Voltammetry Retrospective

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implantation and after removal from the tissue. The use of plasticizer-free membranes with internally tethered ionophores and sites may be the solution for sensors of extended lifetimes in chronic, in vivo applications.

In summary, microfabricated potentiometric sensors are close to making the move from discrete samples and test technology to continuous, real-time in vivo measurements. However, a decisive requirement for success will have to be a well-defined need—either established or predicted—in medical practice.

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Voltammetry Retrospective

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The 20th century coincided with the rise and maturation of electroanalytical chemistry, with voltammetry at the core of the field. Within a span of just over 75 years, a large number of different methods were developed, instruments were designed and constructed, and a rigorous theoretical and mathematical framework was established. This Report traces the development of voltammetry and some of its many applications. Our coverage of the historical aspects are brief (we probably overemphasize U.S. contributions), and we apologize to those who have contributed to this field to whom we have failed to give adequate recognition. Detailed accounts of the history of electrochemical methods can be found in references 1 and 2.

Voltammetry involves the application of a potential that varies with time and the measurement of the corresponding current that flows between the working and reference electrodes (Figure 1). One can think of the potential as the intensive variable (energy in V or J/C) applied to the working electrode, and one can think of the current as the extensive variable (current in A or C/s) corresponding to the rate of an electrode reaction in response to the potential perturbation. Thus, the resulting voltammogram of current versus potential may be either transient or steady-state (Figure 2), in which a potential ramp serves as the potential perturbation.

Voltammetry can therefore be broadly defined as the exploration of the three-dimensional space that interrelates potential (E), current (i), and time (t) (Figure 3). Both of the voltammograms in Figure 2 feature a plateau or limiting current that corresponds to the point at which the concentration of electroactive species at the electrode surface drops to zero and the flux to the electrode surface (and hence the current) reaches a maximum value. Because the limiting current is controlled entirely by diffusion, it can be used to determine any variable that contributes to its magnitude. Most often this process involves
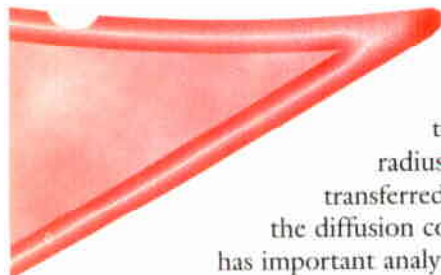
determining the bulk concentration, but it is sometimes useful to determine electrode area or radius, the number of electrons transferred in the electrode reaction, or the diffusion coefficient. Thus, voltammetry has important analytical applications, some of which are highlighted in this article.

The potential at which the wave occurs, reported as the value at one-half of the limiting current ($E_{1/2}$), is characteristic of the electrode reaction and hence of the species undergoing the electron-transfer reaction. The position and shape of both the transient and steady-state voltammograms are also highly dependent on the presence of homogeneous and heterogeneous kinetic limitations. Thus, voltammetry is a very popular technique for initial electrochemical studies of new systems and has proven very useful in obtaining information about complicated electrode reactions.

Early voltammetry and polarography

Although considerable research in electrochemistry dates back to Faraday's work in the early 19th century with important contributions to the understanding of mass transfer by Cottrell and Sand in the early 20th century, applying these techniques to chemical problems was rare. The birth of voltammetry really occurred with Heyrovsky's experiments in Czechoslovakia in 1922 (*3*). Measuring the surface tension of mercury had been of interest since Lippman's work in the late 19th century because these measurements provided information about the nature of the liquid–metal interface (and because the capillary electrometer could also serve as a sensitive null-point detector for balancing potentiometric bridges). Kucera in Czechoslovakia had been working on such electrocapillary measurements with the dropping mercury electrode

(DME), in which a bulb containing mercury is attached to narrow capillary tubing. The mercury drops that fall from the capillary were weighed as a function of potential.

Heyrovsky realized that by measuring the current while the potential of the electrode was changed, he could obtain information about the nature of the species in solution that were reduced at the mercury drop. Following this discovery, he and his colleagues worked out the theory for the processes that occur during electrolysis at the DME. The earliest measurements of *i–E* curves were done manually by applying a potential with a potentiometer and measuring the microamp-level currents with a light-beam galvanometer, a tedious process. In 1925, Heyrovsky and Shikata developed an automatic instrument to photographically record *i–E* curves (Figure 2a) and called it a polarograph. This term now means voltammetry at the DME. The polarograph was one of the first automated recording analytical instruments and ushered in the field of instrumental analysis.

