensors were fabricated into single-use test strips and otherwise functioned in complete analogy to classical electrochemical systems. Stripping voltammetry was demonstrated on these devices and proposed as a nontoxic alternative to mercury film electrodes.

A very sensitive ion-transfer voltammetric method was proposed for the detection of simple salts in flow injection analysis (V45). While the principle of detection was the same as in other ITIES systems, the detection limit could be drastically lowered by utilizing an array of microinterfaces containing a gellified organic solvent and by avoiding a background electrolyte in the aqueous stream (the selectivity of the detector is not high). Interestingly, the authors found that the best linearity and lowest detection limits were found with a double pulse amperometric approach, by stepping the potentials to values that lead to the consecutive extraction of anions and cations into the organic phase. The associated differential current gives information on the electrolyte concentration and appears to be quite applicable in single-salt solutions, such as in ion chromatography eluents. Nominal detection limits were cited to be extremely low (1 ppt), but the method is likely useful down to low-ppb levels.

Anion sensing and recognition remains a challenging task because of the limited availability of suitable molecular guests for anions. An unusual mechanism for the indirect amperometric anion sensing with ITIES was reported by the use of a dual ionophore system (V46). The potassium-transfer wave for an organic phase containing a potassium and a nitrate ionophore was

found to increase with higher nitrate concentrations in the sample. While this phenomenon was explained with a lowered effective Gibb's energy of transfer for potassium by nitrate, it seems likely that spontaneous (zero current) coextraction of the potassium nitrate salt rendered the interface less polarizable and thereby modulated the potassium uptake wave. Such an effect should perhaps be rather considered an interference than an interesting new mechanism, but future work will show what this concept holds.

Ion-transfer voltammetric sensors consist of two Nernst diffusion layers for each interface, since the transfer of an ion leads to its depletion at the sample side and its accumulation on the organic-phase side. Ordinarily, the sensor is operated in a way that the observed current is given by limited mass transport from the sample to the interface, in complete analogy to metallic voltammetric electrodes. A recent paper explores organic phases of high viscosity (and therefore smaller diffusion coefficients) to give current responses that are limited by mass transport from the interface to the organic bulk (V47). It was shown that such a technique reveals a great deal of detail about ion transport and complexation in the organic phase and may yield devices that have characteristics more akin to potentiometric than amperometric sensors. Multianalyte detection capability was demonstrated via a multipulse detection mode and its functioning was directly compared to that of ion-selective electrodes.

An interesting electrochemical method for the very sensitive detection of hydrazines was reported, by the use of supported bilayer lipid membranes incorporating DNA strands with a lipophilic tail (V48). The detection occurred via a transient current signal, or spike, which was evidently caused by a short disturbance of the ion transport properties of the bilayer. The mechanism for hydrazine detection was not completely understood, but while the DNA provided orders of magnitude improvement in detection limit (to sub-ppb levels), it did not appear to selectively bind the hydrazine. Different hydrazines were found to give current spikes at different times, and this feature allowed the researchers to accurately assess the concentrations of hydrazines in sample mixtures. Many possible interferences were shown not to be problematic, but peptides and lipids had to be removed prior to analysis.

**Combined Electrochemical/Spectroscopic Sensing Systems.** Spectroelectrochemical sensing as a multimode sensing strategy is being pursued by the group of Heineman. The main concept of this research is to achieve improved sensing selectivity by combining different chemical strategies into one single device. Earlier papers demonstrated the combined power of electrochemical control, the chemical selectivity of surface coatings, and the spectroscopic selectivity of optical detection into one device. An extension of this direction involves the use of a chemical mediator for the detection of optically silent analytes (V49). Electroactive mediators are long established in biosensor devices, and here ruthenium(II)tris(2,2'-bipyridyl) embedded in an electrode surface layer was used to mediate the redox reaction of ascorbate at the electrode. Since the ruthenium complex has different optical properties in its reduced and oxidized form, the presence of the ascorbate analyte was found to modulate the absorbance changes of the mediator in a cyclic voltammetric scan. The price of this approach is that any substance that can interact with the mediator

can cause a serious interference, and therefore, much of the elegance of the multimode sensing approach may be lost in this case. In another work by the same group, planar waveguide technology was reported for this spectroelectrochemical sensing approach (V50).

Electrically conductive diamond thin films were introduced as a new type of optically transparent electrode materials for spectroelectrochemical sensing applications (V51). The material was found to be optically transparent from ~225 nm to at least 1000 nm. Basic spectroelectrochemical experiments were conducted to illustrate the utility of the material.

Low-cost screen-printed electrodes were utilized to generate luminol electrochemiluminescence, the extent of which was limited by the availability of the reactant hydrogen peroxide in solution (V52). This principle was used to optically detect choline in the presence of choline oxidase as a model system, which produced hydrogen peroxide and hence changed the light intensity produced at the electrode. It was argued that this strategy, although electrochemically controlled, eliminates many interferences suffered by classical electrochemical sensors. A related strategy, but within a more classical electrode housing shielded from ambient light, involved the coating of a platinum electrode with a silica gel membrane containing Ru(II)2,2'-bipyridyl as electrochemiluminescent material for the detection of oxalic acid and amino acids (V53). A sensitive detection of chlorpromazine, which is a coreactant in the electrochemiluminescence reaction of tris(2,2'-bipyridine)ruthenium(II), was accomplished by selective preconcentration of the analyte onto a lauric acid-modified carbon paste electrode followed by electrochemiluminescence detection (V54). Detection limits were close to nanomolar concentrations. The method was successfully used for the detection of chlorpromazine in urine, with a 10-min measuring time. A careful fundamental study in the long series by Bard examined the effect of electrode surface hydrophobicity on the electrochemiluminescence of the same compound involving the coreactant tripropylamine (V55). Light intensities were found to increase drastically with hydrophobic surfaces, which was explained by an increased anodic oxidation rate of the coreactant at the electrode.

**Electrochemical Microscopy.** Spatially resolved chemical analysis, or chemical microscopy, continues to be an extremely important direction in analytical chemistry. In the long series of excellent papers by Bard on scanning electrochemical microscopy, recent work utilized a voltammetric potassium ion-selective micropipet (see voltammetric ion transfer sensors above) to map the potassium concentration gradients at a bilayer lipid membrane containing potassium channels (V56). This careful work demonstrates that a wide variety of electrochemical sensing principles can be utilized for chemical imaging purposes.

The long-standing problem of maintaining a constant substrate distance in scanning electrochemical microscopy has been addressed by the group of Wipf by applying an additional high-frequency ac voltage to the scanning microelectrode (V57). The resulting high-frequency ac current, which was shown to depend on the distance between tip and substrate, could easily be separated from the low-frequency chemical imaging signal by filtering. The distance information was used in a feedback control

to maintain a constant distance of the imaging electrode from the substrate.

The same general problem of distinguishing topographic and chemical information was addressed by the use of combined scanning electrochemical microscopy and atomic force microscopy (AFM). The AFM mode was used to assess topographic information, while the same probe, with the platinum metal only exposed at the cantilever tip, acted as the imaging microelectrode. Constant distance imaging functioned serially, by first acquiring a topographic image in contact mode AFM and then using that information to perform chemical imaging at a fixed distance from the substrate. A step further from this sequential approach appears to be the integrated ultramicroelectrode at a fixed distance from an AFM cantilever tip (V58). Here, topographic and electrochemical imaging could be performed at the very same time.

A powerful approach to chemical imaging was described by the group of Umezawa, by utilizing scanning tunneling microscopy with chemically modified tips (V59). Rather than relying on an electrochemical reaction at the surface of a microelectrode, as in the works described above, the chemical information is obtained from a distinctive chemical affinity between the imaging tip and the substrate that alters the tunneling current. Gold tips that were modified with 4-mercaptopyridine were found to image porphyrins on surfaces differently if they contained a Zn(II), a Ni(II) metal center, or no metal at all. The mechanism was explained by facilitated electron tunneling upon metal coordination interactions with the substrate. Unlike electrochemical microscopy, this technique provides atomic resolution and has the promise to become a very powerful method for fundamental chemical studies at the molecular level.