The classic DME is rarely used now, having been replaced by the static mercury drop electrode. However, the DME had an enormous impact on the development of voltammetry until the early 1960s. Because mercury has an atomically smooth surface, a high hydrogen overpotential (which allows a large negative potential range in aqueous solutions), a continuously renewable surface as it drops (which means less contamination and highly reproducible behavior), polarography was widely used for studying metal ions in solution. It is too bad that the prevailing— almost pathologic—fear of mercury has greatly decreased the use of these electrodes.

Voltammetry comes to the United States

Interest in polarography in the United States largely began following a visit by Heyrovsky in 1933. Kolthoff, Furman, and their respective groups did the initial work in the United States. They constructed polarographs and initiated studies on analytical applica-
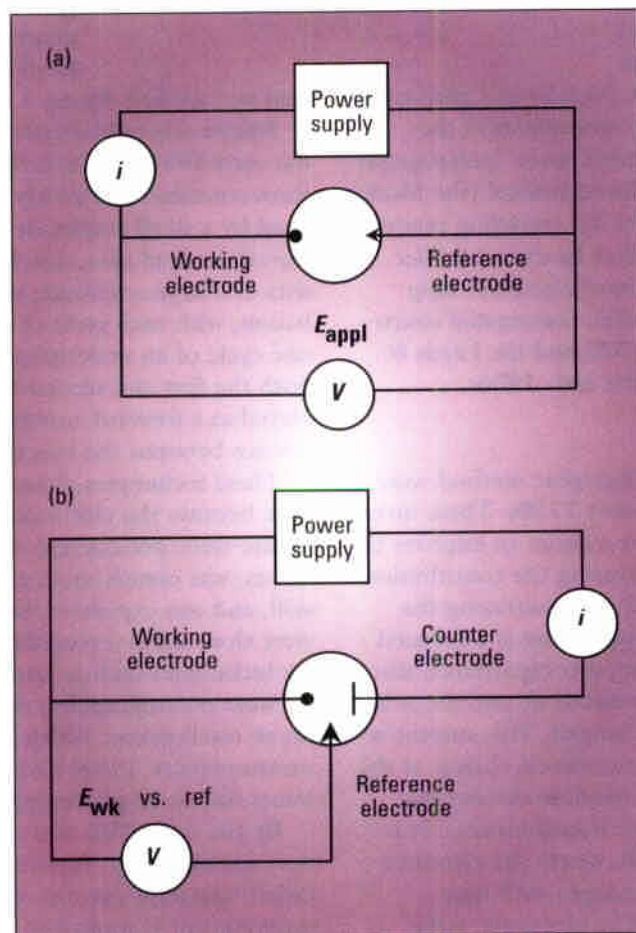

FIGURE 1. Basic voltammetry.

(a) Apparatus for voltammetry with a two-electrode cell, appropriate for use in solutions of low resistance and microelectrodes. (b) Apparatus for voltammetry with a three-electrode cell. In practice a potentiostat that automatically controls the potential of the working electrode with respect to a reference electrode is used.

tions, especially metal ions. The term "voltammetry" was first introduced in 1940 (4) to describe experiments in which the current as a function of potential at a solid working electrode is measured. The first and second edition of the classic monograph *Polarography* by Kolthoff and Lingane helped spread the technique rapidly during the 1940s and early 1950s. During this same period, work in polarography was being done in several European countries other than Czechoslovakia, and in Japan and Australia.

In these early days, voltammetric work with solid electrodes made of platinum, gold, or carbon was secondary compared with studies involving the DME. Even in the second edition of *Polarography* in 1952, the chapter on solid electrodes is only 21 pages long. Commercial instruments first became available from D. V. and J. Nejedly in Czechoslovakia, and they began selling their instruments in the United States in 1939. The trademark name "polarograph" was licensed to Sargent, who produced manual (the Model III) and then photographic (Model XI) recording models. Other instruments, such as the Fisher Instruments Elecdropode, also appeared. The advent of electronic strip chart recorders led to more convenient automated instruments, such as the Sargent Model XXI and the Leeds & Northrup Electrochemograph in the early 1950s.