Electrochemiluminescence is known to be a promising approach to microscopic imaging, since the light can be very locally generated at the imaging microelectrode tip in complete analogy to near-field microscopy, but without a conventional light source. A recent paper has shown that the electrochemiluminescence from the imaging fiber can be made selective for NADH and, hence, yield spatially resolved chemical information for such an analyte (V60). Of course, the issue of distinguishing chemical from topographical information needs to be addressed here as well.

**Reference Electrodes.** The tremendous challenge of realizing microfabricated reference electrodes is illustrated in a paper by Nann and Urban (V61). A previously reported so-called dynamic hydrogen reference electrode was tested and improved in view of its miniaturization and incorporation into flow cells. The rather unusual reference electrode was subjected to a constant anodic current, which eliminated most of the pH dependence in the range of pH 4 and 10. This was explained by the creation of a locally constant pH environment by the electrode reaction. However, phosphate, sulfate, and even nitrate caused potential changes of up to 400 mV in some cases, and the use of a hydrogel coating was needed to alleviate influences of flow rate on the potential.

## ELECTROCHEMICAL BIOSENSORS

The biosensor field continues to advance at an accelerated pace. Devices are now being used with some success in clinical chemistry, food industry, and environmental fields. It is clear that the overall trend in the research literature continues to center around new chemical strategies and performance issues as



evidenced by the large number of publications dealing with required high specificity, high sensitivity, rapid response, and flexibility of use. Attention for sensors based on DNA interactions continues as the selectivity and robustness of nucleic acid chemistry spurs enormous promise in the advancement of the diagnosis of genetic diseases, the detection of infectious agents, the measurement of differential genetic expression, forensic science, drug screening, and environmental monitoring. Much attention goes also to combining chemical and biological approaches to technological advances in the fields of micromachining and microfabrication techniques, which has led to single-use disposable devices, sensing arrays, or more sophisticated devices capable of fully integrating multiple analytical processes. A recent technical report from two IUPAC divisions (*B1*) recommends definitions and classification of electrochemical biosensors since this is an increasingly diverse field that continues to grow. Interesting reviews include enzyme-based biosensors (114 references) (*B2*), capacitive biosensors (57 references) (*B3*), creatinine biosensors (24 references) (*B4*), analytical aspects of biosensors (150 references) (*B5*), invasive glucose biosensors (85 references) (*B6*), a glucose sensor retrospective review (33 references) (*B7*), and electrochemical DNA sensors by Palecek et al. (39 references) (*B8*) by Wang (45 references) (*B9*), and by Takenaka (59 references) (*B10*). Stochastic sensors are mentioned in the voltammetry section above.

**Enzyme-Modified Electrodes.** With much attention being placed on enhancing the reproducibility and stability of the electrode surface, several reports focused on enzyme immobilization methods and electrode assembly of the biocatalytic layer. Darder et al. (*B11*) reported the incorporation of membrane-bound dehydrogenases (D-fructose, D-gluconate, and cytochrome  $b_2$ ) into an octyldithionitrobenzoic layer chemisorbed on gold electrodes. The chemisorbed layer, composed of a long chain in a short-length thio acid, provides an electrostatic and hydrophobic environment that appears to stabilize the enzyme-bound membrane. A fructose sensor employing this approach showed a significantly stable catalytic signal for at least 25 days and was used for the determination of fructose in citrus juice with negligible interference from ascorbic acid. Sung and Bae (*B12*) reported the incorporation of a poly(2-acrylamido-2-methylpropanesulfonic acid)-conjugated glucose oxidase as a dopant during the electropolymerization of a polypyrrole conducting film. The enzyme maintained its activity after conjugation, and the electrode displayed a sensitive amperometric signal toward glucose concentrations up to 20 mM, with response time of less than 30 s at low applied potentials. Electropolymerization of polypyrrole was also used in the presence of coenzyme pyrroquinoline quinone to construct a sensor for the detection of thiols (*B13*). The electrochemical properties of entrapped coenzyme in the PPy film were influenced by the applied potential during electropolymerization, and as in the previous case, the sensitivity depended on the thickness of the film. Both parameters could be optimized to yield stable and reproducible responses for the determination of cysteine, homocysteine, penicillamine, N-acetylcysteine, and glutathione.

In a more general approach, Narvaez et al. reported the use of layer-by-layer polyelectrolyte self-adsorption deposition on a negatively charged alkanethiolated gold electrode surface that interfaced redox enzyme layers (e.g., fructose dehydrogenase,

horseradish peroxidase, and horseradish peroxidase–alcohol oxidase) with positively charged poly[vinylpyridine]Os(bpy) $_2$ Cl] (*B14*). A layer-by-layer deposition was also shown with fourth-generation poly(amidoamine) dendrimers exhibiting a 32% dendrimer modification level of surface amines to ferrocenyl groups for optimum conditions of the enzyme–dendrimer network formation, the electrochemical interconnectivity of ferrocenyls, and the electrode sensitivity to the analyte glucose (*B15*). Similarly, in both deposition approaches, the analytical performance of the biocatalytic sensors varied as a function of the number of layers applied onto the electrodes. The sensing capabilities including linear range, signal amplitude, and sensitivity could therefore all be customized by the multilayer approach, providing versatility and a promising strategy to sensor miniaturization. An additional attractive feature of these assemblies may also result from the enhancement in the chemical stability of the enzymes. The structural integrity of the multilayered network that provides electrostatic encapsulation for the polyelectrolyte-type deposition, or the multiple covalent bonds in the case of the dendrimers, is likely to act as a stabilizing medium that preserves the functionality of the enzyme over time.

While stability is indeed a determinant characteristic for the development of robust and long-lasting biosensors, other features of catalytic enzymes are being modified or enhanced through the use of modern methods of molecular biology. Thus, protein-engineered enzymes possessing a different Michaelis constant that allowed for the expansion of the dynamic range in glucose measurements was reported by Yamazaki et al. (*B16*). Carbon paste electrodes packed with engineered pyrroloquinoline quinone glucose dehydrogenase (PQQGDHs) exhibited an 25-fold increased  $K_m$  over the wild-type PQQGDHs. A composite electrode was constructed, enabling the determination of glucose concentration in the 0.5–30 mM range. An extended range glucose sensor (3–70 mM) was proposed by employing two engineered PQQGDHs, His775Asp and His775Asn.

Various aspects of enzyme kinetics, enzyme loading, stability, sensitivity, and dynamic range, as well as reproducibility of different amperometric biosensor strategies, were discussed by Boutelle and co-workers with a view to the development of biosensor systems for neurochemical application (*B17*). Reactor beds comprising ferrocene mediation of immobilized enzyme, a redox osmium hydrogel-based system, and a conducting polymer polyaniline approach, all using horseradish peroxidase as the biocatalytic enzyme, were developed and compared in a flow injection system. While the conducting polymer approach offered enhanced reproducibility and had the advantage of adaptation to almost any electrode geometry, it suffered from low sensitivity. The ferrocene-mediated system was, however, the method of choice for higher concentration of analytes, as it possessed the greatest linear range and excellent stability. The osmium polymer hydrogel system, on the other hand, seemed preferable for low concentrations of analytes provided that high level of interferences could be controlled or excluded. Indeed, an osmium redox hydrogel system appeared suitable for the design of a miniaturized pyruvate sensor reported by Heller's group (*B18*). The sensor relied on an electrically wired recombinant pyruvate oxidase

enzyme, deposited on a miniaturized gold-platinized electrode tip, that required no  $O_2$  for its operation. The sensor was able to track pyruvate concentrations in undiluted calf serum in the 0.1–5 mM range, with a detection limit of 30  $\mu$ M. Interference from ascorbate was excluded by placing a microdialysis membrane over the tip of the electrode, and serum components or pH changes did not affect the response. Exclusion membranes fabricated by sequential chemisorption of polyanions and polycations were equally effective in removing blood components and excluding transition metal ions during the in vivo application of coated redox polymer wired glucose oxidase electrodes (B19). The micromembranes allowed customization of electrode parameters, such as sensitivity, dynamic range, and drift rate, and were subsequently used to monitor induced glycemia changes in nondiabetic rats providing accurate clinical data.