Variations on a theme

Many variations of the basic polarographic method were developed during the 1940s and early 1950s. These investigations were motivated largely by a desire to improve the sensitivity of polarography by decreasing the contribution of the capacitive (charging) current and increasing the speed of the experiments. Charging current is associated with charging the electrical double-layer capacitance that exists at the interface between the electrode and the solution as the electrode potential is changed. This current is nonfaradaic (e.g., does not cause a chemical change at the electrode surface) and produces a baseline current that must be subtracted in voltammetric measurements. It is particularly troublesome at a DME, where the electrode area, and hence the capacitance, changes with time.

In the early 1950s, Barker built an electronic pulse polarograph. In this technique, the potential is changed from a fixed potential to a new value for a short period of ~50 ms. The current is measured just before the pulse ends. Because the charging current decays more rapidly than the faradaic current, the measured current at the
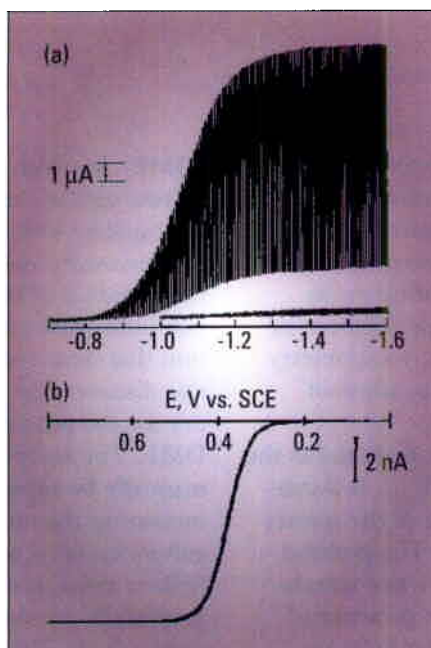

FIGURE 2. Steady-state voltammograms.

(a) Typical polarogram for a reduction reaction obtained at a DME. (b) Typical voltammogram for an oxidation obtained at an RDE or UME.

end of the pulse is largely faradaic. Normal pulse and differential pulse polarographies are among the most sensitive techniques for directly measuring trace concentrations.

Breyer and co-workers in Australia developed ac polarography in which a small ac potential is applied to the dc ramp, with detection of the ac current. Extensive work in this technique was later done by Smith and co-workers in the United States and by the Sluyters in The Netherlands. In the late 1940s, fast linear potential sweeps were applied at the DME, so that the complete potential sweep occurred during a single drop as the voltammogram was recorded on an oscilloscope. The Czechoslovakian group investigated a related technique, oscillographic polarography, in which a large amplitude sinusoidal potential excitation was applied during a single drop.

Square-wave polarography was developed by Barker in the early 1950s. In its earliest form, the potential waveform consisted of a slowly changing dc potential modulated by a small amplitude square wave. The potential waveform used now, developed by the Osteryoungs, consists of a large amplitude symmetrical square-wave perturbation, with each cycle of the square wave coinciding with one cycle of an underlying staircase. Current is sampled on both the first and second half of the cycle and can be displayed as a forward current, a reverse current, or the difference between the two measured currents.

These techniques, however, were not widely used at the time because the electronic instrumentation, such as the square-wave polarograph marketed by Mervyn Instruments, was complicated, required considerable operator skill, and was expensive. In addition, strip chart recorders were slow and x–y recorders had not yet appeared. Thus, for techniques such as linear potential sweep and triangular wave polarographies, the i–E curves had to be recorded on an oscilloscope, which limited the precision of the measurements. It was also very inconvenient because the traces had to be photographed with a 35-mm camera.

By the late 1950s and early 1960s, however, the situation was changing. Interest in chronopotentiometry (also called "constant current voltammetry"), in which a constant current is applied to the electrochemical cell and the potential–time response recorded, became widespread, spurred by the work of Delahay and his monograph *New Instrumental Methods in Electrochemistry*. In chronopotentiometry, the constant current applied to the electrode causes an electroactive reactant to be reduced to product

at a constant rate. The potential of the electrode attains values that are characteristic of the electroactive couple and varies with time as the concentration ratio of the electroactive couple changes at the electrode surface. One can think of the process as a titration of the electroactive reactant in the vicinity of the electrode by a continuous flux of electrons. Eventually, the concentration of the electroactive reactant drops to zero at the electrode surface and the flux of the reactant to the surface is insufficient to accept all of the electrons being forced across the electrode–solution interface. The potential of the electrode then rapidly changes toward more negative values until a new, second reduction process can start. The period after application of the constant current for this potential transition to occur is called the "transition time". This time is related to the concentration and diffusion coefficient of the reactant and is the chronopotentiometric analog of the peak or limiting current in controlled potential experiments. The shape of the potential–time curve is governed by the heterogeneous rate constant of the electrode reaction.