In another in vivo approach (B20), amperometric carbon fiber enzyme-modified microelectrodes containing redox polymer gel layers were used to demonstrate selectivity response for glutamate, choline, and glucose in rat striatum extracellular space after pharmacological manipulation. In this case, no protective membrane was used given the low applied potentials over the electrodes (–100 mV vs Ag/AgCl). In an interesting study, the surface of carbon fiber electrodes that were modified following covalent attachment of dehydrogenase and oxidase enzymes could be restored in a spatially ordered approach by the use of a laser interference pattern ablation technique (B21). The contrast in areas of constructive versus destructive interference aided in the reactivation of electron transfer in areas immediately adjacent to stripes of covalently attached enzymes. Such a technique appears to be a powerful and effective approach toward the patterned construction of micrometer-sized surfaces for use in in vivo or other applications for a variety of enzymes that possess deactivation thresholds above the laser intensity required. Electrocatalytic modification of the patterned surface following the use of this technique enhanced sensitivity by more than 1 order of magnitude over a totally derivatized electrode.

Screen-printing techniques based on the use of metal-loaded inks for the deposition of metal layers onto planar supports appear to be the most promising technology for biosensor commercialization on a large scale. Several authors discussed particular technical challenges observed in the fabrication of disposable screen-printed systems. Smyth and collaborators performed voltammetric and scanning electron microscopy studies to show that the effective surface area of graphite increased with increasing curing temperature, and a single voltammetric scan in acidic media was sufficient to induce morphological effects on the electrode surface similar to those obtained with high curing temperature (B22). Erlenkotter et al. reported on a flexible amperometric screen-printed three-electrode system for multianalyte detection (B23). They showed that even though the Pt electrode surface was not ideal for the ferricyanide/ferrocyanide couple, the sensors proved to be reproducible and well suited for the determination of  $H_2O_2$  and thus for their development based on oxidases as biologically active catalysts. The combination of two pretreatment steps, additional curing step, and an additional electrochemical preconditioning step helped to reduce background current and settling time. Sensors with immobilized sarcosine oxidase were optimized and demonstrated sensitivities of  $2.30 \pm 0.07$  nA  $M^{-1}$  sarcosine.

Patel et al. fabricated three-electrode amperometric screen-printed formats and used a mixture of alcohol oxidase with poly-(carbomoyl)sulfonate hydrogel for enzyme immobilization in the development of alcohol sensors (B24). The study involved the assessment of alcohol oxidases of various sources and the comparative evaluation of a wide range of performance characteristics. The low-cost printed sensors were tested with wine samples, and the results obtained were compared with an official reference method revealing results that could be determined within 10% error. The sensors showed good reproducibility with standard deviations less than 3% and good stability of up to 3 weeks at 4 °C.

**Immunosensors.** Key fundamentals of immobilization, orientation, and specific properties of antibodies on transducer surfaces were approached by several workers. Korri-Youssoufi et al. synthesized a polypyrrole and a poly(bithiophene) polymer, containing activated ester groups covalently linked to conjugated backbone via a linear spacer, to form the basis of conducting polymer-based sensors that transduce the antigen–antibody interaction (B25). Indeed, the current intensity of cyclic voltammograms for antigen *N*-2,4-dinitrophenyl-L-lysine polymer was decreased by about 30%, and a positive 100-mV shift of the oxidation potential was observed in the presence of monoclonal anti-dinitrophenyl clone SPE-7, antibody. The electrochemical response of polymer–antigen and polymer–antigen–antibody system was shown to depend on the hydrophobic character of the synthesized polymers.

In an elegant approach, a site-oriented immobilization of antibodies making use of native sulfide groups of immunoglobulin (IgG) was reported on Au surfaces (B26). In this study, IgG was split into two half-IgG fragments to expose thiol groups and immobilization of antibody fragments was carried out by simple adsorption. The strategy led to a binding capacity similar to that of gold surfaces with traditionally unsplit linked antibodies. In addition, the binding was shown to be 20–30 times higher than for nonspecifically adsorbed intact IgGs. Furthermore, high antigen binding constants were maintained and the immobilization procedure provided orientation of IgG fragments in terms of the similar distance between the binding site of the antibody and the surface of the gold support, causing no distribution of the apparent affinity constants. The validity of the immobilization method was tested with a range of immunoglobulins of different specificity using peroxidase as the antigen and resorting to biocatalytic reduction of  $H_2O_2$  with catechol as the mediator. The stability of this system was studied in a flow arrangement revealing no significant loss of binding affinity after 3–4 h of continuous flow and a biocatalytic current reduction of  $H_2O_2$  that decayed by less than 10% after 1 h.

The surface structure of anti-rabbit-IgG covalently attached to a mixed (butanethiol/thioctic acid) self-assembled monolayer probed by AFM was reported by Dong and Shannon (B27). The surface was characterized in terms of epitope density and average height (7.1 nm), and diameter (7–10 nm) of captured antibody was measured. Different compositions of the mixed self-assembled monolayer allowed manipulation of  $\sim 2$  orders of magnitude in the density of immobilized antibody. Interrogation of antibody–antigen binding with rabbit IgG revealed a 22.8% average efficiency

for rabbit-IgG antibody arrays. To test biological activity of the surface and validate AFM measurements, the authors prepared rabbit-IgG antigen arrays over the same mixed self-assembled monolayer structures and used alkaline phosphatase-labeled monoclonal anti-rabbit-IgG and the generation of *o*-aminophenol for voltammetric transduction in a competitive heterogeneous detection scheme. Another scanning probe microscopy report illustrated the advantage of this technique with an electrochemical scanning Pt electrode in a sandwich electrochemical immunoassay involving microdomains of paramagnetic, surface-modified beads (B28). The surface of the beads was coated with a model anti-mouse-IgG antibody bearing accessible Fab groups responsible for the binding of analyte mouse-IgG. Alkaline phosphatase label attached to the captured analyte as a conjugate of a second anti-mouse-IgG catalyzed the hydrolysis of 4-aminophenyl phosphate to redox-active *p*-aminophenol that was detected as a function of the concentration of captured mouse-IgG. The use of scanning probe microscopy is particularly encouraging in immunosensing since surface-patterned immunoreactive arrays can then be massively interrogated for multianalyte or multisample assays.

Many synthetic and chemical immobilization strategies of immunoreagents have been put to use in the direct transduction of the antigen–antibody binding reaction. Direct reading immunosensors are of significant interest to many researchers since they represent a true alternative to immunoassay technology given their simplicity, speed of analysis, and potential for miniaturization and for fabricating multianalyte sensors. In this context, Lillie et al. investigated the use of electrochemical impedance spectroscopy as a reagentless platform for immunosensing (B29). A conducting poly(pyrrole) film loaded with avidin or antibody to luteinizing hormone (LH) was deposited on gold interdigitated electrodes and two-electrode impedance spectroscopy was used to both improve sensitivity and observe polaronic and electronic charge transfer through the polymer. A calibration curve constructed for monoclonal antibodies to LH in the range of 1–400 IU/L was found to be suitable to cover the clinical range of the hormone. Response of the system to D-biotin and two other biotin derivatives was shown to be sensitive to electrode pretreatment.