This technique involved simple instrumentation and theoretical treatments, and was further developed by Reilley, Murray, Reinmuth, Bard, and others in the early 1960s. This work led to a new understanding of electrochemical kinetics and mathematical methods of treating these systems. Tafel plotters began to give way to Laplace transformers! Moreover, it encouraged applying electroanalytical techniques to chemical problems beyond analyzing metal ions, such as kinetic studies of short-lived species in homogeneous reactions. Methods were proposed in which a constant charge was rapidly injected into an electrode and the potential–time response was monitored. However, such coulostatic methods never became popular.

Advances in electrochemical methods were also driven by new instrumentation. Operational amplifiers, first based on vacuum tubes and later on transistors and integrated circuits, were used for constructing electrochemical instruments. Polaroid Land cameras and x–y recorders for recording oscilloscope traces became available. These developments led the second wave of instrumentation, in which the earlier mechanical approach to generating waveforms was replaced by transistorized instruments capable of complex experiments, such as pulse polarography. Typical instruments included those

produced by Princeton Applied Research, for example, Models 170, 173, and 174. Interest in solid electrodes, especially platinum and carbon, grew for studying the oxidations of organic molecules as described in Adam's *Electrochemistry at Solid Electrodes*, published in 1969.

An important advance in solid electrode voltammetry was the introduction of the rotating disk electrode (RDE) and later the rotating ring-disk electrode (RRDE) by Levich and co-workers in the former Union of Soviet Socialist Republics. Although steady-state voltammograms had previously been obtained for stirred solutions with many different electrode configurations, most of these voltammograms were not amenable to rigorous mathematical treatments. The RDE, however, showed hydrodynamic behavior that could be treated mathematically, which allowed the RDE to be applied to solution and kinetic studies. The RDE and RRDE could also be used to study rapid homogeneous reactions under steady-state conditions in which the time variable is associated with the angular velocity or rotation rate of the electrode. Bruckenstein, Miller, Albery, and others developed these electrodes and applied them to electrochemical problems.

Many other related methods were described. For example, further increases in sensitivity could be obtained by depositing a metal in a stationary mercury drop, a thin mercury film, or a solid electrode surface for an extended time and then measuring the current when anodically stripping it back into solution. Early work in stripping analysis was done by Rogers and Shain in the early 1950s. The major advantage of stripping analysis, compared with direct voltammetric analysis of the original solution, is that the material to be analyzed is preconcentrated 100- to 1000-fold or more so that the voltammetric (stripping) current is less perturbed by the charging current. Stripping analysis is especially useful for analyzing very dilute solutions down to picomolar concentrations. It is most frequently used for determining metal ions (e.g., Bi, Cd, Cu, In, Pb, and Zn), either alone or in mixtures, by cathodic deposition followed by anodic stripping with a linear potential scan (anodic stripping voltammetry). An increase in sensitivity can be obtained by using pulse polarographic, square-wave, or coulostatic techniques during the stripping step.

Linear scan and cyclic voltammetry at stationary mercury drops and solid electrodes became popular techniques, spurred largely
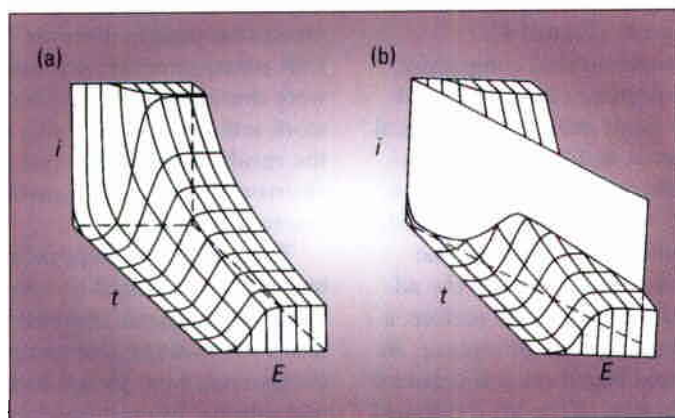

FIGURE 3. Three-dimensional voltammetry.