A direct approach was also used for the attomolar-level detection of 15.5-kDa interferon- $\gamma$  (B30). Here, a wall jet-flow-through cell-type arrangement using Au electrodes modified with self-assembled monolayers of cysteine or acetylcysteine was used. In a series of on-line steps, the self-assembled monolayers were activated via carbodiimide/succinimide treatment followed by antibody attachment and deactivation of succinimide groups by ethanolamine. The monitoring of the various steps of the fabrication and the formation of the immunocomplex were monitored via ac impedance and chronoamperometry. While the potential step approach revealed poor sensitivity toward the binding of interferon- $\gamma$  (apparently due to unsuitable instrumentation), the ac impedance technique proved successful. The problem of nonspecific adsorption that typically plagues immunosensing surfaces was observed on both cysteine and acetylcysteine self-assembled monolayers. The latter assembly proved, however, more versatile since the protein could be removed after KCl injections without inducing damage of the surface. Cumulative injections of 0.02 fg of interferon- $\gamma$  followed by 100 mM KCl injections, to account for nonspecific adsorption, translated in an

upper detection limit of  $\sim 0.14$  fg/mL and a detection limit below 0.02 fg/mL. The immunosensor could be regenerated by using a sequence of potential pulses in the same flow with complete removal of the attached antibody and bound interferon- $\gamma$ . The repeatability of the entire described process using the same electrode was found to be within 10%.

Measuring redox-active products originated by the biocatalytic activity of enzyme-labeled immunoreagents continues to be one of the most popular methods because of its high sensitivity. Thus, a flow system arrangement coupled with ac adsorptive stripping voltammetry was used by Costa-Garcia and co-workers to demonstrate detection of pneumolysin and interleukin at picogram per milliliter levels by employing a conventional ELISA approach with alkaline phosphatase label (B31). Liu et al. also reported on sensitive amperometric immunosensors utilizing protein A-coupled polyaniline–perfluorosulfonated ionomer composite electrodes for the detection of rabbit immunoglobulin G (RigG) with goat anti-RigG-labeled urease (B32). Given the special affinity of protein A with RigG, the electrode was coated with a thin layer of protein A on top of the polyaniline–Nafion layers to facilitate immobilization and removal of RigG during the immunoanalysis. The analysis performed yielded a dynamic range of 50–2000 ng/mL and a detection limit of 64 pM. The electrodes could be regenerated repetitively through a mild change of the pH of the buffer solution.

In an elaborate strategy (B33), Willner's group reported on the use of chronopotentiometry and Faradaic impedance spectroscopy for the transduction of an amplified immunosensing scheme that consisted of the biocatalyzed precipitation of an insoluble product onto a Au electrode surface. The approach involved reacting a dinitrophenyl-antigen (DNP-antigen) functionalized electrode with complementary analyte–antibody goat IgG–dinitrophenyl–antibody. The antigen–antibody complex formed over the surface was further exposed to a horseradish peroxidase–anti-antibody conjugate (mouse IgG–anti-goat-IgG–Fc-specific-HRP) that acted as a biocatalyst of the oxidative precipitation of 4-chloro-1-naphthol by  $\text{H}_2\text{O}_2$  to insoluble benzo-4-chlorodienone precipitate. All measurements were made in the presence  $[\text{Fe}(\text{CN})_6]^{4-/3-}$  as redox indicator. Impedance measurements of the electrode transfer resistance occurring as a function of the precipitate accumulated on the electrode and chronopotentiometric measurements, where total electrode resistances are recorded, indicated that the amount of precipitate depended on the concentration of the analyte–antibody and the time interval employed for the biocatalytic precipitation. A variation of this scheme may also involve amplification of the signal by the use of a biotin-tagged HRP-functionalized liposome (B34). In this case, the electrode exhibiting the antigen–antibody complex was exposed to rabbit IgG–anti-goat–Fc-specific-biotin conjugate and further exposed to the amplifying liposome through an avidin bridge.

The use of immunosensors for clinical applications requires that ideally these devices exhibit a quasi-continuous monitoring characteristic or alternatively that their surface be capable of renewal. Toward this end, a paraffin–graphite–*Schistosoma japonicum* antigen-based electrode formed the basis of a renewable amperometric immunosensor for the detection of *S. japonicum* antibodies in rabbit serum (B35). The serum samples containing various infectious degrees were mixed with *S. japonicum*-labeled



horseradish peroxidase to form the incubation solution of a competitive binding method. Renewed surfaces were obtained by removing 0.1 mm of the outer paste layer of the electrode and polishing with alumina paper. Using *o*-aminophenol as a substrate, the conditions of the assay were optimized to yield calibration curves in the 0.36–14  $\mu\text{g/mL}$  range, which was suitable for clinical applications. A relative standard deviation (RSD) of the measurements of 6.4% was obtained by repeating the measurements with freshly polished electrodes. Another clinically oriented approach that required, however, no regeneration given its disposable principle was reported for a portable immunosensor in the amperometric detection of anti-hantavirus antibodies in human blood serum (*B36*). The amperometric immunosensor was based on a recombinant nucleocapsid protein adsorbed on highly dispersed carbon particles that served as the immunoelectrode. Detection was made through the use of an enzyme label approach in a flow injection arrangement, but no analytical performance data were provided.

**DNA Sensors.** Much development in the DNA biosensor area focuses on the design of selective molecular interfaces capable of appropriate electrochemical transduction of a DNA hybridization event. Thus, the study and application of metal chelates, e.g., dipyrrophenazine complexes of osmium(II) (*B37*), and miscellaneous redox markers, e.g., methylene blue (*B38*), demonstrated their utility as DNA intercalators that change their oxidation potential upon the hybridization event. Compounds that may offer higher binding affinity and greater discrimination between single- and double-stranded DNA are preferred. Takenaka et al. reported on a ferrocenylnaphthalene diimide derivative as the electrochemical promoter ligand that was able to show considerably stronger binding to intact DNA than to denatured DNA (*B39*). The superior thermodynamic and kinetic characteristics of this intercalator with double-stranded DNA were used for a practical quantitative assay by using a gold electrode with differential voltammetric detection. The sensitivity of the assay could be lowered to roughly 10 zmol by reducing the density of the probe DNA and masking the unmodified region of the electrode. In another practical application, daunomycin was used as the intercalator in a double-stranded DNA assembly to detect polymorphisms of human apo E genotypes in blood samples (*B40*). The rather simple approach consisted in depositing the oligonucleotide probe on the surface of a disposable screen-printed graphite electrode at a controlled potential and then the DNA analyte solution amplified by polymerase chain reaction (PCR) was dropped on the electrode for hybridization. The electrode was subsequently immersed in a solution with daunomycin for intercalation and then in buffer to conduct chronopotentiometric measurement at a constant current.

The convenient synthetic chemistry of ferrocene was used in alternative approaches, either by site-specific incorporation of ferrocenyl moieties into oligonucleotides that can be used as signaling probes for hybridization reactions (*B41*) or by employment of ferrocenyl groups as functionalization units of polypyrrole that can also bear a grafted oligonucleotide (*B42*). Indeed, in the latter case, an amino-terminated oligonucleotide was grafted onto the polymer to constitute the assembly of a modified electrode that could serve to detect complementary DNA at a  $\sim 0.1\text{-pmol}$  level of target. Electrochemical DNA probing is deemed generally suitable as far as sensitivity is concerned, with detection limits

lower than picomole amounts of analyte (see below). However, several of the factors that complicate DNA analysis are evidenced by the variability of the electrode performance and the difficulty in developing actual electrochemical devices. Therefore, approaches that may lend themselves to more automated processes will continue to attract attention, such as prefunctionalization of nucleotide probes, the use of conducting polymers, and other simple immobilization techniques.

In an original approach, Armistead and Thorp immobilized single strands of DNA on indium tin oxide electrodes for the electrocatalytic oxidation of guanine bases by  $\text{Ru}(2,2'\text{-bipyridine})^{2+}$  in solution (*B43*). The immobilization resulted in a particularly strong adsorption of the single strand, when performed in a medium that contained mostly DMF as the solvent. Cyclic voltammograms and chronoamperometric signals of the catalyst were obtained as a result of the oxidation of the immobilized guanine by  $\text{Ru}(\text{III})$  and varied linearly with the extent of immobilization. Immobilized strands that contained higher guanine content showed also higher signals. Detectable catalytic currents were produced with as little as 550 amol of a DNA strand adsorbed. El-Maali and Wang also resorted to  $\text{Ru}(2,2'\text{-bipyridine})^{2+}$ , which they incorporated in a carbon paste electrode for DNA detection in a flow injection amperometric analysis (*B44*). In contrast to the work of Thorp, here the electrocatalytic system is reversed (i.e., single-strand DNA is added in solution and catalyst is immobilized) but essentially leads to the same enhancement of the signal that results from the oxidation of guanine. The response of the system in this case was highly reproducible, and a detection limit of 24 ppb was obtained using FIA.

Impedance measurements were used to probe a complementary sequence of a single-stranded probe oligonucleotide by employing a carboxylic pending terthiophene monomer that was polymerized on the surface of a glassy carbon electrode (*B45*). An amino-functionalized oligonucleotide related to sickle cell anemia was then covalently attached. Impedance spectra provided a relatively straightforward means to discriminate matched and mismatched oligonucleotide sequences following hybridization. While this approach represents an advantage from a fabrication standpoint and serves as a direct signal to the formation of the duplex, it neither confirmed nor amplified the formation of the double-stranded DNA complex at the sensor surface.

Enhanced selectivity can be achieved by the use of peptide nucleic acid (PNA) probes. Indeed, the superior recognition and hybridization characteristics of solution-phase PNA chemistry were implemented in a gold electrode modified with self-assembled monolayers of PNA (*B46*). In this case, the authors relied on the neutral backbone of PNA that effectively replaces the negatively charged phosphate backbone of DNA adjacent to the electrode. Given that PNA highly discriminates mismatch DNA and has a stronger affinity for complementary DNA than its DNA counterpart, the use of an ion-channel mimetic concept could be demonstrated. Thus, the buildup of DNA negative charge following the hybridization reaction was effective in creating an electron-transfer barrier for the electrode transfer between the gold electrode and the redox promoter  $[\text{Fe}(\text{CN})_6]^{4-/3-}$ . A one-base mismatch in an oligonucleotide was detected but the sensitivity was relatively low.

Enhancing the sensitivity for the electronic transduction of DNA-sensing processes on surfaces has been accomplished by many chemical strategies. A detailed study on the amplification of oligonucleotide-DNA interactions and single-base mismatches employing negatively functionalized liposomes was reported by Willner's group (*B47*). In one approach, a thiolated oligonucleotide complementary to target DNA was immobilized on a gold electrode followed by probe DNA analyte reaction to form a double-stranded assembly. The resulting assembly was further reacted with an oligonucleotide functionalized liposome complementary to the other end of the single-stranded target DNA to allow the formation of a three-component double-stranded assembly functionalized by the liposomes. The deposition of negatively charged liposomes on the electrode surface resulted in a charged interface that repelled the  $[\text{Fe}(\text{CN})_6]^{4-/-3-}$  redox indicator, enabling electronic transduction by Faradaic impedance spectroscopy yielding a detection limit of  $1 \times 10^{-12}$  M. A full order sensitivity enhancement could be obtained by a modified approach. Here, the modified oligonucleotide gold electrode was reacted with target DNA that was pretreated with a different biotinylated oligonucleotide forming a three-component double-stranded assembly that was amplified via association of avidin and biotin-labeled liposomes to the sensing surface. With the secondary association of avidin and biotin liposomes, a dendritic-type amplification of DNA analysis was obtained.

In yet another innovative approach, Wang and co-workers resorted to potentiometric stripping analysis of gold particle tags as a manner to amplify DNA hybridization (*B48*). The hybridization of a target oligonucleotide to a magnetic bead-linked oligonucleotide probe was followed by binding of streptavidin-coated metal gold nanoparticles to the captured DNA. An acid dissolution step was performed prior to detecting the gold tag at a disposable thick-film carbon electrode. Relevant experimental variables that were shown to affect the sensitivity included amount of gold particles and magnetic beads, duration of the hybridization step and the gold dissolution step, and finally parameters of the potentiometric stripping technique. Once all conditions were optimized, the resulting sensitivity approached the low-nanomolar range. While avenues to increased sensitivity can be envisioned with such an approach, the detection scheme involves multiple steps that add complexity to the assay. They can be best thought of in lab-on-a-chip type analytical formats. In a very similar approach, a sensitive DNA detection method was developed by the hybridization of the target DNA with its complementary capture strand attached to a Au nanoparticle probe (*B49*). The nanoparticle was oxidatively dissolved to  $\sim 10^5$  mol of Au(III) per particle, which was detected at a disposable microband electrode. In the last step lies again the amplification step of this measurement principle. The detection limit was found to be as low as 5 pM DNA. Unfortunately, this principle is also more an assay than a chemical sensor principle because of its irreversible character.

Enzyme labels involved in the bioelectrocatalytic reaction of DNA also provide a strategy for highly sensitive methods. A hybridization assay at a disposable screen-printed carbon electrode was used for the detection of human cytomegalovirus DNA (*B50*). The scheme relied on the adsorption of PCR-amplified DNA sequences adsorbed on the surface of the electrodes which were subsequently hybridized with a biotinylated probe and detected

via enzyme label binding. The use of streptavidin–peroxidase converted *o*-phenylenediamine substrate into the electrochemically active product 2,2'-diaminoazobenzene that was measured via differential pulse voltammetry, yielding a detection limit of 0.6 amol/mL. The scheme proved to be 23 000 more sensitive than the gel electrophoresis technique and 83-fold more sensitive than a colorimetric assay performed in microtiter plates.

## ELECTROCHEMICAL SENSORS AND DETECTORS IN FLUIDIC SYSTEMS

The field of electrochemical sensors has long realized the potential for its integration into fluidic systems. This trend strongly continues today with the growing importance of integrated sensing and separation devices. In fact, many researchers no longer see a clear distinction between a chemical sensor and an integrated separations device. They are based on different principles but serve the same purpose. Excellent examples for very effective pseudochemical sensor systems come from the group of Kennedy. A recent paper describes the *in vivo* microdialysis probe sampling of amino acids, followed by on-column preconcentration, stripping, separation, and on-line electrochemical detection (*F1*). Another example describes the detection of glucose in rat brain (*F2*), by utilizing microdialysis sampling, liquid chromatography, and electrochemical detection with an enzyme-modified electrode utilizing glucose oxidase, Nafion, and cobalt tetraaminophthalocyanine coated on a glassy carbon electrode.

Much of the lab-on-a-chip research movement was originally strongly motivated by chemical sensors research. The integration of sampling, derivatization, separation, and detection on a single device, as demonstrated recently on microchips (*F3*), will allow one to tackle more difficult sensing tasks than with classical sensor configurations. Examples for this direction include Wang's "lab on a cable" approach (*F4*), where a traditional electrochemical flow system with an integrated enzymatic reaction step is scaled down to a cable platform (with a 5.5-cm outer diameter). Even in cases where the detector still plays a central role in the sensing step, researchers have realized that its integration into an adequate fluidic environment is important. One "fluidics cube" biosensing approach utilized a complex passive fluid circuit for reagent and sample handling, while the actual sensor was a traditional biosensor array (*F5*).

It is clear that the fundamental review series has significant difficulty in covering true interdisciplinary research areas. Since this specific review focuses on electrochemical sensors, only novel or interesting electrochemical detection schemes are discussed here. Rather than grouping them by application or by separations method, they are discussed here in the order of relevant detection principles. Some reviews include the integration of biosensors in separation devices (74 references) (*F6*), pulsed amperometric detection of carbohydrates (169 references) (*F7*) and other organics in liquid chromatography (51 references) (*F8*), enantioselective electrochemical detectors for drug screening (44 references) (*F9*), electrochemical detection methods for capillary electrophoresis by Kappes and Hauser (90 references) (*F10*) and Matysik (109 references) (*F11*), potentiometric detectors in fluidic systems (45 references) (*F12*), and fluidics in modern clinical analysis (149 references) (*F13*).

**New Methods.** Many "lab on a chip" devices are scaled-down versions of their larger benchtop counterparts and do not really

introduce new chemical principles. The coulometric nanotitration cell described recently appears to be an elegant approach to electrochemical reagent handling and delivery in a microfluidic environment (F14). Here, a programmed current–time profile was used to perform on-line redox and pH titration experiments, followed by potentiometric detection. It can be easily envisioned that microcoulometry will play a very important part in future integrated fluidic systems, since the amount of infused reagent can be precisely controlled electrochemically.