Representation of the three-dimensional *i–t–E* surface for a Nernstian reaction. The typical steady-state voltammogram represents a cut parallel to the *i–E* plane. (b) A cut representing a linear potential sweep across this surface. (Adapted from Ref. 6.)

by Nicholson, Shain, Savéant, and Vianello in the early 1960s (Figure 4). In these techniques, the potential is ramped linearly at rates of 0.01–10^5 V/s, with the resulting current recorded as a function of potential (which is equivalent to recording current versus time). In a qualitative way, this technique amounts to traversing the three-dimensional i–t–E realm (Figure 3). It is the interplay of these three parameters that leads to the complexity in the theory of linear and cyclic voltammetry. Experimentally, the potential scan is begun at a potential well-positive of the standard potential for a reduction. When the electrode

FIGURE 4. Typical cyclic voltammogram.

potential reaches the vicinity of the standard potential, reduction begins and current starts to flow. As the potential continues to grow more negative, the surface concentration of the oxidized species must drop and the flux to the surface (and hence the current) increases. As the potential moves past the standard potential, the surface concentration drops to near zero and mass transfer of the oxidized species to the surface reaches a maximum rate, followed by a decline as the depletion effect sets in. A peaked current–potential curve is observed. If the experiment is stopped at this point, a linear scan voltammogram is recorded. If the direction of the potential scan is reversed in a positive direction back to the initial potential, an anodic current flows as the electrochemically generated reduced species is reoxidized, leading to the recording of a cyclic voltammogram (Figure 4).

Cyclic voltammetry, despite its theoretical complexity, quickly became one of the most popular electrochemical methods and was widely used in fields outside of analytical chemistry to obtain thermodynamic and kinetic information about organic, organometallic, and inorganic species. Chronocoulometric methods, in which a charge is recorded after a potential step, were introduced by Anson in the mid-1960s and were especially useful for studying the adsorption of electroactive species on an electrode surface, a topic of continuous interest and sometimes annoyance. At about the same time, investigations began on voltammetry in thin-layer cells, in which a thin film of liquid (2–50 μm) is held between two electrodes or between an electrode and an insulating wall. These cells, which contain microliter volumes, were among the earliest analytical techniques that examined such small volumes.
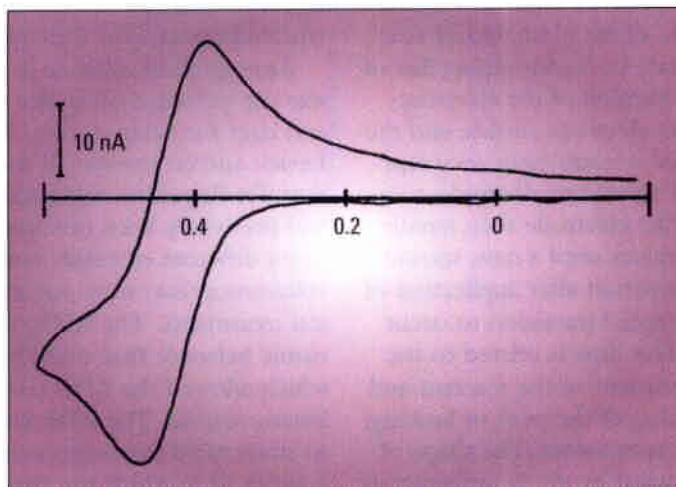
In the late 1950s, the use of aprotic solvents, such as acetonitrile, extended the range of voltammetric measurements to much more positive and negative potentials than were available in water, even with platinum and gold electrodes, and to species insoluble in water. Researchers began to use spectroscopic methods to study reactions in electrochemical cells. In the early 1960s, Geske and Maki introduced electron spin resonance (ESR) to study electrogenerated species by placing the electrode directly into a cell in the cavity of the spectrometer (although physicists advised that it wouldn't work). This technique became a favorite for studying radical ions generated at electrodes. Work in the early 1970s by Goldberg and Bard showed how the high-resistance effects of the usual ESR cells could be ameliorated and how cells could be constructed so that cyclic voltammograms could be run and ESR signal intensity recorded as a function of potential. In the mid-to-late 1960s, Kuwana experimented with transparent indium tin oxide electrodes and Murray and Heineman with minigrids to monitor the optical absorbance of electrogenerated species. In these spectroelectrochemical experiments, the optical absorbance response could be plotted as a function of potential or time.