Another microanalytical approach coupled the detection principle of mercury thin-film microvoltammetry with the high selectivity and preconcentration capability of supported liquid membranes to obtain a potentially powerful microanalytical approach for the assessment of heavy metals in environmental samples (F15). The liquid membrane acted as a selective transporter/preconcentrator for the analyte and a barrier for undesired sample species and is chemically much more sophisticated than traditional Nafion or hydrogel coatings. It can be hoped that more work will be done in this very promising direction.

**Redox Detectors.** A rotating disk electrode was explored as a detector for capillary electrophoresis (F16). As expected from hydrodynamic theory, this type of detector decreased the detection limit somewhat (2.5-fold) relative to a stationary electrode. Moreover, separation efficiency was improved because of increased efficiency of mass transport to the detector, and the electrode was found to be less prone to chemical passivation because of shorter effective contact times with the analyte.

A miniaturized wall-jet type flow cell was used as an electrochemical detector in capillary electrophoresis (F17). If equipped with an interdigitated microarray, the detector showed greatly enhanced response at low flow rates with analytes that undergo reversible redox chemistry because of electrochemical cycling effects. In the same work, the flow cell was shown to also be useful with an enzyme detector. Other authors have also emphasized the benefits of interdigitated microelectrodes for the detection of catecholamines in tissue samples after separation with HPLC, citing 10-fold improvement in detection limits over conventional detectors (F18).

A decoupling technique in electrophoretic plastic microfluidic chips was demonstrated to facilitate on-chip electrochemical detection (F19). A palladium metal film was thermally evaporated onto the chip across the separation channel, and electrochemical detection was performed downstream from this decoupler, also with thermally deposited working electrodes to avoid alignment issues. Another paper used a wet chemistry gold deposition procedure for the fabrication of detection electrodes on microfabricated capillary electrophoresis glass chips, with a 4-fold improvement in detection efficiency compared to thick-film-based detectors (F20).

For the first time, a carbon paste electrochemical detector was incorporated into polymeric capillary electrophoresis microchips (F21). The carbon paste electrodes were placed onto the polymeric half of the chip with which the channel-containing polymer was covered. Carbon paste electrodes can be doped with suitable catalysts, which can be used to significantly tune the detector selectivity. This was demonstrated here with a cobalt phthalocyanine dopant for the selective on-chip detection of thiols. In

different work on tuning the chemical selectivity of flow detectors, a sol–gel amperometric detector was used in capillary electrophoresis for the determination of cytochrome *c* (F22). The carbon composite sol–gel electrode was chemically modified with copper(I) oxide for increased electrocatalytic response to the oxidation of cytochrome *c*. The theme of electrocatalysis was also exploited in the case of polyaniline-based electrochemical detectors (F23). In that case, the sensitive electrochemical response to Cr(VI) by this polymer was used in flow injection analysis for the detection of the toxic metal in seawater samples. The addition of an anion-exchange column to the flow system lowered the detection limits to just 4 ppt.

In the spirit of work by Johnson (F24), electrochemically silent analytes were detected at a platinum electrode in capillary electrophoresis (F25). By using a modified square wave voltammetric method, a concentration-proportional response was found for a number of analytes, including amines, alcohols, antibiotics, and amino acids. The analytes were thought to generate an electrochemical response by chemisorption onto the electrode surface, with  $10^{-8}$  M detection limits.

Another interesting amperometric detection method for non-electroactive analytes in capillary liquid chromatography was presented (F26). The detection method was based on the reaction with bromine, which was first on-line electrogenerated and then again reduced at a second electrode placed downstream. If an analyte was present that could react with bromine, the amount of detected bromine at the second detector was reduced accordingly. The method was applied to the detection of peptides that contained a disulfide bond.

**Electrochemiluminescence.** Electrochemiluminescence is now being widely explored in a number of fields and has gained in importance as a detector principle in fluidic systems as an alternative to laser-induced fluorescence detection. This method does not require a light source, which greatly simplifies the experimental setup and avoids background light. It is in some way a hybrid system between an electrochemical and an optical detector. Most reports focus on the electrogenerated chemiluminescence of ruthenium(II) complexes, which may appear to be a rather exotic class of analytes to be of general use. However, such compounds are often used as markers in bioanalysis, for example, with magnetic beads that are placed near an electrode surface for excitation (F27) or in combination with compounds that influence the chemiluminescence properties of the ruthenium(II) (F28). This approach was found to also work for the detection of neutral molecules in micellar electrokinetic chromatography, by postcolumn addition of the ruthenium(II) complex (F29). Alternatively, it may find use as a background electrolyte, which is displaced in the presence of other analytes and lead to zones of decreased light intensity at the detector (F30). This last concept has been demonstrated on a microfluidic platform, although the results are not yet fully convincing. The elegance of using electrochemistry for selective and spatially confined light generation is very attractive, and more imaginative ways that exploit this technology will surely emerge in the future.

**Nonredox Detectors.** An indirect amperometric detection scheme for non-redox-active ions in liquid chromatography was reported (F31). A carbon paste electrode was coated with a polyionic polymer and doped with a redox-active ion. That marker



exchanged with the ion in the contacting eluent and could be amperometrically detected at the electrode. While the approach is interesting, the irreversible loss of redox-active markers in the fluid stream would likely pose problems in routine applications.

Another interesting approach for the amperometric detection of non-redox-active species in capillary zone electrophoresis utilized a liquid/liquid microinterface (*F32*). As with other such detection systems, the observed current originates in the rate of transfer of ions from the aqueous to the organic phase. The present system was used for the detection of hydrophobic ions such as choline and acetylcholine. Hydrophilic ions are known to be detectable with the same principle by using complexing agents in the organic phase. This detection approach is very similar to that of potentiometric sensors but has the often cited advantage of yielding current signals that are proportional to sample concentrations. On the other hand, the use of simple liquids such as 2-nitrophenyl *n*-octyl ether as the organic phase make the lifetime of such devices much shorter compared to their potentiometric counterparts.

Ion-selective electrodes (ISEs) were also used as detectors in fluidic systems, here of the simplest kinds without ionophore (*F33*). The first application of ISEs as detectors in microchips was reported (*F34*), although with still unsatisfactory results with regard to the current state of the art of ISEs. An array of selective solid-state ISEs including a solid-state pseudoreference electrode was developed as a compact detector in ion chromatography (*F35*). The high chemical selectivity of the detector array was used to fully resolve otherwise poorly separated chromatographic peaks.

## ELECTROCHEMICAL GAS SENSORS

The electrochemical gas-sensing field is merely a subset of the very active gas-sensing community. The following electrochemical gas sensor reviews are noted: potentiometric gas sensors for use at high temperatures (18 references) (*G1*), amperometric and potentiometric sensors based on zirconia materials (35 references) (*G2*), work function sensors based on FETs (30 references) (*G3*) and Kelvin probes (21 references) (*G4*), amperometric gas sensors based on solid electrolytes (45 references) (*G5*), oxygen sensors (132 references) (*G6*), electronic noses for bioelectronic olfaction (47 references) (*G7*) and for bioprocess monitoring (39 references) (*G8*), tin dioxide as gas-sensing material (17 references) (*G9*), conducting polymer arrays (175 references) (*G10*), and porous silicon as a gas-sensing material (116 references) (*G11*). The electrochemical analysis of gases dissolved in solution is discussed in the voltammetric and potentiometric sections.