The availability of electrochemical techniques that could probe the solution chemistry of species with short lifetimes and the growing use of aprotic solvents with vacuum line cells or inert atmosphere boxes led to studies by many groups on organic systems. These studies, coupled with ESR measurements, demonstrated that electrode reactions were dominated by one-electron transfers and that earlier work indicating irreversible two-electron reactions were the result of homogeneous reactions following the first electron transfer, often involving water (so-called ECE-reaction schemes).

These ESR and electrochemical studies pointed to the importance of radical ions in organic reactions at a time when most organic chemistry was still being described in terms of "pushing electron pairs". In fact, many aromatic compounds were shown to form quite stable radical anions and cations. Interest in generating these species led Chandross and Visco at Bell Labs, Hercules at MIT, and Bard and co-workers at University of Texas to almost simultaneously study the annihilation reaction between radical cations and anions generated at an electrode. This reaction pro-

duced excited states and light emission in the phenomenon called electrogenerated chemiluminescence (ECL). Now, in voltammetric experiments, the electrodes emitted light.

Computers leave their mark

The first impact of mainframe computers in the early 1960s was in computation—Herman and Bard even managed to get a computer program printed in *Analytical Chemistry* in an article about cyclic chronopotentiometry, but that practice was short-lived. However, what did have a major impact were digital simulation methods, mainly the work of Feldberg. This approach allowed complex electrochemical mechanisms to be treated, even when the mathematics was daunting. Development of these methods continued, and they became more efficient. When small computers became more powerful and less expensive, commercial programs such as *DigiSim* were used to simulate the cyclic voltammetric response. Today, problems can be treated with a few keystrokes that would have been impossible to deal with 30 years earlier.

Computers also had a major impact on electrochemical instrumentation. When minicomputers, such as the PDP8, became available, they were used to generate the potential programs, for example, in pulse polarography and to record the resulting responses using A/D and D/A converters (5). However, the power of these computers was limited and they were costly. Moreover, considerable programming effort, often in assembly language, was needed to run an experiment. The situation changed with the advent of microcomputers, and computer-controlled electrochemical instruments became a reality. Thus, in the mid-1980s, He and Faulkner described an electrochem-

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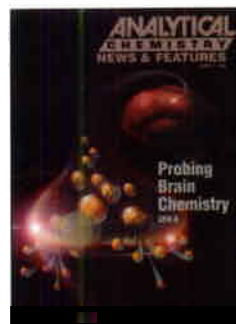
ical instrument that could perform many voltammetric experiments by selecting from a menu on the computer screen. This approach has evolved into the third wave of modern instrumentation based on computer control and recording, with analog-integrated circuit interfaces for potentiostatic control, such as those produced by Bioanalytical Systems, CH Instruments, Eco Chemie, Cypress Instruments, and many others.

What's been going on lately

Following the burst of activity in the 1960s and early 1970s, interest began to turn to the electrodes themselves and to a better understanding of how the surfaces could be modified to carry out desired processes. Electroanalytical chemists started talking about designing and engineering modified electrodes. Initial efforts involved covalently attaching monolayers to electrodes, which was done by Hubbard, Kuwana, Murray, and others, followed by the controlled formation of polymer layers on electrodes by Miller, Bard, Murray, and co-workers in the late 1970s. This work led to a large number of investigations of different types of polymers, including poly(vinylferrocene), polyelectrolytes (Nafion), and electronically conducting polymers (polypyrrole). Savéant, Andrieux, and co-workers made important contributions to understanding the voltammetry of these modified electrodes that allowed determining the various processes that control the rates. More recently, a whole array of different electrode modification strategies, including coatings made of clays, zeolites, inorganic crystals, enzyme layers, organic metals, and composites, has been investigated. Enzyme-modified electrodes have been especially important for designing sensors and have led to commercial products for glucose determination.