**High-Temperature Potentiometric Gas Sensors.** High-temperature potentiometric gas sensors based on zirconia materials are well established, for example, in the automotive industry for the monitoring of exhaust gases. Research in this direction continues, with an emphasis on new materials and lower temperature operating ranges. A thin zirconium acid phosphate membrane was shown to be responsive to oxygen at temperatures as low as 150 °C, while some other, oxidizable gases (hydrocarbons and alcohols) started to give potentiometric responses at temperatures just above 200 °C (*G12*). A nitric oxide sensor was reported based on a NO<sup>+</sup> conducting material placed between the sample

gas and the reference gas (*G13*). A Nernstian NO response extended down to 100 ppm nitric oxide levels. Only oxygen was found to be a substantial interference. A nitrogen dioxide sensor was reported based on lithium conducting materials LiNdSiO<sub>4</sub> and LiSmSiO<sub>4</sub>, with Nernstian NO<sub>2</sub> slopes at 150 °C (*G14*). A paper focusing on car exhaust sensors reported on the tunable selectivity of a NiCr<sub>2</sub>O<sub>4</sub> membrane to nitrogen oxide gases (*G15*). A bias voltage of +175 mV versus the reference electrode provided a selective response to NO over NO<sub>2</sub>, while a negative bias of -250 mV gave preference of NO<sub>2</sub> over NO. Other typical exhaust gases did not interfere.

**Work Function Sensors.** As gaseous species interact with a sensing material that has charge-transfer characteristics, the work function of the material may change. This sensing principle is now being utilized by a growing number of scientists to develop gas sensors. Traditionally, work functions were measured with the Kelvin probe, which utilizes a physically vibrating capacitor. The reason for the growing interest in work function gas sensors is probably twofold. On one hand, the work function change can also be measured with field effect transistors (FETs), which are quite attractive for miniaturization purposes. On the other hand, it allows the analytical chemist to develop gas sensors based on more subtle interactions and a wider range of materials than with the established chemiresistive sensors. For a good review with 30 references on the state of the art of work function gas sensors, see ref *G3*.

Traditional FET-based gas sensors utilize a metallic gas-sensitive material, and research in this direction continues. One paper described a layer of platinum or gold on a hybrid suspended gate FET device to measure ozone at 130 °C with detection limits in the low-ppb level (*G16*). However, much of the current literature focuses on new materials and on sensors that can operate at room temperature. A paper reported on a screen-printed film of barium carbonate to fabricate a work function carbon dioxide sensor (*G17*). At room temperature, the sensor was found to be cross-sensitive to humidity, which complicated the response behavior. A rather preliminary paper reported on the behavior of molecular porphyrin films on FET-based gas sensors (*G18*). While it showed that monolayers of such molecules can be effective for gas-sensing purposes, the results were not yet convincing. A careful study characterized FET-based sensors with different conductive polymer sensing layers in view of toluene-sensing applications (*G19*). The polymers, for example, poly(9-vinylcarbazole), were mixed with carbon black and sprayed onto the device. This departure from electropolymerized polymers opens up interesting new directions for gas-sensing materials.

A new gas-sensing principle that is related to work function sensors is based on dc emission currents from heated surfaces (*G20*). The emitted current was found to change with the work function of the material and was stated to show a higher sensitivity than ordinary work function sensors. Inorganic salts such as barium nitrate were carefully tested under various conditions.

**Amperometric Gas Sensors.** An amperometric sensor for formaldehyde gas was developed based on a porous metallic membrane, which was backside contacted with an acidic electrolyte (*G21*). This gas-sensing approach, originally reported in the late 1980s, directly oxidizes the analyte gas at a gold electrode deposited on a Nafion membrane. The active reaction area is the

three-phase contact zone between gas, metal, and electrolyte. The principle can be used for the detection of a number of different gases and had here a detection limit around 10 ppb. In different work, the reduction waves of  $O_2$ ,  $CO_2$ , and  $N_2O$  at a gold microdisk electrode could be fully resolved individually by using the solvent dimethyl sulfoxide (G22). Ordinarily, the electrochemical waves of these gases overlap with each other, and it was argued that this finding could have implications for the measurement of anesthetic expired gas or in blood gas analysis. The porous metallic electrode material used in such gas-sensing devices was proposed to be replaced with an inexpensive alternative, reticulated vitreous carbon, a high surface carbon electrode material (G23). In a sensor configuration for the detection of nitrogen dioxide, both electrode materials were directly compared. While the gold electrode showed better dynamic behavior, the carbon material-based sensor was found to show improved sensitivity, higher stability, and smaller dependence on the relative humidity of the sample. Another paper proposed the use of a solid polymer electrolyte, polyacrylonitrile–dimethyl sulfoxide–tetrabutylammonium perchlorate, as an alternative to the liquid electrolyte in such a gas-sensing configuration for the measurement of carbon dioxide (G24). Together with a Au working electrode and Ag counter/reference electrode, this approach yielded an all-solid-state electrochemical gas sensor with good properties. A competing approach utilized either the solid proton conductor Nafion or poly(benzimidazole) sputtered with a porous Au layer as the working electrode (G25). This all-solid-state amperometric gas sensor was tested for the detection of oxygen, with characteristics similar to commercially available sensors. The same general sensing principle was also used by others to determine gases that can be adsorbed and desorbed at electrode surfaces. In an example, aromatic gases were detected by adsorbing the gases onto a platinum electrode (G26). The amount of adsorbed material was estimated by superimposing an ac voltage of low amplitude to the adsorption potential and used to adjust the adsorption time. Subsequently, the gases were electrochemically desorbed and the current was related to the concentration of the gas. Analysis of the desorption signals was used to distinguish the analyte gas from interfering gases, and “realizable” detection limits were estimated at 0.5 ppb for many aromatic gases.

Zhao et al. proposed to replace steady-state electrochemical methods in thin-layer electrochemical gas-sensing techniques, such as the Clark electrode, by transient electrochemical techniques (G27). It was shown that the transient nature of the electrochemical response could be utilized for multicomponent analysis, for example, for the assessment of  $O_2$  and  $N_2O$  gas mixtures. To achieve this goal, steps were taken to minimize non-Faradaic charging currents that would otherwise interfere with the analysis.

**Electronic Noses.** The original idea of fabricating electronic noses was to develop sensors that could evaluate odor as perceived by humans, for example, to assess the quality of air or of food products. These are characteristics that have not traditionally been the focus of classical analytical techniques. Much work in this direction still continues. For example, conducting polymer composite detector arrays were used as electronic noses in a study to evaluate their capability to predict human perceptual descriptors of odor (G28). Single-component odorants were each found to

produce a characteristic response pattern of the array. A correlation between such odor measurements and the so-called human perceptual odor space was attempted, with good results in some cases. Unfortunately, an accurate prediction of human values was not possible for more than just a few descriptors. A similar study evaluated the capability of conducting polymer arrays to differentiate aroma patterns of coffee (G29). Solid-phase microextraction-gas chromatographic analysis on the same samples revealed the actual volatile chemicals responsible for the odor difference, which was not possible with the sensor array. Nonetheless, only the array was reported to differentiate the samples successfully according to geographical origin. Just one abnormal coffee sample was evaluated, which could be identified by both methods.

Electronic noses require maximum orthogonality for proper discrimination of vapor compounds. Ulmer et al. have demonstrated that this can be best achieved by utilizing more than one type of transduction principle (G30). In this work, a number of different chemiresistive sensors were combined with quartz crystal microbalance modules coated with various polymers. It was shown that the tested single-component vapors could be resolved adequately only by combining both types of measuring principles.

Unlike the traditional goal of electronic noses to assess vapor qualities, rather than individual components, such devices are also being explored to be used as traditional chemical detectors. Much excellent work in this direction is being done with surface acoustic wave sensors, which are not reviewed here. An interesting example evaluates conducting polymer composite vapor detectors for the measurement of nerve agent simulants (G31). Detection limits in laboratory air samples were, with  $0.05\text{--}0.2\text{ mg/m}^3$ , found to be lower than the EC50 value. A number of potential interferences were also tested, and the nerve gas simulants retained their characteristic response pattern in the presence of various background gases. It was emphasized that a real working nerve agent detector would also utilize other preconcentration or separation principles in addition to the type of electronic nose characterized here. It is clear that the analysis of specific minor components in complex mixtures, as in this example, either require detector materials with high selectivity or need to be coupled to a separation device.