Instrumentation that allowed measurement of currents in the nanoamp, picoamp, and even femtoamp range made it possible to do studies with micrometer-sized (or smaller) electrodes called ultramicroelectrodes (UMEs) or microelectrodes. Microelectrodes were originally developed for biological and medical research, and it was not until the late 1970s that electrochemists began investigating the advantageous properties of these small electrodes. Fleischman initiated much of this activity because he sought to understand electrode mechanisms under conditions of high current density. At the same time, carbon-based microelectrodes were developed separately by Adams and Gonon for in vivo determinations of catecholamines. In 1981, Wightman wrote the first comprehensive review on the properties and prospective applications of microelectrodes. The large impact of microelectrodes is rooted in their ability to support very useful extensions of electrochemical methodology into the domains of time, media, and space that were previously either completely or practically inaccessible. Advantageous properties of microelectrodes include a relative immunity to the effects of solution resistance, a dramatically reduced double-layer capacitance, and increased current density. New domains that have been explored include submicrosecond electro-

chemistry, electrochemistry in low-conductivity media, and electrochemistry under time-independent conditions.

Ultramicroelectrodes combined with scanning probe techniques showed how electrodes could be spatially manipulated with very high resolution to study electrode surfaces. In the late 1980s, Wightman, Engstrom, and co-workers showed how a concentration profile at an electrode could be mapped with a UME. Kwak, Fan, Lev, and Bard introduced scanning electrochemical microscopy (SECM) and the concept of scanning a surface and determining information about surface chemistry and topography from the feedback current. The SECM has since been used for many different types of surfaces and for kinetic studies of rather fast heterogeneous and homogeneous reactions. CH Instruments introduced a commercial SECM in 1998.

Work also continued on the interaction of light with electrodes in a field broadly known as photoelectrochemistry. Early work in this area in Czechoslovakia, the former Union of Soviet Socialist Republics, the United Kingdom, and the United States mainly concerned photoelectron ejection from metal electrodes. Later work centered on semiconductor materials as electrodes, which also greatly increased the repertoire of solid electrodes that could be used in voltammetry; more importantly, it led to new insights into the nature of the electrode/solution interface and the electron-transfer process there. Recording the i–E behavior in the dark and under irradiation was useful in mapping the energy states at the semiconductor/solution interface. In the same area of light and electrochemistry, ECL also advanced and, with the discovery of co-reactants, led to reactions carried out in aqueous solutions. There are now commercial ECL instruments for immunoassays and DNA analysis.

Another area of growth is voltammetric detectors for HPLC and CZE. Electrochemical detectors, incorporating microelectrodes in an on-column configuration, were first introduced by Manz and Simon in 1983 for HPLC, and by Wallingford and Ewing in 1987 for CZE. At that time, amperometry was the electrochemical mode most commonly used because of its sensitivity and simplicity. However, this mode was soon found to be limiting because the potential of the electrode is held at one value, and only those species that are oxidized or reduced at that potential are detected. To extend the detectable range of analytes as they elute from a column, fast-scan linear sweep and cyclic voltammetry were introduced to HPLC during the 1980s by Jorgenson and to CZE in 1996 by Ewing. Baranski used square-wave voltammetric detection for CZE in 1998. HPLC and CZE with fast-scan voltammetry have led to exciting investigations of single cells in which femtomolar concentrations of neurotransmitters have been measured.

A look ahead
A large number of methods have been described for exploring the i–E–t domain, though many, such as oscillo-

graphic polarography and coulostatic methods, have fallen by the wayside and it is unlikely that new approaches with significant advantages will be introduced. Chemistry has been moving in the direction of higher speed and smaller size, and voltammetry will also evolve in this direction. Thus, the development of spatially resolved electrochemical techniques for analyzing materials in small domains on surfaces and channels in membranes can be expected, and this will have a huge impact in biological studies. One should note that electrochemistry does not suffer from size limitations caused by diffraction that are typical of optical techniques. However, it is difficult to see how electrochemical techniques will ever approach the picosecond and femtosecond domains routinely studied by laser methods.

Electrochemical sensors will continue to develop, and sensor arrays, where voltammetry can simultaneously be performed on many different microelectrode pads, appear to be on the horizon. These sensors and arrays could form the basis of immunoassays, DNA probes, and enzyme-based arrays. Electrochemistry is easily integrated into small areas, so if chemistry on a chip becomes a reality, electrochemical schemes for synthesis and analysis should be right there, in the forefront.

Suggested reading
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