**Chemiresistive Gas-Sensing Materials.** The largest number of papers dealing with chemiresistive gas sensors and so-called electronic noses still utilize metal oxide-based semiconducting materials such as  $SnO_2$  as the sensory element. An interesting feature of these materials appears to be that their selectivity can be tuned to some extent. One paper, for example, reports that thick- and thin-film sensors of essentially the same  $SnO_2$  sensory material provide some orthogonality in their selectivity, with the former being more sensitive to reducing vapors and the latter to oxidizing gases (G32). This characteristic was studied in view of the measurement of air pollutants such as ozone, nitrogen dioxide, nitrogen oxide, and carbon monoxide. It was also reported that multilayer Pt/ $SnO_2$  films gave improved sensitivity to CO (G33), which was thought to originate in the higher available surface area of the sensing film.

The selectivity of  $SnO_2$  sensory materials can also be altered by using noble metal additives as dopands. A careful structural analysis of such doped materials found metallic, 2+ and 4+ oxidation states of the noble metals (mainly Pt, Pd, and Au) on

the sensing surface (G34). Their possible role as having either an electronic or a chemical influence on the selectivity to CO and CH<sub>4</sub> and the role of nanoparticle clusters were discussed. A related study by Capone et al. reported on tin oxide films doped with Pd, Pt, and Os and prepared by sol-gel processes (G35). FT-IR, XRD, and SEM analysis was obtained in order to relate the microstructure and morphology to the dopant metal and to sensing characteristics. This study was performed in view of the analysis of air pollutants. Different dopants were also utilized to enhance the sensitivity to volatile alkanes in the presence of varying levels of humidity (G36). Here, the oxides of Co and Cr as dopants gave improved sensor stability. In a brief paper, metal oxide-sensing materials were explored in view of "bad breath" analysis, i.e., in the recognition of gases such as NH<sub>3</sub>, H<sub>2</sub>S, CH<sub>3</sub>SH, indole, and putrescine in the presence of ethanol and, of course, humidity (G37). The final choice was WO<sub>3</sub>, rather than SnO<sub>2</sub>, because of its drastically lower cross-sensitivity to humidity and ethanol. However, response times were slow (up to 20 min), and too little analytical data were presented that could have fully convinced the reader.

The group of the late Dr. Göpel reported on the long-term stability characteristics of SnO<sub>2</sub>-based CO sensors and compared them with traditional electrochemical gas sensors for CO (G38). Within an 8-month period, all sensors drifted, with a 20–60% standard deviation for the measurement of CO for the entire time. A good complementarity of both types of transduction principles at low and high CO concentrations was reported. In other work, such long-term drifts were proposed to be eliminated with a calibration method that utilizes a drift compensation algorithm (G39). It was argued that sensor drift over several months could be eliminated by this technique but that the calibration samples needed to be highly correlated to the actual sample composition for a proper drift correction.

Materials other than SnO<sub>2</sub> were also explored for gas-sensing applications. The conductivity change of porous silicon was shown to be catalyzed after sputtering gold clusters into the porous sensing layer (G40). The resulting films were characterized with surface spectroscopy and shown to preferentially respond to nitrogen oxides relative to CO, CH<sub>4</sub>, or methanol. However, humidity was found to be a serious interference. A sol-gel method was developed for coating glass substrates with a platinum-dispersed TiO<sub>2</sub> thin film, with nanosized TiO<sub>2</sub> grains (G41). If the film was fired under a reducing atmosphere, a high sensitivity to H<sub>2</sub>, trimethylamine, and NH<sub>3</sub> was observed, but reducing gases such as CO and CH<sub>4</sub> showed no response. Another report that described a mixed-oxide thin film containing TiO<sub>2</sub> and FeO<sub>3</sub> studied the structural and morphological characteristics of the films as a function of the iron concentration (G42). Iron was found to inhibit the grain growth of TiO<sub>2</sub> and to increase the carbon monoxide response sensitivity of the films. Another nanotechnology approach to gas sensing involved the growth of a palladium mesowire array on a graphite surface and subsequent transfer of the array onto a cyanoacrylate film (G43). The array was found to exhibit a very rapid, sensitive resistance decrease as a function of hydrogen gas concentration. It was believed that the response originates in the closing of nanoscopic gaps in the wires in the presence of adsorbing hydrogen gas. A related paper described the decoration of single-walled carbon nanotubes with Pd nano-

particles (G44). The coated nanotubes were metal contacted individually and showed a reversible electrical resistance change in the presence of 4–400 ppm concentrations of hydrogen gas in air.

Related to the work by Lewis described above (electronic noses), a crystalline block copolymer was grafted onto a carbon black surface with a chemical mediator (G45). The resistivity of the composite was found to drastically and reversibly increase upon exposure to dichloromethane, chloroform, THF, and carbon tetrachloride. Poor polymer solvents had only a small effect on the resistance. A linear relationship between electrical resistance and vapor concentration was found, and long-term stability and reproducibility were reported to be good. An alternative to carbon black-filled polymer composite detectors was described, by utilizing poly(thiophene)-poly(styrenesulfonate) as the conductor in a matrix of different insulating polymers (G46). The composites were found to have superior characteristics over carbon black systems for the measurement of polar analytes but were inferior for nonpolar substances. It was therefore proposed to use this material as a welcome addition to carbon black-based vapor detection arrays. A chemiresistive gas-sensing principle similar in mechanism to carbon black composite materials was introduced that appears to be quite universal (G47). Conductive carbon particles were embedded into a number of sensing polymers and provided electrical continuity in those films. Upon exposure to different gases, film swelling increased the average particle distance, thus increasing the composite film resistance. In this heterogeneous arrangement, different sensing polymers could be used to cover the full range of gas solvation characteristics. High solvent concentrations posed problems with this technique, but the results were otherwise promising. As with related work on surface acoustic wave sensors, it was found with an improved pattern recognition technique that the maximum speciation accuracy for binary gas mixtures is achieved with an array of three to four sensor elements, not more.

## CONCLUSIONS

The diversity of electrochemical sensing principles is extremely large and quite stimulating. Potentiometric sensors have reinvented themselves in recent years, and some important advances in that field have emerged. This is the oldest and largest electrochemical sensor field and one of the best described. In many ways, it serves as a role model for other sensor areas. The largest diversity of sensing approaches is observed with voltammetric sensors and detectors. Much of this richness is due to excellent past long-term fundamental advances, which found their way into modern chemical sensor research. Ion-transfer voltammetry, for example, was long a fundamental field of research but is now being used to fabricate useful, miniaturized devices that can be integrated into microfluidic chips. A very important trend of electrochemical sensor research is clearly spatially resolved chemical sensing, also called chemical imaging. While the field of scanning electrochemical microscopy is today a relatively mature field, further advances will drastically reduce the resolution and the selectivity of such imaging techniques. The area of electronic noses appears to become better related to other chemical sensor research. Indeed, some excellent, self-critical



work has recently appeared that assesses reasonable possibilities and limits of this research direction. This is a welcome change from the earlier, overoptimistic, and often uncritical attitude in this field. Some areas, such as electrochemical gas sensors, are mostly driven by engineers and materials scientists. In consequence, one sometimes finds that the engineering aspects of the sensing devices are solved before the chemistry has been worked out, with the motto "we'll put some chemical sensing layer there". This dangerous trend has a long tradition and already gave rise to many disappointments and is also observed in other sensor fields (optical and thermal sensors, for example). Analytical chemists know that the chemical aspects of sensor development are extremely challenging and should be included in the overall system design from the beginning. Therefore, a truly interdisciplinary research effort with a strong chemical emphasis and realistic goals is required for optimal success in this field. Overall, these are happy times for chemical sensor research. While the use of the word "sensor" has been far overstretched in recent years to mean nearly anything of chemical interest, excellent and very innovative work is being performed in this field by a very diverse group of researchers. Chemical sensors are at the heart of the development of compact, self-contained devices for chemical analysis, which play an increasingly important role in our society. Their importance, complexity, and diversity will only increase in the years ahead.

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